Ageing Research Reviews 80 (2022) 101697

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

The hormetic and hermetic role of IL-6

Laura Forcina [a], Claudio Franceschi [b], Antonio Musarò [c,*]

[a] DAHFMO-Unit of Histology and Medical Embryology, Sapienza University of Rome, Via A. Scarpa, 14, Rome 00161, Italy
[b] Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy
[c] DAHFMO-Unit of Histology and Medical Embryology, Sapienza University of Rome, Laboratory affiliated to Istituto Pasteur Italia – Fondazione Cenci Bolognetti, Scuola Superiore di Studi Avanzati Sapienza (SSAS), Via A. Scarpa, 14, Rome 00161, Italy

ARTICLE INFO

Keywords:
Interleukin-6
IL-6 signalling
Ageing
Hormesis
Skeletal muscle
Inflammaging

ABSTRACT

Interleukin-6 is a pleiotropic cytokine regulating different tissues and organs in diverse and sometimes discrepant ways. The dual and sometime hermetic nature of IL-6 action has been highlighted in several contexts and can be explained by the concept of hormesis, in which beneficial or toxic effects can be induced by the same molecule depending on the intensity, persistence, and nature of the stimulation. According with hormesis, a low and/or controlled IL-6 release is associated with anti-inflammatory, antioxidant, and pro-myogenic actions, whereas increased systemic levels of IL-6 can induce pro-inflammatory, pro-oxidant and pro-fibrotic responses. However, many aspects regarding the multifaceted action of IL-6 and the complex nature of its signal transduction remains to be fully elucidated. In this review we collect mechanistic insight into the molecular networks contributing to normal or pathologic changes during advancing age and in chronic diseases. We point out the involvement of IL-6 deregulation in aging-related diseases, dissecting the hormetic action of this key mediator in different tissues, with a special focus on skeletal muscle. Since IL-6 can act as an enhancer of detrimental factor associated with both aging and pathologic conditions, such as chronic inflammation and oxidative stress, this cytokine could represent a "*Gerokine*", a determinant of the switch from physiologic aging to age-related diseases.

1. Introduction

Interleukin-6 is pleiotropic cytokine, promptly produced by different cells and tissues, that exerts a wide range of physio-pathologic effects. How a single molecule, as IL-6, displays contradictory roles and can promote different and opposite effects remained unclear for long time. IL-6 represented a sort of hermetic molecule that can act as double-edge sword or a Janus-like factor (Kokje et al., 2016; Muñoz-Cánoves et al., 2013). Nevertheless, a considerable number of studies clarified that the "hermetic" role of IL-6 can be explained considering the concept of hormesis, in which a molecule can exert negative or beneficial actions depending on the intensity, the persistence, and the nature of the response it evokes. Of note, circulating IL-6 levels are undetectable or very low under physiologic conditions but increase significantly in several diseases associated with inflammation and fibrosis (Gabay, 2006; Pelosi et al., 2017, 2015; Petrillo et al., 2017). It is also generally accepted that the dual nature of IL-6 action is related to the activation of different signaling pathways (Forcina et al., 2018, 2019a; Fuster and Walsh, 2014; Muñoz-Cánoves et al., 2013). The classic signaling regulates tissue homeostasis and promotes the anti-inflammatory activity of IL-6. IL-6 transignalling, mediated by the sIL-6R (detailed below), can promote a chronic inflammatory status, influencing the quality of leucocytic populations at the site of inflammation by inducing a shift from neutrophilic to macrophagic accumulation. A role for IL-6 in regulating T and B lymphocytes has been also reported, demonstrating that it can induce B and Th17 cells and can inhibit Treg differentiation, favoring the persistence of the inflammatory response (Bettelli et al., 2006; Kimura et al., 2007; Veldhoen et al., 2006) This leads to an impaired physiologic resolution of the inflammatory response and therefore to the induction of inflammation-related fibrosis.

2. IL-6 expression: transcriptional regulation and signal transduction

The biological activity of IL-6 is the result of a multi-level regulation involving gene expression regulation, post-transcriptional mechanisms, the site and the time of production, the specific responsiveness of target cells, the activation of signalling pathways and downstream effectors. The complex transcriptional regulation of IL-6 gene involves several cis-regulatory elements and trans-acting factors. IL-6 gene promoter

* Corresponding author.
E-mail addresses: laura.forcina@uniroma1.it (L. Forcina), claudio.franceschi@unibo.it (C. Franceschi), antonio.musaro@uniroma1.it (A. Musarò).

https://doi.org/10.1016/j.arr.2022.101697
Received 12 April 2022; Received in revised form 24 June 2022; Accepted 14 July 2022
Available online 16 July 2022

contains transcriptional control motifs involved in the regulation of gene expression through the interaction of trans-regulatory factors. Cis-acting elements includes glucocorticoid response elements (GREs), activator protein 1 (AP-1)-binding site, cyclic AMP (cAMP)-response element (CRE), NF-IL6-binding sequence and a putative binding site for (NF)-κB transcription factor. (Luo and Zheng, 2016). In accordance with the regulatory prominence of these regions, it has been reported that polymorphisms in the promoter of IL-6 gene, such as − 572 G/C, − 597 G/A, − 1363 G/T, − 2954 G/C and − 174 G/C SNP, can affect IL-6 expression and have been associated with differences in the susceptibility to diseases (Luo and Zheng, 2016; Terry et al., 2000; Tumu et al., 2013; Von Linsingen et al., 2005).

In addition, the transcriptional rate of IL-6 is influenced by the action of trans-regulating factors including NF-κB, activator protein (AP)− 1, CCAAT/enhancer binding protein (C/EBP), and cAMP response element (CRE)-binding protein (CREB) (Akira, 1997; Hershko et al., 2002; Vanden Berghe et al., 2000). Noticeably, these key transcription factors not only exert a differential influence on IL-6 expression, depending on the cell type and the nature of the stimulus, but can also act in a cooperative/synergistic manner (Luo and Zheng, 2016; Vanden Berghe et al., 2000).

2.1. The molecular specificity of the IL-6 classical and transignalling

The multifaceted action of IL-6 strictly reflects the complexity of its signal transduction that can have a wide range of impacts, depending on the activated receptor system and on the persistence of stimulation (Fig. 1).

Based on the activation of receptor systems, IL-6 can respectively exert regenerative and anti-inflammatory activities or promote pro-inflammatory pathways and tissue wasting.

IL-6 is a small glycoprotein protein of 21–28 kDa with a four-helix bundle structure characteristic for the IL-6 cytokine family, and its signal transduction needs the formation of an α/β receptor complex

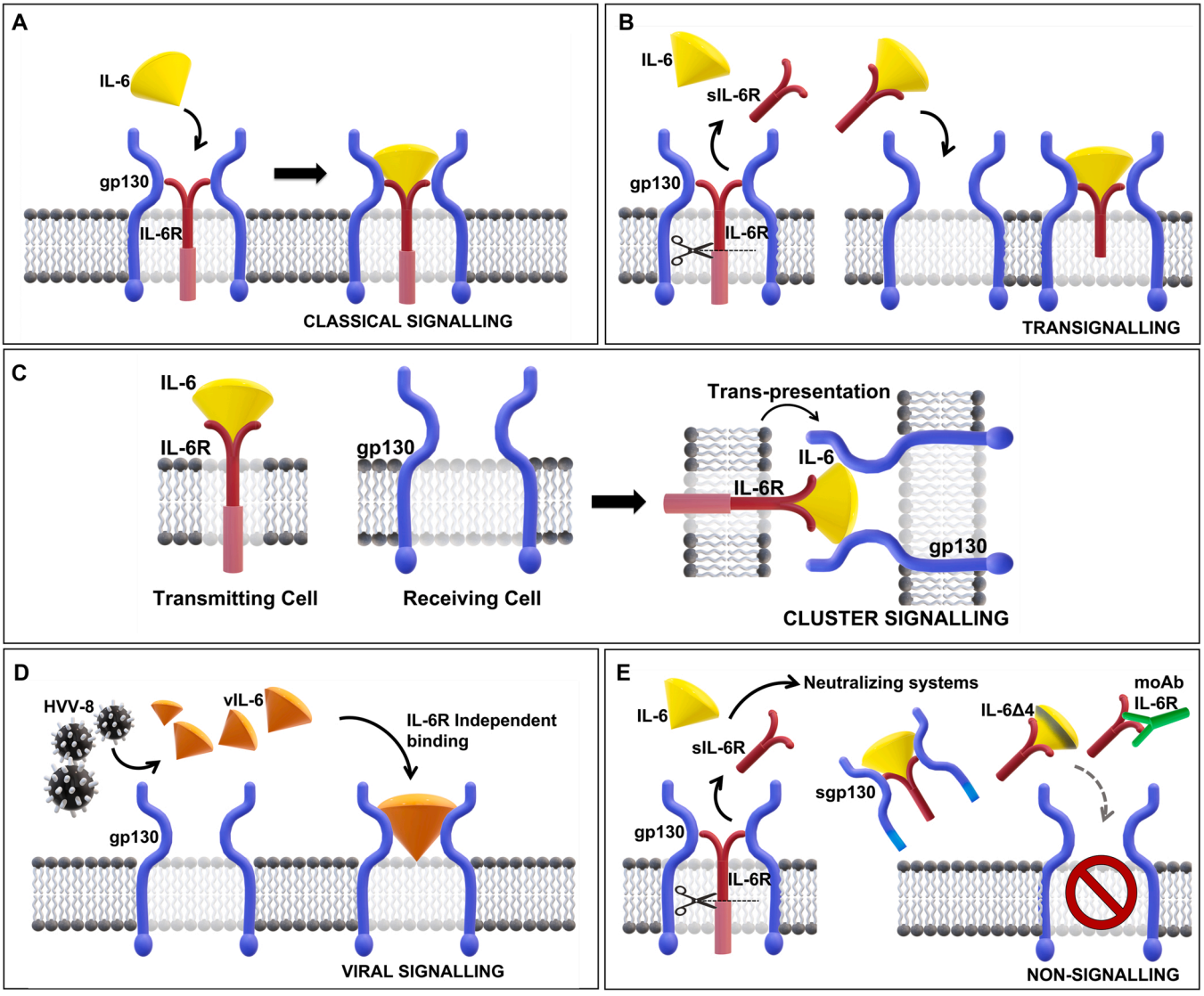

Fig. 1. IL-6 variants and receptor complexes activating or inhibiting signal transduction. (A) IL-6 classical signalling activated by IL-6 binding to membrane IL-6R and gp130 protein. (B) membrane IL-6R can be released as a soluble isoform (sIL-6R) that is able, in turn, to interact with IL-6 activating an alternative signalling, transignalling, in otherwise not responsive cells. (C) IL-6 can be trans-presented by a transmitter cell, expressing IL-6R on the cell surface, to a receiving cell which express only gp130 receptor. This cluster signalling has been described between dendritic cells and T cells. (D) The viral protein vIL-6, homologous of human IL-6, cand directly bind gp130, independently from IL-6R, mimicking IL-6 actions. (E) IL-6 transignalling can be inhibited by endogenous and exogenous molecules. A soluble isoform of gp130 (sgp130) neutralizes IL-6/sIL-6R complex; the IL-6 variant IL-6Δ4, being unable to bind gp130, cannot activate signal transduction sequestering sIL-6R; the administration of monoclonal antibodies (moAb) directed against sIL-6R can inhibit the formation of IL-6/sIL-6R complex.

(Fig. 1A). As a first event, IL-6 cytokine binds the specific α-receptor, glycoprotein 80 (also known as IL-6R, IL-6Rα or CD126). This binding event, that occurs with a low affinity, is known to be non-signalling. As identified by X-ray crystallographic and cryo-electron microscopy studies, IL-6 bound to IL-6R occurs via a conserved site, defined as site I (Boulanger et al., 2003; Skiniotis et al., 2005; Veverka et al., 2012).

The resulting complex constitutes a composite interface, namely site II, necessary to the interaction with the β-receptor glycoprotein (gp) 130 (also known as CD130 or IL6ST). The link between the IL-6/IL-6R complex and gp130 is mediated by fibronectin type III domains D2 and D3 on gp130 protein, while another contact site has been identified as the D1 domain, allowing the formation of a clustered complex made of two molecules of each protein component (Veverka et al., 2012). Structural biology studies proposed an evolutionary modification of binding sites in which the original complex involved specific interactions between IL-6 and IL-6R (site I) and between gp130 and IL-6/IL-6R (site III), with a later inclusion of nonspecific interactions contributing to the stabilization of the receptor cluster. Interestingly, the IIa IL-6 region involved in the interaction between IL-6/IL-6R and gp130 is very poorly conserved across mammalian, with only a single residue unchanged between mouse and human (Veverka et al., 2012). Sequence alignments between murine and human revealed for IL-6 an amino acid identity and similarity score of 41.6% and 65% respectively, and scores of 53.4% and 65.8% for IL-6R (Weidle et al., 2010). Furthermore, it has been reported that murine IL-6 can act in a species-specific manner, showing no affinity to the human IL-6R. In contrast, human IL-6 is able to bind murine receptors (Weidle et al., 2010). IL-6 alone, without the α-receptor, is not able to bind gp130 receptor and thus to initiate the signal transduction (Figs. 1B, 1C). An exception is reported for viral IL-6 (vIL-6). Viral IL-6 protein is a homologous of the human cytokine, sharing a 25% sequence homology, that retains the capability to directly bind and activate gp130, without engaging IL-6R (Fig. 1D) (Adam et al., 2009; Hoischen et al., 2000; Neipel et al., 1997). This peculiar factor, mimicking various IL-6 activities, is encoded by the genome of the Human herpesvirus 8 (HHV-8), also called Kaposi's sarcoma-associated herpesvirus, known to interfere with immune response.

The specific nature of the connection between IL-6 and IL-6R is part of the complex regulation of its signalling pathway. Indeed, IL-6R is exposed on the membrane of few cell types, including hepatocytes, immune cells, and some endothelial cells. On the other hand, the gp130 protein is widely, although not ubiquitously, expressed (Wilkinson et al., 2018). The gp130 receptor is a common signal transducer for a family of cytokines such as that of leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary neurotrophic factor (CNTF), IL-11, cardiotrophin-1 (CT-1), cardiotrophin-like cytokine factor 1 (CLCF1), Inteleukin-27 (IL-27), Interleukin-35 (IL-35), and Interleukin-39 (IL-39) (Collison et al., 2012; Forcina et al., 2018; Jones and Jenkins, 2018; Murakami et al., 2019; Rose-John, 2018). This means that cells expressing both α and β receptors can respond to IL-6 stimulation in a classical transduction, also called cis-signalling. The activation of the classic pathway, through membrane-bound receptors, has been associated with anti-inflammatory, pro-regenerative and protective responses in target cells and tissues (Fuster and Walsh, 2014).

Nevertheless, cells that lack the expression of the membrane IL-6R can be otherwise stimulated by IL-6 cytokine. An alternative signal induction, called IL-6 cluster signalling, has been recently described between dendritic cells (DCs) and T cells. (Heink et al., 2017; Korn and Hiltensperger, 2021). In particular, Heink and colleagues observed that IL-6 can be trans-presented by DCs, expressing IL-6R on cell surface and thus operating as transmitter cells, to receiving T cells, which express only the β receptor (Heink et al., 2017) (Fig. 1C).

A soluble isoform of IL-6R (sIL-6R) has been detected in various body fluid, including blood and urine (Adam et al., 2009; Honda et al., 1992; Novick et al., 1989). This soluble receptor derives, in both human and mouse, from the proteolytic release of the ectodomain through the action of specific A Disintegrin and Metalloproteinase (ADAM) proteases (Fig. 1B). In particular, the constitutive release of IL-6R is mainly mediated by ADAM10, whilst the inducible shedding is mediated by ADAM17. It has been also demonstrated that glycosylation is an important regulatory mechanism in terms of proteolysis and sIL-6R generation, whereas it is not dispensable for trafficking, stabilization, and signalling of the IL-6R (Riethmueller et al., 2017). Although in human, but not in mice, sIL-6R also derive from alternative mRNA splicing, the shedding of receptor is through to be responsible for the bulk of serum sIL-6R (Conceição et al., 2021; Dimitrov et al., 2006; Honda et al., 1992; Jones et al., 2001; Riethmueller et al., 2017; Schumacher et al., 2015). Contrasting data have been reported about the prevalent involvement of one or the other mechanism (Chalaris et al., 2010; Ferreira et al., 2013; Garbers et al., 2014; Reich et al., 2007; Schumacher et al., 2016). Of note, Riethmueller and colleagues generated a polyclonal antibody (ds6R) able to distinguish sIL-6R, deriving from alternative splicing from the full-length, and cleaved sIL-6R in human serum. By using ds6R they observed that only a 15.1 ± 2.8% of total sIL-6R in human serum derived from alternative splicing (Riethmueller et al., 2017).

In addition, it has been recently reported the localization of membrane-IL-6R on circulating microvesicles, suggesting the existence of another mechanism generating sIL-6R with the full-length IL-6R initially released through microvesicles and only subsequently shed into soluble form (Schumacher et al., 2015). While the functional role of sIL-6R needs of a further investigation, its prominence in physiopathology is mainly ascribed to the induction of the so called transignalling. Noticeably, most cells presenting both α and β receptor showed a higher expression of gp130 respect to IL-6R, indicating that IL-6R abundance is a limiting factor for IL-6 stimulation and that sIL-6R can otherwise amplify IL-6 signal (Rose-John, 2012). This transignalling is known to amplify the IL-6 biological activity with pro-inflammatory and pro-oxidant implications (Mihara et al., 2012).

Upon IL-6/IL-6R stimulation, either cis- and trans-signalling results in the activation of non-covalently associated janus kinases (JAKs), responsible for the phosphorylation of tyrosine residues within the cytoplasmic region of gp130. Phosphorylated gp130 recruits signal transducers and activators of transcription (STAT1 and STAT3). The phosphorylated forms of these factors can in turn form active dimers (homo- and hetero-dimer) and translocate into the nucleus where they mediate the transcription of IL-6 dependent genes. Of note, although IL-6 can regulate STAT1-inducible genes in absence of STAT3, it has been proposed a prominent role for STAT3 in driving the transcriptional output of L-6 cytokine (Costa-Pereira et al., 2002; Hirahara et al., 2015).

As a negative feedback, IL-6 dependent STAT3 activation also leads to the transcription of SOCS3 (suppressor of cytokine signalling 3), the negative regulator of IL-6 signalling pathway. Furthermore, IL-6/IL-6R complex can induce a gp130/SHP-2 (Src homology 2 domain-containing protein tyrosine phosphatase-2)/ERK (extracellular-signal-regulated kinase)/MAPK (mitogen-activated protein kinase) pathway.

To date, how cells sense trans- and classic signalling is largely unknown. A proposed mechanism underlying the differences in response to the different signalling comprises the ratio of membrane-bound IL-6R to gp130 on the cell surface (Reeh et al., 2019). Furthermore, it has been observed that, after ligand binding, the signalling complex undergoes rapid internalization, and thereby to termination of signalling, in a mechanism mediated by dileucine-like-motifs in the cytoplasmic domain of gp130 (Dittrich et al., 1994; Scheller et al., 2011; Wang and Fuller, 2017). Internalized receptors can undergo either degradation or recycling; it has been suggested that the internalization of IL-6 receptor complex is a prerequisite for activation of the Jak/STAT signalling cascade and that, after internalization and activation of signalling, both the IL-6R and gp130 are recycled back to the cell surface, a process that is enhanced by IL-6 (Flynn et al., 2021). Although several findings supported the requirement of IL-6 binding for the endocytosis of receptors (Dittrich et al., 1994; Doumanov et al., 2006; Flynn et al., 2021; Martens et al., 2000), recent works reported a constitutive and IL-6

independent mechanism of gp130 and IL-6R internalization (Flynn et al., 2021; Fujimoto et al., 2015).

How and whether differences in the quantity and/or quality of intracellular signalling exist between the classic and transignalling remain to be elucidated.

As described for IL-6R, also soluble isoforms of the beta receptor exist in body fluids, being generated by alternative mRNA splicing events, alternative polyadenylation, and shedding (Wolf et al., 2016a, 2016b). The full-length soluble gp130 receptor (sgp130) and the sgp130-E10 isoform are present in blood serum, while a shorter isoform (gp130-RAPS) can be detected in urine and synovial fluid under physio-pathological conditions (Narazaki et al., 1993; Rose-John, 2012; Sommer et al., 2014; Zhang et al., 1998). Recent works addressed the potential biological impact of the three different isoforms sgp130, also revealing a cell type-specific expression pattern of sgp130 isoforms in primary human immune cells and different established human cell lines. It has been shown that sgp130 is able to bind the IL-6/sIL-6R complex. Thus, in contrast to the stimulatory action of sIL-6R, the soluble isoforms of gp130 exerts an inhibitory function by sequestering IL-6/sIL-6R complexes (Fig. 1E) (Jostock et al., 2001; Müller-Newen et al., 1998; Reeh et al., 2019). Of note, secretion of sgp130-E10 and sgp130-RAPS also showed an inhibitory function, albeit less efficient compared with the full-length sgp130 (Wolf et al., 2016a). This suggests that the three isoforms showed not only a differential expression in primary human leukocytes, but also a variable efficacy in blocking IL-6 transignalling, suggesting the existence of a fine control or protective mechanism by which immune cells can prevent the activation of IL-6 transignalling (Wolf et al., 2016a, 2016b).

Interestingly a potential inhibitory isoform of IL-6, namely IL-6Δ4, which lacks the IL-6 exon 4, has been identified in human lung specimens (Bihl et al., 2002). This transcript encoded for a 17 kDa IL-6 isoform that retains the ability to form a stable complex with IL-6R. IL-6Δ4 not only lacks residues necessary for IL-6/IL-6 homodimerization, but also those required for the interaction with gp130. These data suggested that IL-6Δ4 might act as a competitor of the native IL-6, sequestering IL-6R without activating the gp130-mediated signal transduction (Bihl et al., 2002) (Fig. 1E).

3. Local/transient versus systemic/persistent effects of IL-6

Since the cellular responses to the IL-6/sIL-6R complex can be dramatic, a control mechanism should be necessary to control the activation of the transignalling. In the serum of healthy subjects, IL-6 levels are quite undetectable or ranging between 2 and 6 pg/ml (Rose-John, 2012; Scambia et al., 1994). These levels can reach the order of micrograms (μg) or nanograms (ng) under inflammatory or pathologic conditions. In contrast, the levels of sIL-6R and sgp130 significantly exceed the IL-6 quantity, being sIL-6R physiologically in the range of 75 ng/ml and sgp130 levels have been found at around 250–400 ng/ml (Honda et al., 1992; Rose-John, 2012). As elegantly described by Rose John (Rose--John, 2012) this concentration ratio implies that circulating IL-6 is readily bound by sIL-6R and the complex is neutralised by sgp130. Only when IL-6 levels exceed the levels of sIL-6R and sgp130, it is free to act systemically (Rose-John, 2012).

Interestingly, it has been demonstrated that type 2 diabetes patients displayed high levels of circulating IL-6 with a concomitant significant reduction in both sIL-6R and sgp130 serum levels, compared with healthy control subjects (Aparicio-Siegmund et al., 2019). The authors of the study speculated that chronic overload of the buffer system due to high levels of IL-6 may contribute to the reduction in both sIL-6R and sgp130 serum levels and thus significantly disturb the buffer system (Aparicio-Siegmund et al., 2019). Altogether these observations clearly indicated how the optimal concentration of IL-6 and of its signalling components is determinant to guarantee homeostasis.

Indeed, a low and/or time-controlled release of IL-6 is associated with anti-inflammatory, antioxidant, and homeostatic actions. In contrast, at deregulated levels, IL-6 can act as a pro-inflammatory, pro-oxidant and pro-fibrotic mediator, contributing to chronic diseases.

Overall, the biphasic/opposite role of IL-6 activity can be explained by the concept of hormesis, in which a stressor can exert negative or beneficial actions depending on the intensity, the persistence, and the nature of the response it evokes (Fig. 2).

IL-6 is produced by many cell types, including immune and non-immune cells, and is well recognised as a warning molecule, promptly activating the response against various stressors such as infections and tissue damage (Mauer et al., 2015). In infected lesion IL-6 production is stimulated by pathogen-associated molecular patterns (PAMPs) through the activation of pathogen-recognition receptors (PRRs) on immune cells. On the other hand, traumatic events lead to sterile inflammation and IL-6 production through the stimulation of TLRs by damage-associated molecular patterns (DAMPs), which are molecules released by damaged cells. Both mechanisms induce the activation of the NF-kB pathway, a master regulator of the inflammatory response leading to the expression of pro-inflammatory cytokines and chemokines, including IL-6. Once produced, IL-6 can locally act at the site of the lesion and can reach target tissues and organs through bloodstream. Under warning conditions, one of the main targets of circulating IL-6 is liver, where IL-6 induces the release of a wide range of acute phase proteins such as C-reactive protein (CRP), serum amyloid A (SAA), fibrinogen and haptoglobin (Heinrich et al., 1990). Acute phase proteins, in turn, influence the stages of inflammation exerting both pro- and anti-inflammatory actions, favouring tissue repair or inducing pathologic changes. C-reactive protein is involved in the activation of the complement system. Furthermore, it can recognize pathogens and constituents of damaged cells, contributing to stimulate the elimination of targeted cells (Gabay and Kushner, 1999). SAA is known to influence cholesterol metabolism and the adhesion/chemotaxis of phagocytic cells and lymphocytes. However, elevated levels of SAA have been associated with secondary amyloidosis in chronic inflammatory conditions and to the establishment of a pro-metastatic niche (myeloid cell/fibrosis accumulation) in a murine model of cancer (J. W. Lee et al., 2019). It has been recently reported that SAA exerts a direct action on T naïve cells, promoting TH17 differentiation and response amplification. Interestingly, the induction of a pathogenic/pro-inflammatory differentiation program by SAA involved the collaborative action of STAT3-activating cytokines, including IL-6 (Lee et al., 2020). Haptoglobin (Hp) and Hepcidin are physiologically involved in the iron homeostasis and, when deregulated, are correlated to the inflammation-related iron alteration (Cronjé et al., 2017; L. Forcina et al., 2019a, 2019b; Kemna et al., 2005; Weinstein et al., 2002). Fibrinogen can increase the permeability of blood vessels at the inflammatory lesion, where it is enzymatically converted to polymeric fibrin (Davalos and Akassoglou, 2012; Weisel and Litvinov, 2013). On the other hand, excessive fibrinogen accumulation and fibrin deposition contribute to pathologic fibrogenesis. Since IL-6 is the main stimulator of the acute phase response, the deregulation of systemic levels of this cytokine and/or its long-lasting persistence in bloodstream can contribute to secondary pathogenic mechanisms associated with a chronic stress response, including metabolic alterations, anaemia, impaired growth, and muscle mass.

3.1. Skeletal muscle as a source and a physio-pathologic target of IL-6

Skeletal muscle tissue, based on its metabolic, immunological, and mechanical activities, is known to influence the homeostatic balance of the entire organism, by releasing specific signalling molecules. During physical activity, muscle releases a series of factors and peptides, known as myokines, that stimulate muscle growth and hypertrophy, increase fat oxidation, enhance insulin sensitivity, and induce anti-inflammatory actions (Fig. 2) (Pedersen et al., 2003). These molecules are not only responsible for the autocrine regulation of metabolism in muscle tissue, but also contribute to the regulation of adipose tissue, liver, and brain, with a para/endocrine action (Carson, 2017; Lee and Jun, 2019).

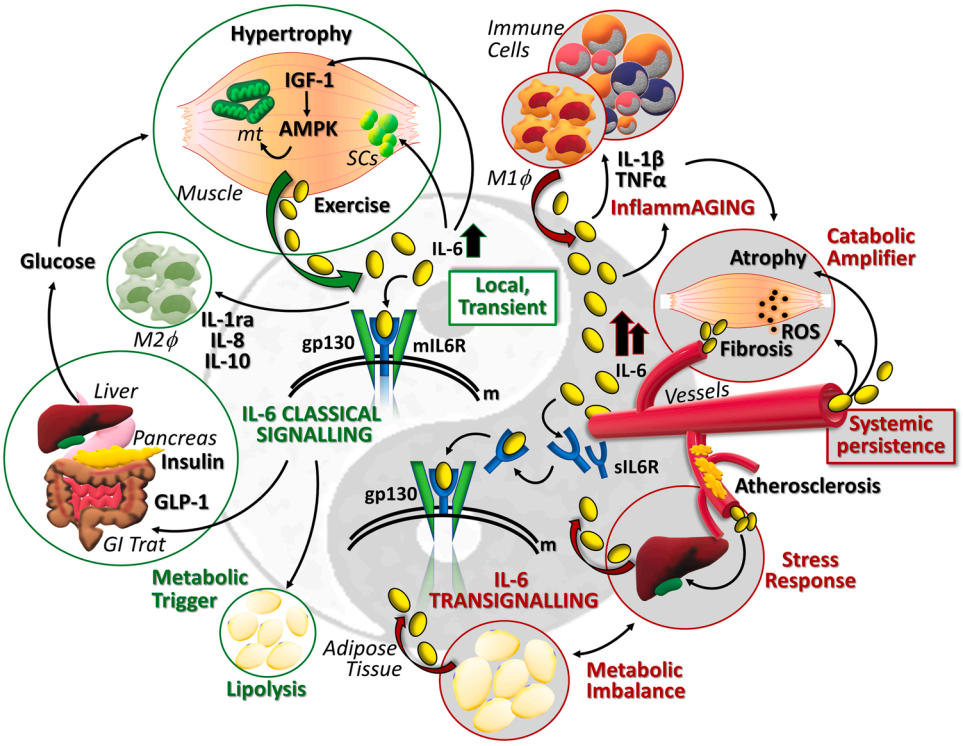

Fig. 2. The effects of IL-6 depending on concentration, persistence, and signal transduction. Muscle-derived IL-6, released upon physical exercise acts both locally and systemically on skeletal muscle and other tissues. The transient production of IL-6 positively influences muscle homeostasis and whole-body metabolism by enhancing glucose production/uptake, insulin secretion/sensitivity, lipolysis, hypertrophic and anti-inflammatory mechanisms. In contrast, the persistence of high-level IL-6 is associated with muscle atrophy, redox imbalance, insulin resistance and chronic inflammatory response. Mt (mitochondria); IGF-1 (Insulin-like growth factor-1); AMPK (Adenosine monophosphate-activated protein kinase); SCs (Satellite cells); m1ϕ/m2ϕ (m1/m2-like macrophages); IL-1β (Interleukin-1 beta); TNFα (Tumour Necrosis Factor alpha); ROS (Reactive oxygen species); sIL6R (soluble IL-6 receptor); m (membrane); GI (Gastro-intestinal trat); GLP-1 (Glucagon-like peptide-1); IL-1ra (Interleukin-1 receptor antagonist); IL-8 (Interleukin-8); IL-10 (Interleukin-10).

Among myokines, IL-6 is expressed and released by both type I and type II muscle fibers and exerts its effects both locally, within the muscle, and on peripheral organs, acting in a hormone like fashion. Specifically, in skeletal muscle, IL-6 acts through the gp130/IL-6R complex, resulting in the activation of different anabolic pathways, including AMP-kinase, phosphatidylinositol 3-kinase, increasing glucose uptake and fat oxidation, regulating the behaviour of satellite cells (SCs), the adult stem cell reservoir of the muscle (Fig. 2). Accordingly, mice lacking IL-6 showed reduced proliferation of SCs and SCs-derived myoblasts, and impaired incorporation of nuclei into growing myofibers under overloading conditions (Serrano et al., 2008).

Muscle-released IL-6 acts also in endocrine manner, increasing hepatic glucose production and lipolysis in adipose tissue, and regulating tissue homeostasis. Of note, the peak IL-6 level is reached at the end of the exercise or shortly thereafter, followed by a rapid decrease towards pre-exercise levels. The rapid down-regulation of IL-6 levels in both muscle and plasma represents an important and critical parameter which guarantee the maintenance of tissues homeostasis (Pedersen et al., 2001; Petersen and Pedersen, 2005). This is an important mechanism that guarantee the maintenance of muscle and organs function and suggests that physical activity selectively adjusts the signalling network of cytokines toward lower levels of inflammation. Interestingly, Kistner and collaborators proposed a model in which IL-6, when released by skeletal muscle upon physical exercise, can act as a short-term energy allocator based on the following considerations: i) it is secreted from muscle in response to an energy deficit, ii) it liberates somatic energy through lipolysis and iii) it enhances muscular energy uptake and transiently downregulates immune function (Kistner et al., 2022 for a review). Thus, modelling IL-6 as an energy allocator elucidates how it can perform seemingly contradictory metabolic effects across the body (Kistner et al., 2022).

Indeed, it has been demonstrated that physical activity is associated with lower circulating levels of proinflammatory biomarkers, including IL-6, in both young and older population (Elosua et al., 2005). Nevertheless, skeletal muscle, along with other tissues, is also a target of IL-6 produced by other sources, which exerts opposite effect compared to the IL-6 myokine. Indeed, IL-6 is not only secreted by skeletal muscle but also by various cell types and tissues and organs, including activated immune, stromal and endothelial cells, adipose tissue, and liver (Tanaka et al., 2014).

The catabolic effects of IL-6 are normally associated with prolonged and high levels of the cytokine into the circulation, as confirmed by several studies. Chronic administration of IL-6 to animal models, obtained through various experimental approaches (systemic administration, local infusion or in vivo electroporation) significantly affects muscle mass, muscle protein content, and muscle growth (Bodell et al., 2009; Carson and Baltgalvis, 2010; De Benedetti et al., 1997; Pelosi et al., 2021). Indeed, chronic exposure to elevated levels of this cytokine leads to muscle atrophy, exacerbates muscle diseases (Haddad et al., 2005; Pelosi et al., 2015; Serrano et al., 2008) and interferes with myogenic differentiation in C2C12 myoblasts (M. Pelosi et al., 2014). Noticeably, IL-6 cytokine is known to be released by different type of tumours associated with cachectic conditions (Jones and Jenkins, 2018; Kistner et al., 2022; Petruzzelli et al., 2014; Rupert et al., 2021). In a murine model of cancer cachexia, it has been described that IL-6 chronically released by C26 carcinoma cells plays an important role in inducing the browning of white adipose tissue and the development of cachectic phenotype (Petruzzelli et al., 2014). Furthermore, in pancreatic adenocarcinoma (PDAC) has been proposed that the development of cachexia can involve the establishment of an IL-6 transignalling loop between malignant cells, fat, and muscle (Rupert et al., 2021).

Based on this evidence and on the fact that cancer cells compete with other cells for energy, it has been recently hypothesized that cancer cells can co-opt short-term energy-allocation mechanisms, such as IL-6, to gain continued access to somatic energy, which may sustain cancer proliferation (Kistner et al., 2022).

Contrasting actions and pleiotropic functions of this factor has been associated with the complexity of signalling pathways it can induce, as well as with the hormetic nature of the signal transduction. In line with its pleiotropic functions, IL-6 emerges as an elective candidate to link the inflammatory and the oxidative aspect of aging and age-related diseases, as the two faces of the same coin.

Although the causal relation between inflammation and disability has to be still clarified, one of the most corroborate hypothesis is that

inflammatory mediators may be determinants of physical decline exerting catabolic effects on skeletal muscle tissue (Schaap et al., 2006).

In particular, IL-6 is known to be involved in the regulation of muscle protein degradation. As observed in murine models, increased levels of this cytokine were associated with significant increase of cathepsin levels in skeletal muscle (Tsujinaka et al., 1996), with the reduced phosphorylation of ribosomal protein kinase S6K1 (Haddad et al., 2005) and to the enhanced expression of markers of the ubiquitin-proteasome pathway, the muscle-specific E3 ubiquitin ligases MAFbx/Atrogin1 and Muscle RING Finger-1 (MURF-1) (Forcina et al., 2019c). Also in vitro studies, performed on myogenic cell line, showed that exogenous IL-6 induced proteolysis by activating intracellular proteases. In particular, different authors reported increased lysosomal and ubiquitin-related proteins and enzymatic activity (cathepsins B and L, proteasome, ubiquitin ligase E3 α-II) in C2C12 myoblasts treated with IL-6 (Belizário et al., 2016; Ebisui et al., 1995; Kwak et al., 2004).

Although the connection between immune system and muscle tissue has been considered as a unidirectional signalling, mounting evidence indicate skeletal muscle as a regulator of immunological and inflammatory processes (Afzali et al., 2018). Indeed, since age-dependent alterations of the intrinsic immunological properties of skeletal muscle are described (Duggal et al., 2018; Quinn et al., 2010), a potential central role of muscle tissue in contributing to immune dysfunction during aging has been proposed (Afzali et al., 2018). Duggal and colleagues reported that physical activity can ameliorate major features of immunosenescence. When compared with sedentary elder, master cyclists showed reduced signs of a decline in thymic output, inflammaging and increased Th17 cell responses (Duggal et al., 2018). Interesting, active elders showed increased circulating levels of IL-7 and IL-15, which are immunoregulatory myokines, and lower levels of IL-6. Although it is well known that IL-6 production is transiently induced by physical exercise, the described results on elder athletes are in accordance with the concept of pre-conditioning and hormesis. Indeed, a stressor can exert negative or beneficial actions depending on the intensity, the persistence, and the nature of the response it evokes. Furthermore, the exposure to a low dose of a substance, with high-dose negative effect, can induce adaptive and protective mechanisms (Martucci et al., 2017).

Indeed, despite the homeostatic action of pulse IL-6 secretion upon physical exercise, the persistence of high-level IL-6 is mainly associated with pro-inflammatory effects, enhancing T-cell recruitment and expansion, antibody production from B-cells, lymphocyte trafficking and abrogating of de novo regulatory T-cell (Treg) differentiation (Nelke et al., 2019; Schaper and Rose-John, 2015).

IL-6 not only is a pro-inflammatory cytokine with a well-established role in the shift between acute and chronic inflammation, but it has been also recognised as a pro-oxidant factor able to disturb the systemic and local redox balance under physio-pathologic conditions (Forcina et al., 2019c, 2019b; Pelosi et al., 2017, 2015; Petrillo et al., 2017; Rose-John, 2012). It has been reported that high levels of IL-6 in the bloodstream of transgenic animals (NSE/hIL-6 mouse model) (De Benedetti et al., 1997) exert a local effect on skeletal muscle homeostasis. In particular, the persistent stimulation of IL-6 signalling enhanced the generation and accumulation of free radicals in the diaphragm muscle of adult mice overexpressing IL-6 (Forcina et al., 2019b). Interestingly, IL-6 deregulation significantly impaired the endogenous antioxidant defence mediated by the nuclear factor erythroid 2-related factor 2 (Nrf2). The imbalance between ROS production and detoxification has been associated with the occurrence of oxidative damage and with the alteration of molecular regulative circuits, resulting in the significative reduction of myofiber size and strength (Forcina et al., 2019b). More recently, the loss of muscle mass and force-generating capability in presence of deregulated levels of IL-6 has been further associated to both loss and switch of more resistant slow-type I oxidative fibers toward more sensitive fast type II glycolytic fibers (Pelosi et al., 2021). These observations suggested that the persistence of supra-physiologic amounts of serum IL-6 can induce muscle atrophy through multiple wasting mechanisms: i) activating catabolic pathway of protein degradation; ii) promoting a slow to fast shift in fiber type composition; iii) enhancing the establishment of pro-oxidant conditions that can preferentially affect fast fibers, which present a lower antioxidant defence; iv) reducing the expression of antioxidants and thus weakening slow-oxidative fibers that are known to be subject to elevated levels of ROS because of their oxidative metabolism.

4. Looking at Interleukin-6 as a "*Gerokine*": the spectrum of IL-6 actions in healthy and bad aging

Aging represents an inexorable process that involves dynamic changes of biological mechanisms critical for survival. Although the age-related modification of some physiologic conditions can be considered as benign features of aged organisms, the progressive deterioration of physiological and biochemical functions significantly affects the quality and the duration of life. Nevertheless, the molecular mechanisms associated to healthy or bad aging are largely unknown.

The causes of ageing can be numerous: from genome to exposome, with positive and negative factors that can affect length and/or quality of life. In this context, define the factors, pathways and conditions that can discriminate the individual's health status also represent an important issue for the predictive medicine. Among factors, IL-6 is a pleiotropic cytokine involved in aging and age-related diseases and a wealth of studies on humans and animal models highlighted the correlation between IL-6 levels and aging-related syndromes (Mladen Jergovic et al., 2020). While the presence of a low-grade inflammation is not specifically associated with peculiar clinical signs, the persistence of inflammatory mediators in bloodstream is through to contribute to unhealthy aging, increasing the risk of developing pathologies such as cardiovascular disease, cancer, sarcopenia, neurodegeneration, and frailty (Beyer et al., 2012; Jenny et al., 2012; Payette et al., 2003; Quaglia et al., 2014; Trichopoulos et al., 2006; Vasan et al., 2003). Indeed, an elevation of key inflammatory factors has been reported as predictor of mortality in unhealthy elderly individuals (Bruunsgaard et al., 2003; Ferrando-Martínez et al., 2013; Giovannini et al., 2011; Puzianowska-Kuźnicka et al., 2016; Wassel et al., 2010). It has been demonstrated that IL-6 serum levels, out of an extensive battery of potential inflammaging markers, were most robustly associated with all-cause and cause-specific mortality in very old people, whereas low baseline IL-6 serum levels represent the best predictor for both survival and no or infrequent hospitalizations (Adriaensen et al., 2015; Akbaraly et al., 2013; Harris et al., 1999). Interestingly, centenarian people, displaying an exceptional longevity, seem to retain the ability to efficiently repair DNA damage and are likely to be protected against inflamm-aging (Storci et al., 2019). Indeed, cells isolated from centenarians showed low levels of DNA damage and a peculiar anti-inflammatory molecular pattern. In particular, dermal fibroblasts isolated from centenarians presented a reduced expression of pro-inflammatory factors, such as specific micro-RNAs associated with age-related inflammatory diseases, and low levels of IL-6 cytokine compared with aged people (Storci et al., 2019). Interestingly, the identification of an inflammatory clock of aging (iAge), which can be used as a metric for healthy/unhealthy aging, led to the observation that centenarians display lower inflammatory clock index (protecting phenotype) tracking with exceptional longevity (Sayed et al., 2021). Table 1.

IL-6 can represent a good candidate in triggering age-related pathological changes and, in that regard, it has been defined as a cytokine for gerontologists by William Ershler in 1993 (Ershler, 1993). Furthermore, the GG single nucleotide polymorphism (SNP) in the IL-6 gene promoter (−174 G/C), that has been associated to the enhanced IL-6 expression in both in vitro and in vivo studies, was reported in negative correlation with longevity (Bonafè et al., 2001; Di Bona et al., 2009; Fishman et al., 1998; Giacconi et al., 2004; Hoffmann et al., 2001; Olivieri et al., 2002). Furthermore, a recent study performed on a mouse model with inducible IL-6 expression (IL-6$^{TET\text{-}ON/+}$ mice) reported that elevated IL-6 serum

Table 1
Factors enhanced during aging, exerting nonmonotonic effects.

	Acute/Low-Level	Chronic/High-Level	References
GDF-15	It is recognised as a *mitokine* with cardioprotective and neuroprotective actions.	Circulating levels of GDF15 are associated with cardiovascular diseases, insulin resistance and type 2 diabetes, neurodegeneration, and mortality.	(Conte et al., 2022, 2020, 2019; Liu et al., 2021; Martucci et al., 2020)
IGFBP1	IGFBP1 protects from senescence in vitro.	IGFBP1 levels increase with aging and correlate with the severity of coronary atherosclerosis in aging patients.	(Nolte et al., 2015; Wu et al., 2019)
IL-6	Anti-inflammatory and pro-regenerative actions. IL-6 local and transient production is involved in satellite cell proliferation and hypertrophic muscle growth.	Pro-inflammatory, catabolic action. Alteration of muscle redox balance. Increased levels of IL-6 during aging have been associated with sarcopenic condition and mortality.	(Forcina et al., 2019a, 2019c; Maurel et al., 2007; Muñoz-Cánoves et al., 2013; Pelosi et al., 2021; Resliany Rachim et al., 2020; Serrano et al., 2008)
PTH	Intermittent exposure to PTH increase bone mass; it has been approved as a therapy for osteoporosis.	Persistent high-level PTH causes bone loss. PTH levels increase with age and correlate with age-related syndromes such as frailty, osteoporosis, and sarcopenia.	(Carrivick et al., 2015; Li et al., 2019; Miller et al., 2016; Murthy and Duque, 2021; Wells, 2011)
ROS	Low levels of ROS modulate protein structure and function, activate signal transduction pathways, and modulate gene expression. ROS stimulate antioxidant and repair processes.	Damage of DNA, proteins, and lipids; cell death and mutation. Induction of oxidative stress and cell senescence.	(Davalli et al., 2016; Martin and Barrett, 2002; Poljsak et al., 2013)

levels are directly associated with age-related frailty, proposing spleen neutrophils as the main source of IL-6 (Mladen Jergovic et al., 2020). Noticeably, elevated levels of IL-6 have been found in human cells and murine model of Hutchinson–Gilford progeria syndrome (HGPS) (Squarzoni et al., 2021). HGPS is a rare syndrome inducing premature aging in children and it is characterised by skin alterations, osteoporosis, lipodystrophy and cardiovascular disfunctions (Filgueiras-Rama et al., 2018; Gonzalo et al., 2017; Hamczyk et al., 2018; Squarzoni et al., 2021). In this context, Squarzoni and colleagues recently reported that IL-6 neutralization, obtained by anti-IL6 receptor antibody, ameliorates the features of accelerated aging in HGPS fibroblast and progeroid mice (Squarzoni et al., 2021). These results suggested a role for IL-6 and its signalling in contributing to aging-related alterations, highlighting a potential therapeutic use of IL-6 inhibitors in ameliorating the quality of life in elderly. Indeed, IL-6 is a pleiotropic factor that, when deregulated, has been associated to inflammatory diseases and a role for this cytokine in ageing and age-related diseases has been proposed over time.

It is well known that IL-6 is normally low or undetectable in healthy adults, while a sensible elevation of serum IL-6 amounts with advancing age has been extensively described. Interestingly, a further elevation of IL-6 concentrations has been reported in very old people (Akbaraly et al., 2013; Bermejo-Martin et al., 2020; Puzianowska-Kuźnicka et al., 2016). Moreover, although authors reported contrasting data, a wealth of studies support the potential correlation of IL-6 levels with aging and chronic morbidity (Maurel et al., 2007; Puzianowska-Kuźnicka et al., 2016). Experimental conditions, stratification parameters and the medical health screening of enrolled subjects may explain contradicting results (Alley et al., 2008; Ferrucci et al., 2005).

For Instance, in 2001, a study performed on twenty young (aged 20–30 years) and twenty six elderly (>65 years) men, reported no differences in serum IL-6 levels between the two groups, with variable but low IL-6 levels (<100 pg/ml) in both young and elderly healthy subjects (Beharka et al., 2001).

In contrast, Wyczalkowska-Tomasik and colleagues investigated the dynamic of changes of serum levels of IL-6, IL-8, TNF, IL-6R, TNF-R1, and CRP according to age (Wyczalkowska-Tomasik et al., 2016). In this study they included healthy individuals of 20–90 years of age divided for decade of life and into subgroups of ≥ 65 or < 65 years. It has been observed that healthy older people presented low serum levels of pro-inflammatory factors, in accordance with the low-grade nature of inflammaging. However, detected levels were higher in elder participants than in younger population, highlighting the importance of considering the adjustment of normal ranges in the elderly (Wyczalkowska-Tomasik et al., 2016).

A prospective population-based study evaluated, among other factors, blood levels of IL-6 as a potential predictor of mortality only in nonagenarians. Although an elevation of circulating IL-6 has been reported in subjects lost at the follow-up than in those who survived, when data were adjusted for risk factors, IL-6 levels did not emerge as a significant predictor of mortality (Jylha et al., 2007).

In contrast, Reuben and colleagues (Reuben et al., 2000) reported a 43% 4-year mortality rate in elderly people with high IL-6 levels (≥3 pg/ml), whilst subjects presenting low amounts of IL-6 into circulation (IL-6 <3 pg/ml) showed a 19% mortality rate. Another study, considering 3044 middle-aged adults, reported that the persistence of high levels of IL-6 sensibly reduced the odds of successful aging at the 10-year follow-up. In particular, the authors highlighted a correlation between increasing IL-6 levels (>2 pg/ml) and increasing probability of cardiovascular disease and death, in a dose–response fashion (Akbaraly et al., 2013). Since IL-6 levels are increased not only with advancing age but also in concomitance with pathologies, that are critical risk factors for mortality, IL-6 has been proposed as both a cause and a consequence of morbidity (Maurel et al., 2007).

More recently, results from a PolSenior study, considering ≥ 65 years old seniors ($n = 4979$ individuals), revealed a significant association of elevated levels of serum IL-6 and CRP with poorer physical and cognitive performance. Puzianowska-Kuźnicka and colleagues (Puzianowska--Kuźnicka et al., 2016) reported a general, age-dependent, increase of IL-6 levels in human subjects. Furthermore, stratifying subjects for diseases or healthy aging, they observed that a longer survival was associated with lower concentrations of IL-6 in individuals with aging-related diseases/disability and also in the successfully aging subgroup (Puzianowska-Kuźnicka et al., 2016). Accordingly, it has been recently highlighted a correlation between IL-6 levels and the severity of sarcopenia, a condition critically impairing physical function and quality of life in elderly (Resliany Rachim et al., 2020; Rong et al., 2018). Interestingly, IL-6 levels increased according to the severity of sarcopenia with an IL-6 concentration of 67.47 pg/ml associated with probable sarcopenia, 135.36 pg/ml in the sarcopenic group, and 287.99 pg/ml in subjects affected by severe sarcopenia (Resliany Rachim et al., 2020).

Noticeably, increased amounts of pro-inflammatory mediators such as TNFα, IL-1β and IL-6 into circulation has been implicated in the pathogenesis of age-related conditions and has been also proposed as biomarkers of vulnerability for cognitive disorders (Warren et al., 2018). Indeed, peripheral and local inflammation can play a determinant role in promoting brain degeneration. A chronic inflammatory condition has been associated with the occurrence of morphologic signs of brain alteration, dementia, and psychiatric disorders. On the other hand, a concomitance of both systemic inflammation, highlighted by elevated levels of serum C-reactive protein (CRP), and neuroinflammation have been found in Alzheimer's Disease (AD) patients.

Regarding pro-inflammatory factors that can play a central role in inducing age-dependent defects in aged brain, IL-6 is of particular relevance. Indeed, circulating levels of IL-6, which are normally quite undetectable, are known to increase during aging and several studies have correlated the persistence of plasma IL-6 with cognitive impairments in aged individuals (Godbout and Johnson, 2004; Warren et al., 2018; Weaver et al., 2002). The deregulation of IL-6 production in aging has been described as a possible consequence of the immunosenescence. In fact, it has been described that the tightening regulation of the immune system decline over time leading to the unwarranted release of pro-inflammatory cytokines, including IL-1β, TNFα and IL-6. Accordingly, it has been reported that lymphoid cells isolated from aged individuals are able to spontaneously secrete IL-6 (Daynes et al., 1993). In reference to the psycho-neuro-inflammatory theory, the age-related alteration of the peripheral immune system can contribute to the establishment of a local pro-inflammatory milieu specifically in the aged brain. It has been postulated that the dysregulation of the immune communication between peripheral and central nervous system can play a prominent role in the development of pathologic conditions which include Alzheimer's disease (AD), dementia, depression, psychosis, and schizophrenia. Indeed, cytokines, such as IL-6, can pass the blood-brain-barrier (BBB), influencing the neural environment.

However, the increased amount of IL-6 in aged brain has been recognised not only as a consequence of the systemic inflammation, but also as a local maladaptive mechanism in neural cells. During aging neurons undergo morpho-functional changes and start to overproduce inflammatory mediators. In aged mice, a significant increase of IL-6 has been reported in the whole brain and in regions specifically compromised during aging, such as cerebral cortex and hippocampus. Of note, increased amounts of IL-6 in relation with aging can significantly impact adult neurogenesis in the dentate gyrus of the hippocampus, which is known to retain adult neural progenitors in a peculiar stem cell niche (Fig. 3). Moreover, the persistent release of inflammatory cytokines in and out of brain can promote the alteration of the BBB, leading to immune cell infiltration of the central nervous system (CNS). On the other hand, elevated levels of IL-6 in neuro-environment have been reported to induce the activation of microglia and astrocytes (Fattori et al., 1995; Godbout and Johnson, 2004; Gyengesi et al., 2019; Lin et al., 2018), non-neuronal cells involved in the immune regulation of the CNS. Noticeably, microglia isolated from aged murine brain spontaneously release IL-6 (Ye and Johnson, 1999) and transgenic mice characterized by a cerebral overexpression of IL-6 showed a precocious and persistent activation of microglia, that can contribute to the loss of brain volume over time (Gyengesi et al., 2019). Furthermore, transgenic mice characterized by astrocyte production of IL-6 (GFAP-IL6 mice) displayed neuropathologic manifestations including neurodegeneration, impaired hippocampal neurogenesis, astrocytosis and angiogenesis (Campbell et al., 2014, 2010, 1993). Interestingly, the induction of sgp130 expression in GFAP-IL6 model alleviates the gliosis, vascular changes, and rescues neurogenesis (Campbell et al., 2014). These findings not only highlighted a pivotal role of IL-6 deregulation in the development of degenerative changes in central nervous system (CNS) but also suggested that the detrimental impact of IL-6 on CNS can be mainly mediated by transignalling.

Another aspect worth considering is the neurotoxic effect of IL-6 cytokine. Toulmond and colleagues (Toulmond et al., 1992) described that the local infusion of IL-6 was protective against the excitotoxic action of N-methyl-D-aspartate (NMDA) in rat brain. These data are in accordance with the recognised role of IL-6 in mediating the acute response to brain injury and promoting neuro-regeneration. However, in an hormetic fashion, the neuroprotective action of IL-6 has been associated to a transient increase of local levels, whereas a chronic heightened expression of this cytokine has been shown to increase the membrane and current response to NMDA leading to neurotoxicity (Qiu et al., 1998). More recently, a synergic effect of IL-6 on β-amyloid peptide (Aβ) toxicity in AD patients has been reported, further broadening the potential involvement of IL-6 cytokine in the occurrence and progression of neurodegenerative diseases (Rothaug et al., 2016).

A role for IL-6 heightening with advancing age has been also proposed in the development of bone disorders and cardiovascular diseases. Osteoporosis is a multifactorial bone disorder common in elderly. It is characterized by the progressive density reduction and micro-architectural deterioration of bone tissue, resulting in the increase of bone fragility and fractures (Christodoulou and Cooper, 2003; Fajar and Azharuddin, 2017).

Several studies have reported the role of IL-6 in the pathogenesis of osteoporosis and osteolytic bone disorders (Fajar and Azharuddin, 2017; Franchimont et al., 2005; Kudo et al., 2003; Roodman et al., 1992). A

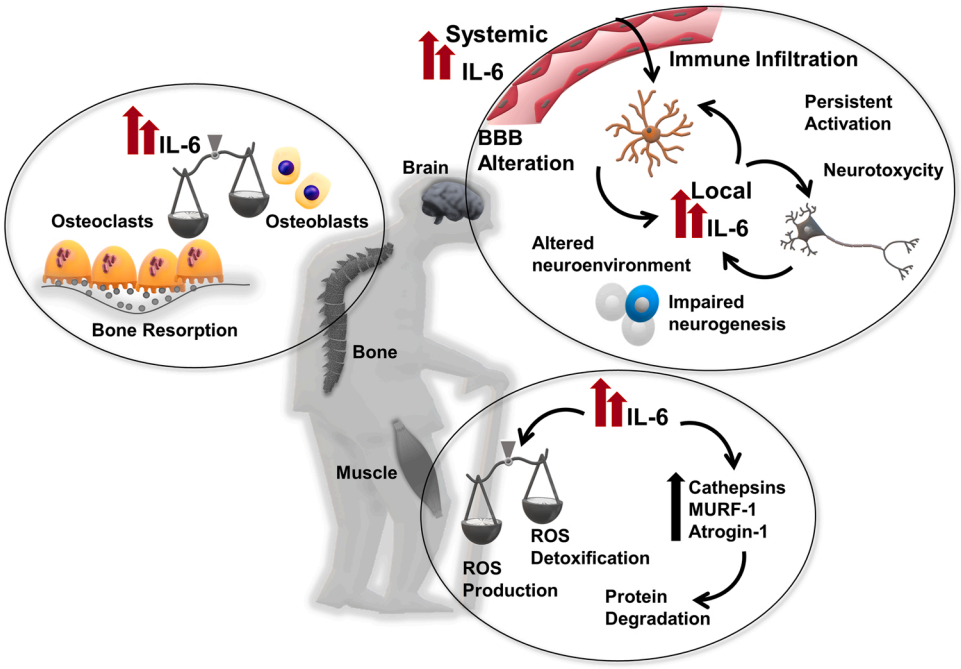

Fig. 3. IL-6 as a "gerokine" affecting the aged brain, bone, and skeletal muscle. A schematic overview of IL-6 actions on different tissues during aging. IL-6 can cross the blood brain barrier (BBB) and can be released by neural cells altering the neuroenviroment, exerting detrimental effects on neurogenesis and neurons. In bone tissue, IL-6 can affect the balance between osteoblasts and osteoclasts, being associated with osteoporosis and osteolytic disorders. In skeletal muscle deregulated levels of IL-6 can exert catabolic actions and alter the local redox balance.

recent meta-analysis study investigating the association between the IL-6 − 174 G/C gene polymorphism and the risk of osteoporosis reported that a positive correlation between G allele and susceptibility to osteoporosis. In contrast, the C allele, associated with reduced plasma levels of IL6, was correlated with a reduced risk of osteoporosis (Fajar and Azharuddin, 2017). The potential role of IL-6 in the regulation of bone turnover and bone loss further derived from several animal studies (De Benedetti et al., 2006; He et al., 2020; Li et al., 2016, 2021; Poli et al., 1994). In 1994, Poli and colleagues described that IL-6 deficient mice were resistant to bone loss caused by ovariectomy-induced estrogen depletion (Poli et al., 1994). More recently, it has been observed that IL-6 KO mice are protected against trabecular bone loss occurring under obesity conditions (Li et al., 2021). A potential mechanism by which IL-6 deregulation can affect bone tissue may involve the disturbance of the balance between osteoblast and osteoclast activities (De Benedetti et al., 2006). In particular, it has been described that IL-6 directly promotes osteoclastogenesis, by a RANKL-independent mechanism, and bone resorption in both in-vitro and in-vivo studies (Heymann and Rousselle, 2000; Kudo et al., 2003). Furthermore, transgenic mice overexpressing IL-6, characterized by osteopenia and severe alterations in cortical and trabecular bone microarchitecture, presented decreased osteoblast and increased osteoclast number and activity (De Benedetti et al., 2006). Interestingly, IL-6 blockade through IL-6-neutralizing antibody (IL-6 nAb) has shown to alleviate the loss of bone tissue induced by modelled microgravity (He et al., 2020).

Aging also represents a risk factor for cardiovascular diseases (CVD). A persistent inflammatory status, and in particular cytokines, have been reported to directly affect vascular cells, causing vascular dysfunction (Cortez-Cooper et al., 2013).

IL-6, based on its role in inflammatory events and in the regulation of fibrinogen synthesis, has been extensively proposed as a marker of vascular risk, cardiovascular burden and CVD events in both humans and rodents (Bao et al., 2015; Patterson et al., 2010; Ridker and Luscher, 2014). Interestingly, increased levels of soluble IL-6R have been also identified as a potential indicator of early vascular changes associated with CVD (Cortez-Cooper et al., 2013).

Thus, although the precise role of IL-6 as a "*gerokine*" has still to be clarified, several studies suggested IL-6 signalling as a key pathway involved in aging, aging-associated diseases, and chronic diseases occurring in advancing age (Akbaraly et al., 2013; Barbieri et al., 2003; Perry et al., 2003) (Fig. 3).

5. IL-6, immune dysregulation, and COVID-19: Keep calm the cytokine storm

Aging is associated with a wide range of physio-pathologic modifications affecting the entire organism and is associated with the increased risk to develop age-related diseases (ARDs) and geriatric syndromes (GSs). Recently, the aged population has been dramatically affected by COVID-19 outbreak all around the World, being the hardest hit population by the pandemic.

The worldwide expansion of Severe Acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as 2019-nCoV, in light of the outbreak in China in December 2019, has rapidly become a "global heart concern". This novel coronavirus, belonging to the Coronaviridae family of single-stranded RNA viruses, can induce a disease condition known as Coronavirus disease (COVID-19), mainly characterised by general clinical features such as fever and respiratory symptoms with a broad range of severity and progression patterns (Tu et al., 2020; Zhai et al., 2020).

Although the majority of affected people developed a mild flu-like symptomatology, with fever, fatigue, sore throat and cough, a not negligible percentage of infected people developed severe pneumonia with lethal consequences. Several epidemiologic studies are revealing that elderly people, with reference to those with concomitant pathologies, showed a major susceptibility to progress to severe disease. It has been reported a higher proportion of patients with IV and V pneumonia severity index (PSI) in the aged cohort compared to the young/middle-aged. Coherently, the mortality rate in old patients (≥60 years of age) is higher compared with middle aged patients (< 60 years of age). Why the spectrum of symptom intensity displayed by SARS-CoV-2 infected people widely vary from asymptomatic to lung lesions, acute respiratory distress syndrome and death is still under investigation.

Important evidence emerged by serological studies is that most of the patients with severe COVID-19 presented increased serum levels of pro-inflammatory cytokines, the so-called cytokine storm. Studies comparing opposite outcomes in COVID-19 patients (discharge and death) highlighted that markers of heart damage and inflammatory mediators, such as CRP, IL-6, and D-dimer, can be recognised as powerful predictors of mortality (Ponti et al., 2020; Sabaka et al., 2021; Velavan and Meyer, 2020). Among cytokines, IL-6 heightening in patients developing severe illness drew great clinical and scientific attention, based also on the involvement of this cytokine in aging and ARDs, that are known to increase the risk of poor outcomes of SARS-CoV-2 infection.

Mounting evidence strongly support the correlation between circulating IL-6 (≥80 pg/ml) and respiratory failure in infected patients (Chen et al., 2020; Coomes and Haghbayan, 2020; Gubernatorova et al., 2020; C. Zhang et al., 2020). Furthermore, serum SARS-CoV-2 nucleic acid (RNAemia), has been detected only in critically ill COVID-19 patients and has been correlated to the severity of the disease (Chen et al., 2020). Interestingly, RNAemia was associated with elevated levels of serum IL-6, as a part of the cytokine storm contributing to a poor prognosis (Bermejo-Martin et al., 2020; Chen et al., 2020; Eberhardt et al., 2020).

In the aged population, with reference to aged men and to people with comorbidities, systemic IL-6 elevation contributes to increase the risk of mortality and ARDs (Kennedy et al., 2016; Mocco et al., 2016). Furthermore, it has been reported that high-level IL-6 can promote lung tissue inflammation and injury (Saver et al., 2015) and foster viral replication (Sacks et al., 2018). As mentioned above, aging is characterized by a progressive immune dysregulation highlighted by the gradual development of a subclinical systemic inflammation, and by the impairment of the immune system. Both inflammaging and immunesenescence seem to play a role in favouring a poorer outcome upon SARS-CoV-2 infection. The progressive decline of the adaptive immune response to pathogens is correlated to a shift of lymphocytes from naïve to memory effector cells (Linton and Dorshkind, 2004; Weng, 2006) and is associated with the upregulation of co-stimulatory molecules and the reduction of antiviral cytokines. Otherwise, the enhanced production of pro-inflammatory cytokines can contribute to tissue damage and to a blunted antiviral response.

In this context it has been extensively described the immune role of IL-6 cytokine in regulating macrophage differentiation, B cell differentiation and IgG production (Garbers et al., 2018). However, in accordance with its anti-inflammatory action, it has been also highlighted a critical role for IL-6 signalling in inducing the IL-4-dependent M2 macrophage polarization, by inducing IL-4R expression, under inflammatory conditions (Garbers et al., 2018; Mauer et al., 2014). Furthermore, IL-6 has a dual action on Th1/Th2 polarization. It is known to promote Th2 differentiation in a NFAT-dependent mechanism and can simultaneously inhibit Th1 by interfering with IFNgamma signalling through SOCS-1 upregulation (Diehl and Rincón, 2002).

Previous studies, performed on animals infected by SARS-CoV1, revealed that aged animals with a severe phenotype showed increased production of IL-6 and a blunted type I IFN response (Bonafè et al., 2020; Smits et al., 2010). Furthermore, IL-6 can inhibit the differentiation of T regulatory cells, inducing the alteration of mechanisms regulating immunological tolerance (Bettelli et al., 2006; Tanaka et al., 2014). On the other hand, several studies have been performed to unveil genetic and molecular mechanisms underlying COVID-19 pathogenesis and COVID-19 susceptibility. Interestingly, it has been reported that genes encoding for host angiotensin-converting enzyme 2 (ACE2), the host

receptor for SARS-CoV-2, and for IL-6, triggering the cytokine storm, are both non-canonical interferon-stimulated genes (non-ISGs). The epigenetic modifications of ACE2 and IL-6 genes have been proposed as biomarkers of COVID-19 susceptibility in vertebrates (Sang et al., 2021). Although IL-6 can early exert protective functions against viral infections, by acting as a pyrogenic and pro-regenerative factor and inducing Th17 activation and differentiation, its extreme deregulation is associate with the cytokine storm, leading to multiple organ failure and to a dampened adaptive immunity (Dienz et al., 2012; Gubernatorova et al., 2020; Yang et al., 2017).

Noticeably, a role for IL-6 deregulation has been proposed in the development of venous thromboembolism (VTE), a severe complication identified in critically ill COVID-19 patients (Eljilany and Elzouki, 2020; Zhou et al., 2020). Indeed, it is well known that inflammatory mediators, such as IL-6, can promote thrombosis by dysregulating coagulation. Indeed, IL-6 is known to contribute to deep venous thrombosis (DVT) (Y. Zhang et al., 2020). Furthermore, a study performed on experimental animal models indicates that IL-6 mediates the thrombocytosis, platelet hyperreactivity, and accelerated thrombus development in a dose-dependent manner (Senchenkova et al., 2013). Accordingly, IL-6 and fibrinogen levels concomitantly increased in COVID-19 patients, supporting the existence of a link between IL-6 and procoagulant conditions in SARS-CoV-2 infected patients (Ranucci et al., 2020).

Since high-level IL-6 is one of the main contributors of the cytokine storm, worsening COVID-19 outcome, and since an increase of IL-6 levels occurs in aged people, which represent the fraction of population more susceptible to critical consequences of SARS-CoV-2 infection, IL-6 could represent a potential therapeutic target. Furthermore, the extent of IL-6 elevation has been also proposed as a marker of disease progression and a prognosis predictor in infected patients (Gubernatorova et al., 2020; Ulhaq and Soraya, 2020).

Among IL-6 inhibitors, Food and Drug Administration (FDA) approved for clinical use two different classes of drugs targeting IL-6 receptor (e.g., sarilumab, tocilizumab) and the cytokine (i.e., siltuximab). Both approaches have been evaluated in patients with COVID-19.

Tocilizumab is a recombinant humanized anti-IL-6 receptor monoclonal antibody (mAb) approved for patients with rheumatologic disorders and recently for cytokine release syndrome induced by chimeric antigen receptor T cell (CAR) T-cell therapy-induced cytokine release syndrome (CRS). Despite contrasting results (Salvarani et al., 2021), reporting no differences in the risk of clinical worsening in COVID-19 patients with pneumonia upon tocilizumab administration, a wealth of studies supported the promising effect of IL-6R neutralization for treating critical ill.

In a non-controlled prospective clinical trial, as well as in studies evaluating efficacy and safety, the effect of Tocilizumab treatment in case of severe or critical SARS-CoV-2 infection has been evaluated, resulting in a decreased percentage of mortality rate and a reduced median hospital and the Intensive care Unit (ICU) length of stay (Dastan et al., 2020; Rosas et al., 2020). Furthermore, Guarald and colleagues reported that tocilizumab reduces the risk of invasive mechanical ventilation or death (Guaraldi et al., 2020) and a low-dose administration has been found to be effective in hospitalized patients with noncritical COVID-19 pneumonia (Strohbehn et al., 2021).

Encouraging results also derived from clinical studies about the use of siltuximab, an anti-IL-6 chimeric monoclonal antibody, neutralising human IL-6.

Siltuximab has been approved for patients with idiopathic multicentric Castleman's disease (MCD) and its administration in COVID-19 patients, requiring ventilatory support, resulted in the reduction (54%) in the risk of 30-day all-cause mortality (Gritti et al., 2021).

It is worth to report that inhibitors of IL-6/IL-6R binding can led to increased concentration of IL-6 into circulation. Furthermore, IL6R genetic variants, such as the common single nucleotide polymorphism (SNP) rs2228145, leading to enhanced levels of serum IL-6R, appears to be protective in case of SARS-CoV-2 infection (Bovijn et al., 2020; Garbers et al., 2014; Jones and Hunter, 2021). These apparently contradictory observations could be due to variation in IL-6 bioavailability. Indeed, IL-6/sIL-6R complex is a target of sgp130, the endogenous inhibitor of IL-6 transignalling and systemic IL-6 can form a binary (IL-6/sIL-6R) active complex and a ternary (IL-6/sIL-6R/sgp130) inactive complex. (Jones and Hunter, 2021; Rodríguez-Hernández et al., 2022). Of note, a recent study reported that IL-6 signalling variables can be considered as disease biomarkers predicting the evolution of SARS-CoV-2 disease. In particular, Rodríguez-Hernández and colleagues considered not only the concentration of the cytokine and soluble receptors in COVID-19 patients, but also the ratio between the binary and the ternary complex (B/T), and the fold molar excess of sgp130 over sIL-6R (FME) to estimate the potential impact of IL-6 transignalling on the severity of the disease. This analysis in survivor COVID-19 patients highlighted the prognostic power of elevated levels of IL-6 and signalling molecules (sIL-6R, sgp130). Furthermore, the authors reported that elevated values of B/T complex ratio and low FME, estimators of transignalling activation, are also predictors of COVID-19 severity in survivor patients (Rodríguez-Hernández et al., 2022).

Further studies to investigate the role of IL-6 and its signalling pathways in fostering pathogenic events in COVID-19 patients, and to unveil potential mechanisms leading to the exacerbation of the disease, would be valuable for research and clinic purpose.

6. Concluding remarks and open questions

Several factors and lifestyle may influence the production and secretion of pro-inflammatory cytokines, leading causes of preventable deaths worldwide. Among cytokines, IL-6 is a pleiotropic factor produced by a variety of cell types that targets a plenty of cell types with a wide range of opposite biological effects and with the ability to induce several different intracellular signalling pathways. How a single signalling molecule is involved in diverse and opposite physio-pathologic processes remains to be fully elucidated.

At first, the dual *yin and yang* activity of IL-6 can be justified considering the concept of hormesis, in which a low dose of a molecule is stimulatory/homeostatic, whereas a high dose is inhibitory/catabolic. Indeed, one important consideration related to this issue is the different expression levels of the cytokine and the length of time the circulating IL-6 is actually elevated; a chronic response versus a somewhat brief increase that returns to baseline.

Increased circulating levels of IL-6 contributes to several pathologic states associated with aging. The complex phenomenon of aging is considered a multifactorial process in which endogenous and environmental factors contribute to the progressive deterioration of the biological functions of the organism. A key role in the maintenance of homeostasis is played by the ability of the organism to adapt to environmental stimuli through dynamic remodelling mechanisms, such as DNA repair, apoptosis, immune response, and antioxidant defence. In this context, the maintenance of robustness or the development of a frail phenotype during aging is thought to be related to the efficiency of the aged organism in repairing molecular damage and/or adapting to the accumulation of damage (Minciullo et al., 2016). However, the molecular mechanisms associated to normal or unsuccessful aging are largely unknown and numerous factors have been proposed as contributors to aging and age-related diseases. Among factors, IL-6 has gained even more attention over time because of its recognised role as inflammatory mediator. However, the precise involvement of IL-6 in aging processes has to be still defined and several aspects contribute to make the comprehensive understanding of IL-6 impact difficult. The complexity of IL-6 signalling pathways, the dose and time-dependent bi-phasic effect of the cytokine, along with the variable amounts of serum levels in aged people must be considered. Indeed IL-6 is not only a pro-inflammatory mediator but also a pro-regenerative and stress-defensive factor exerting hormetic and pleiotropic functions. Besides the basal variability existing among individuals, IL-6 levels have been reported as highly

variable in aged people, depending on decade of age, gender, and comorbidities.

For instance, although plasma IL-6 levels negatively correlate with muscle performance in aging sarcopenia, it has been reported that men have higher levels of IL-6 compared with age-matched women but retains a better muscle condition (Mikó et al., 2018). In addition, circulating levels of IL-6 not always correlate with the effective activation of signal transduction in muscle, with differences observed in the activation levels of downstream targets (Hetzler et al., 2015).

These variables tangle the interpretation of IL-6 data in epidemiological and research studies. It would be valuable for future research to monitor not only IL-6 levels but also the concentration and/or activation of key factors mediating IL-6 action, including receptor systems and downstream mediators. Mounting specific observations might contribute to the direction of future development of personalized therapies based on the individual response of the organism to stressors.

Funding

This work was supported by AFM-Téléthon (23608),France, Fondazione Roma, Italy, Agenzia Spaziale Italiana (ASI) (MARS-PRE 2019-11-U.0), Italy, Ricerca Finalizzata (RF-2016-02364503), Italy and LBI Rehabilitation Research, Austria.

Conflict of interests

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

References

Adam, N., Rabe, B., Suthaus, J., Grötzinger, J., Rose-John, S., Scheller, J., 2009. Unraveling viral interleukin-6 binding to gp130 and activation of STAT-signaling pathways independently of the interleukin-6 receptor. J. Virol. 83, 5117–5126. https://doi.org/10.1128/JVI.01601-08.

Adriaensen, W., Matheï, C., Vaes, B., van Pottelbergh, G., Wallemacq, P., Degryse, J.-M., 2015. Interleukin-6 as a first-rated serum inflammatory marker to predict mortality and hospitalization in the oldest old: a regression and CART approach in the BELFRAIL study. Exp. Gerontol. 69, 53–61. https://doi.org/10.1016/j.exger.2015.06.005.

Afzali, A.M., Müntefering, T., Wiendl, H., Meuth, S.G., Ruck, T., 2018. Skeletal muscle cells actively shape (auto)immune responses. Autoimmun. Rev. 17, 518–529. https://doi.org/10.1016/J.AUTREV.2017.12.005.

Akbaraly, T.N., Hamer, M., Ferrie, J.E., Lowe, G., Batty, G.D., Hagger-Johnson, G., Singh-Manoux, A., Shipley, M.J., Kivimäki, M., 2013. Chronic inflammation as a determinant of future aging phenotypes. Can. Med. Assoc. J. 185, E763–E770. https://doi.org/10.1503/cmaj.122072.

Akira, S., 1997. IL-6-regulated transcription factors. Int. J. Biochem. Cell Biol. 29, 1401–1418. https://doi.org/10.1016/S1357-2725(97)00063-0.

Alley, D.E., Crimmins, E.M., Karlamangla, A., Hu, P., Seeman, T.E., 2008. Inflammation and rate of cognitive change in high-functioning older adults. J. Gerontol. A. Biol. Sci. Med. Sci. 63, 50–55. https://doi.org/10.1093/GERONA/63.1.50.

Aparicio-Siegmund, S., Garbers, Y., Flynn, C.M., Waetzig, G.H., Gouni-Berthold, I., Krone, W., Berthold, H.K., Laudes, M., Rose-John, S., Garbers, C., 2019. The IL-6-neutralizing sIL-6R-sgp130 buffer system is disturbed in patients with type 2 diabetes. Am. J. Physiol. Metab. 317, E411–E420. https://doi.org/10.1152/ajpendo.00166.2019.

Bao, P., Liu, G., Wei, Y., 2015. Association between IL-6 and related risk factors of metabolic syndrome and cardiovascular disease in young rats. Int. J. Clin. Exp. Med. 8, 13491–13499.

Barbieri, M., Ferrucci, L., Ragno, E., Corsi, A., Bandinelli, S., Bonafé, M., Olivieri, F., Giovagnetti, S., Franceschi, C., Guralnik, J.M., Paolisso, G., 2003. Chronic inflammation and the effect of IGF-I on muscle strength and power in older persons. Am. J. Physiol. - Endocrinol. Metab. 284. https://doi.org/10.1152/AJPENDO.00319.2002.

Beharka, A.A., Meydani, M., Wu, D., Leka, L.S., Meydani, A., Meydani, S.N., 2001. Interleukin-6 production does not increase with age. J. Gerontol. Ser. A Biol. Sci. Med. Sci. 56, B81–B88. https://doi.org/10.1093/gerona/56.2.B81.

Belizário, J.E., Fontes-Oliveira, C.C., Borges, J.P., Kashiabara, J.A., Vannier, E., 2016. Skeletal muscle wasting and renewal: a pivotal role of myokine IL-6. Springerplus 5, 619. https://doi.org/10.1186/s40064-016-2197-2.

Bermejo-Martin, J.F., González-Rivera, M., Almansa, R., Micheloud, D., Tedim, A.P., Domínguez-Gil, M., Resino, S., Martín-Fernández, M., Ryan Murua, P., Pérez-García, F., Tamayo, L., Lopez-Izquierdo, R., Bustamante, E., Aldecoa, C., Gómez, J. M., Rico-Feijoo, J., Orduña, A., Méndez, R., Fernández Natal, I., Megías, G., González-Estecha, M., Carriedo, D., Doncel, C., Jorge, N., Ortega, A., de la Fuente, A., del Campo, F., Fernández-Ratero, J.A., Trapiello, W., González-Jiménez, P., Ruiz, G., Kelvin, A.A., Ostadgavahi, A.T., Oneizat, R., Ruiz, L.M., Miguéns, I., Gargallo, E., Muñoz, I., Pelegrin, S., Martín, S., García Olivares, P., Cedeño, J.A., Ruiz Albi, T., Puertas, C., Berezo, J.Á., Renedo, G., Herrán, R., Bustamante-Munguira, J., Enríquez, P., Cicuendez, R., Blanco, J., Abadia, J., Gómez Barquero, J., Mamolar, N., Blanca-López, N., Valdivia, L.J., Fernández Caso, B., Mantecón, M.Á., Motos, A., Fernandez-Barat, L., Ferrer, R., Barbé, F., Torres, A., Menéndez, R., Eiros, J.M., Kelvin, D.J., 2020. Viral RNA load in plasma is associated with critical illness and a dysregulated host response in COVID-19. Crit. Care 24, 691. https://doi.org/10.1186/s13054-020-03398-0.

Bettelli, E., Carrier, Y., Gao, W., Korn, T., Strom, T.B., Oukka, M., Weiner, H.L., Kuchroo, V.K., 2006. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature 441, 235–238. https://doi.org/10.1038/nature04753.

Beyer, I., Njemini, R., Bautmans, I., Demanet, C., Bergmann, P., Mets, T., 2012. Inflammation-related muscle weakness and fatigue in geriatric patients. Exp. Gerontol. 47, 52–59. https://doi.org/10.1016/j.exger.2011.10.005.

Bihl, M.P., Heinimann, K., Rüdiger, J.J., Eickelberg, O., Perruchoud, A.P., Tamm, M., Roth, M., 2002. Identification of a novel IL-6 isoform binding to the endogenous IL-6 receptor. Am. J. Respir. Cell Mol. Biol. 27, 48–56. https://doi.org/10.1165/AJRCMB.27.1.4637.

Bodell, P.W., Kodesh, E., Haddad, F., Zaldivar, F.P., Cooper, D.M., Adams, G.R., 2009. Skeletal muscle growth in young rats is inhibited by chronic exposure to IL-6 but preserved by concurrent voluntary endurance exercise. J. Appl. Physiol. 106, 443–453. https://doi.org/10.1152/JAPPLPHYSIOL.90831.2008/ASSET/IMAGES/LARGE/ZDG0020983720013.JPEG.

Bonafè, M., Olivieri, F., Cavallone, L., Giovagnetti, S., Marchegiani, F., Cardelli, M., Pieri, C., Marra, M., Antonicelli, R., Lisa, R., Rizzo, M.R., Paolisso, G., Monti, D., Franceschi, C., 2001. A gender-dependent genetic predisposition to produce high levels of IL-6 is detrimental for longevity. Eur. J. Immunol. 31, 2357–2361. https://doi.org/10.1002/1521-4141(200108)31:8<2357::AID-IMMU2357>3.0.CO;2-X.

Bonafè, M., Prattichizzo, F., Giuliani, A., Storci, G., Sabbatinelli, J., Olivieri, F., 2020. Inflamm-aging: Why older men are the most susceptible to SARS-CoV-2 complicated outcomes. Cytokine Growth Factor Rev. 53, 33–37. https://doi.org/10.1016/j.cytogfr.2020.04.005.

Boulanger, M.J., Chow, D. chone, Brevnova, E.E., Garcia, K.C., 2003. Hexameric structure and assembly of the interieukin-6/IL-6 α-receptor/gp130 complex. Science 300 (80), 2101–2104. https://doi.org/10.1126/SCIENCE.1083901/SUPPL_FILE/BOULANGER.SOM.PDF.

Bovijn, J., Lindgren, C.M., Holmes, M.V., 2020. Genetic variants mimicking therapeutic inhibition of IL-6 receptor signaling and risk of COVID-19. Lancet Rheumatol. 2, e658–e659. https://doi.org/10.1016/S2665-9913(20)30345-3.

Bruunsgaard, H., Ladelund, S., Pedersen, A.N., Schroll, M., Jørgensen, T., Pedersen, B.K., 2003. Predicting death from tumour necrosis factor-alpha and interleukin-6 in 80-year-old people. Clin. Exp. Immunol. 132, 24–31. https://doi.org/10.1046/J.1365-2249.2003.02137.X.

Campbell, I.L., Abraham, C.R., Masliah, E., Kemper, P., Inglis, J.D., Oldstone, M.B., Mucke, L., 1993. Neurologic disease induced in transgenic mice by cerebral overexpression of interleukin 6. Proc. Natl. Acad. Sci. 90, 10061–10065. ⟨https://doi.org/10.1073/pnas.90.21.10061⟩.

Campbell, I.L., Hofer, M.J., Pagenstecher, A., 2010. Transgenic models for cytokine-induced neurological disease. Biochim. Biophys. Acta Mol. Basis Dis. 1802, 903–917. https://doi.org/10.1016/j.bbadis.2009.10.004.

Campbell, I.L., Erta, M., Lim, S.L., Frausto, R., May, U., Rose-John, S., Scheller, J., Hidalgo, J., 2014. Trans-signaling is a dominant mechanism for the pathogenic actions of interleukin-6 in the brain. J. Neurosci. 34, 2503–2513. https://doi.org/10.1523/JNEUROSCI.2830-13.2014.

Carrivick, S.J., Walsh, J.P., Brown, S.J., Wardrop, R., Hadlow, N.C., 2015. Brief report: does PTH increase with age, independent of 25-hydroxyvitamin D, phosphate, renal function, and ionized calcium? J. Clin. Endocrinol. Metab. 100, 2131–2134. https://doi.org/10.1210/jc.2014-4370.

Carson, B.P., 2017. The potential role of contraction-induced myokines in the regulation of metabolic function for the prevention and treatment of type 2 diabetes. Front. Endocrinol. (Lausanne). 8, 97. https://doi.org/10.3389/FENDO.2017.00097/BIBTEX.

Carson, J.A., Baltgalvis, K.A., 2010. Interleukin 6 as a key regulator of muscle mass during cachexia. Exerc. Sport Sci. Rev. 38, 168–176. https://doi.org/10.1097/JES.0B013E3181F44F11.

Chalaris, A., Adam, N., Sina, C., Rosenstiel, P., Lehmann-Koch, J., Schirmacher, P., Hartmann, D., Cichy, J., Gavrilova, O., Schreiber, S., Jostock, T., Matthews, V., Häsler, R., Becker, C., Neurath, M.F., Reiß, K., Saftig, P., Scheller, J., Rose-John, S., 2010. Critical role of the disintegrin metalloprotease ADAM17 for intestinal inflammation and regeneration in mice. J. Exp. Med. 207, 1617–1624. https://doi.org/10.1084/jem.20092366.

Chen, X., Zhao, B., Qu, Y., Chen, Y., Xiong, J., Feng, Y., Men, D., Huang, Q., Liu, Y., Yang, B., Ding, J., Li, F., 2020. Detectable serum severe acute respiratory syndrome coronavirus 2 viral load (RNAemia) is closely correlated with drastically elevated interleukin 6 level in critically Ill patients with coronavirus disease 2019. Clin. Infect. Dis. 71, 1937–1942. https://doi.org/10.1093/cid/ciaa449.

Christodoulou, C., Cooper, C., 2003. What is osteoporosis? Postgrad. Med. J. 79, 133–138. https://doi.org/10.1136/PMJ.79.929.133.

Collison, L.W., Delgoffe, G.M., Guy, C.S., Vignali, K.M., Chaturvedi, V., Fairweather, D., Satoskar, A.R., Garcia, K.C., Hunter, C.A., Drake, C.G., Murray, P.J., Vignali, D.A.A.,

2012. The composition and signaling of the IL-35 receptor are unconventional. Nat. Immunol. 13, 290–299. https://doi.org/10.1038/ni.2227.
Conceição, M., Forcina, L., Wiklander, O.P.B., Gupta, D., Nordin, J.Z., Vrellaku, B., McClorey, G., Mäger, I., Görgens, A., Lundin, P., Musarò, A., Wood, M.J.A., Andaloussi, S.E., Roberts, T.C., 2021. Engineered extracellular vesicle decoy receptor-mediated modulation of the IL6 trans-signalling pathway in muscle. Biomaterials 266. https://doi.org/10.1016/j.biomaterials.2020.120435.
Conte, M., Ostan, R., Fabbri, C., Santoro, A., Guidarelli, G., Vitale, G., Mari, D., Sevini, F., Capri, M., Sandri, M., Monti, D., Franceschi, C., Salvioli, S., 2019. Human aging and longevity are characterized by high levels of mitokines. J. Gerontol. Ser. A 74, 600–607. https://doi.org/10.1093/gerona/gly153.
Conte, M., Martucci, M., Mosconi, G., Chiariello, A., Cappuccilli, M., Totti, V., Santoro, A., Franceschi, C., Salvioli, S., 2020. GDF15 plasma level is inversely associated with level of physical activity and correlates with markers of inflammation and muscle weakness. Front. Immunol. 11. https://doi.org/10.3389/fimmu.2020.00915.
Conte, M., Giuliani, C., Chiariello, A., Iannuzzi, V., Franceschi, C., Salvioli, S., 2022. GDF15, an emerging key player in human aging. Ageing Res. Rev. 75, 101569 https://doi.org/10.1016/j.arr.2022.101569.
Coomes, E.A., Haghbayan, H., 2020. Interleukin-6 in Covid-19: a systematic review and meta-analysis. Rev. Med. Virol. 30, 1–9. https://doi.org/10.1002/rmv.2141.
Cortez-Cooper, M., Meaders, E., Stallings, J., Haddow, S., Kraj, B., Sloan, G., McCully, K. K., Cannon, J.G., 2013. Soluble TNF and IL-6 receptors: indicators of vascular health in women without cardiovascular disease. Vasc. Med. 18, 282–289. https://doi.org/10.1177/1358863X13508336.
Costa-Pereira, A.P., Tininini, S., Strobl, B., Alonzi, T., Schlaak, J.F., Is'harc, H., Gesualdo, I., Newman, S.J., Kerr, I.M., Poli, V., 2002. Mutational switch of an IL-6 response to an interferon-γ-like response. Proc. Natl. Acad. Sci. 99, 8043–8047. ⟨https://doi.org/10.1073/pnas.122236099⟩.
Cronjé, H.T., Nienaber-Rousseau, C., Zandberg, L., de Lange, Z., Green, F.R., Pieters, M., 2017. Fibrinogen and clot-related phenotypes determined by fibrinogen polymorphisms: independent and IL-6-interactive associations. PLoS One 12, e0187712. https://doi.org/10.1371/journal.pone.0187712.
Dastan, F., Saffaei, A., Haseli, S., Marjani, M., Moniri, A., Abtahian, Z., Abedini, A., Kiani, A., Seifi, S., Jammati, H., Hashemian, S.M.R., Pourabdollah Toutkaboni, M., Eslaminejad, A., Heshmatnia, J., Sadeghi, M., Nadji, S.A., Dastan, A., Baghaei, P., Varahram, M., Yousefian, S., Salamzadeh, J., Tabarsi, P., 2020. Promising effects of tocilizumab in COVID-19: a non-controlled, prospective clinical trial. Int. Immunopharmacol. 88, 106869 https://doi.org/10.1016/j.intimp.2020.106869.
Davalli, P., Mitic, T., Caporali, A., Lauriola, A., D'Arca, D., 2016. ROS, cell senescence, and novel molecular mechanisms in aging and age-related diseases. Oxid. Med. Cell. Longev. 2016, 1–18. https://doi.org/10.1155/2016/3565127.
Davalos, D., Akassoglou, K., 2012. Fibrinogen as a key regulator of inflammation in disease. Semin. Immunopathol. 34, 43–62. https://doi.org/10.1007/S00281-011-0290-8.
Daynes, R.A., Araneo, B.A., Ershler, W.B., Maloney, C., Li, G.Z., Ryu, S.Y., 1993. Altered regulation of IL-6 production with normal aging. Possible linkage to the age-associated decline in dehydroepiandrosterone and its sulfated derivative. J. Immunol. 150, 5219–5230.
De Benedetti, F., Alonzi, T., Moretta, A., Lazzaro, D., Costa, P., Poli, V., Martini, A., Ciliberto, G., Fattori, E., 1997. Interleukin 6 causes growth impairment in transgenic mice through a decrease in insulin-like growth factor-I. A model for stunted growth in children with chronic inflammation. J. Clin. Invest 99, 643–650. https://doi.org/10.1172/JCI119207.
De Benedetti, F., Rucci, N., Del Fattore, A., Peruzzi, B., Paro, R., Longo, M., Vivarelli, M., Muratori, F., Berni, S., Ballanti, P., Ferrari, S., Teti, A., 2006. Impaired skeletal development in interleukin-6–transgenic mice: a model for the impact of chronic inflammation on the growing skeletal system. Arthritis Rheum. 54, 3551–3563. https://doi.org/10.1002/ART.22175.
Di Bona, D., Vasto, S., Capurso, C., Christiansen, L., Deiana, L., Franceschi, C., Hurme, M., Mocchegiani, E., Rea, M., Lio, D., Candore, G., Caruso, C., 2009. Effect of interleukin-6 polymorphisms on human longevity: a systematic review and meta-analysis. Ageing Res. Rev. 8, 36–42. https://doi.org/10.1016/J.ARR.2008.09.001.
Diehl, S., Rincón, M., 2002. The two faces of IL-6 on Th1/Th2 differentiation. Mol. Immunol. 39, 531–536. https://doi.org/10.1016/S0161-5890(02)00210-9.
Dienz, O., Rud, J.G., Eaton, S.M., Lanthier, P.A., Burg, E., Drew, A., Bunn, J., Suratt, B.T., Haynes, L., Rincon, M., 2012. Essential role of IL-6 in protection against H1N1 influenza virus by promoting neutrophil survival in the lung. Mucosal Immunol. 5, 258–266. https://doi.org/10.1038/mi.2012.2.
Dimitrov, S., Lange, T., Benedict, C., Nowell, M.A., Jones, S.A., Scheller, J., Rose-John, S., Born, J., Dimitrov, S., Lange, T., Benedict, C., Nowell, M.A., Jones, S.A., Scheller, J., Rose-John, S., Born, J., 2006. Sleep enhances IL-6 trans-signaling in humans. FASEB J. 20, 2174–2176. https://doi.org/10.1096/FJ.06-5754FJE.
Dittrich, E., Rose-John, S., Gerhartz, C., Müllberg, J., Stoyan, T., Yasukawa, K., Heinrich, P.C., Graeve, L., 1994. Identification of a region within the cytoplasmic domain of the interleukin-6 (IL-6) signal transducer gp130 important for ligand-induced endocytosis of the IL-6 receptor. J. Biol. Chem. 269, 19014–19020. https://doi.org/10.1016/S0021-9258(17)32267-6.
Doumanov, J.A., Daubrawa, M., Unden, H., Graeve, L., 2006. Identification of a basolateral sorting signal within the cytoplasmic domain of the interleukin-6 signal transducer gp130. Cell. Signal. 18, 1140–1146. https://doi.org/10.1016/j.cellsig.2005.09.006.
Duggal, N.A., Pollock, R.D., Lazarus, N.R., Harridge, S., Lord, J.M., 2018. Major features of immunesenescence, including reduced thymic output, are ameliorated by high levels of physical activity in adulthood. Aging Cell 17, e12750. https://doi.org/10.1111/ACEL.12750.
Eberhardt, K.A., Meyer-Schwickerath, C., Heger, E., Knops, E., Lehmann, C., Rybniker, J., Schommers, P., Eichenauer, D.A., Kurth, F., Ramharter, M., Kaiser, R., Holtick, U., Klein, F., Jung, N., Di Cristanziano, V., 2020. RNAemia corresponds to disease severity and antibody response in hospitalized COVID-19 patients. Viruses 12, 1045. https://doi.org/10.3390/v12091045.
Ebisui, C., Tsujinaka, T., Morimoto, T., Kan, K., Iijima, S., Yano, M., Kominami, E., Tanaka, K., Monden, M., 1995. Interleukin-6 induces proteolysis by activating intracellular proteases (Cathepsins B and L, Proteasome) in C2C12 myotubes. Clin. Sci. 89, 431–439. https://doi.org/10.1042/cs0890431.
Eljilany, I., Elzouki, A.-N., 2020. D-dimer, fibrinogen, and IL-6 in COVID-19 patients with suspected venous thromboembolism: a narrative review. Vasc. Health Risk Manag Volume 16, 455–462. https://doi.org/10.2147/VHRM.S280962.
Elosua, R., Bartali, B., Ordovas, J.M., Corsi, A.M., Lauretani, F., Ferrucci, L., 2005. Association between physical activity, physical performance, and inflammatory biomarkers in an elderly population: the InCHIANTI study. J. Gerontol. A. Biol. Sci. Med. Sci. 60, 760–767. https://doi.org/10.1093/GERONA/60.6.760.
Ershler, W.B., 1993. Interleukin-6: a cytokine for gerontolgists. J. Am. Geriatr. Soc. 41, 176–181. https://doi.org/10.1111/j.1532-5415.1993.tb02054.x.
Fajar, J.K., Azharuddin, A., 2017. The association between interleukin 6 −174 G/C gene polymorphism and the risk of osteoporosis: a meta-analysis. J. Taibah Univ. Med. Sci. 12, 212–220. https://doi.org/10.1016/J.JTUMED.2016.07.010.
Fattori, E., Lazzaro, D., Musiani, P., Modesti, A., Alonzi, T., Ciliberto, G., 1995. IL-6 expression in neurons of transgenic mice causes reactive astrocytosis and increase in ramified microglial cells but no neuronal damage. Eur. J. Neurosci. 7, 2441–2449. https://doi.org/10.1111/j.1460-9568.1995.tb01042.x.
Ferrando-Martínez, S., Romero-Sánchez, M.C., Solana, R., Delgado, J., de la Rosa, R., Muñoz-Fernández, M.Á., Ruiz-Mateos, E., Leal, M., 2013. Thymic function failure and C-reactive protein levels are independent predictors of all-cause mortality in healthy elderly humans. Age 35, 251–259. https://doi.org/10.1007/s11357-011-9341-2.
Ferreira, R.C., Freitag, D.F., Cutler, A.J., Howson, J.M.M., Rainbow, D.B., Smyth, D.J., Kaptoge, S., Clarke, P., Boreham, C., Coulson, R.M., Pekalski, M.L., Chen, W.-M., Onengut-Gumuscu, S., Rich, S.S., Butterworth, A.S., Malarstig, A., Danesh, J., Todd, J.A., 2013. Functional IL6R 358ala allele impairs classical IL-6 receptor signaling and influences risk of diverse inflammatory diseases. PLoS Genet 9, e1003444. https://doi.org/10.1371/journal.pgen.1003444.
Ferrucci, L., Corsi, A., Lauretani, F., Bandinelli, S., Bartali, B., Taub, D.D., Guralnik, J.M., Longo, D.L., 2005. The origins of age-related proinflammatory state. Blood 105, 2294–2299. https://doi.org/10.1182/blood-2004-07-2599.
Filgueiras-Rama, D., Rivera Torres, J., Andrés, V., 2018. Electrocardiographic abnormalities in patients with hutchinson-gilford progeria syndrome. JAMA Cardiol. 3, 1024. https://doi.org/10.1001/jamacardio.2018.2100.
Fishman, D., Faulds, G., Jeffey, R., Mohamed-Ali, V., Yudkin, J.S., Humphries, S., Woo, P., 1998. The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. J. Clin. Invest. 102, 1369–1376. https://doi.org/10.1172/JCI2629.
Flynn, C.M., Kespohl, B., Daunke, T., Garbers, Y., Düsterhöft, S., Rose-John, S., Haybaeck, J., Lokau, J., Aparicio-Siegmund, S., Garbers, C., 2021. Interleukin-6 controls recycling and degradation, but not internalization of its receptors. J. Biol. Chem. 296, 100434 https://doi.org/10.1016/j.jbc.2021.100434.
Forcina, L., Miano, C., Musarò, A., 2018. The physiopathologic interplay between stem cells and tissue niche in muscle regeneration and the role of IL-6 on muscle homeostasis and diseases. Cytokine Growth Factor Rev. https://doi.org/10.1016/j.cytogfr.2018.05.001.
Forcina, L., Miano, C., Pelosi, L., Musarò, A., 2019a. An overview about the biology of skeletal muscle satellite cells. Curr. Genom. 20 https://doi.org/10.2174/1389202920666190116094736.
Forcina, L., Miano, C., Scicchitano, B., Musarò, A., 2019b. Signals from the niche: insights into the role of IGF-1 and IL-6 in modulating skeletal muscle fibrosis. Cells 8, 232. https://doi.org/10.3390/cells8030232.
Forcina, L., Miano, C., Scicchitano, B.M., Rizzuto, E., Berardinelli, M.G., De Benedetti, F., Pelosi, L., Musarò, A., 2019c. Increased Circulating Levels of Interleukin-6 Affect the Redox Balance in Skeletal Muscle. Oxid. Med. Cell. Longev. 2019 https://doi.org/10.1155/2019/3018584.
Franchimont, N., Wertz, S., Malaise, M., 2005. Interleukin-6: an osteotropic factor influencing bone formation? Bone 37, 601–606. https://doi.org/10.1016/J.BONE.2005.06.002.
Fujimoto, K., Ida, H., Hirota, Y., Ishigai, M., Amano, J., Tanaka, Y., 2015. Intracellular dynamics and fate of a humanized anti–interleukin-6 receptor monoclonal antibody, Tocilizumab. Mol. Pharmacol. 88, 660–675. https://doi.org/10.1124/mol.115.099184.
Fuster, J.J., Walsh, K., 2014. The good, the bad, and the ugly of interleukin-6 signaling. EMBO J. 33, 1425–1427. https://doi.org/10.15252/embj.201488856.
Gabay, C., 2006. Interleukin-6 and chronic inflammation. Arthritis Res. Ther. 8 Suppl 2, S3. https://doi.org/10.1186/ar1917.
Gabay, C., Kushner, I., 1999. Acute-phase proteins and other systemic responses to inflammation. New Engl. J. Med. 340, 448–454. https://doi.org/10.1056/NEJM199902113400607.
Garbers, C., Monhasery, N., Aparicio-Siegmund, S., Lokau, J., Baran, P., Nowell, M.A., Jones, S.A., Rose-John, S., Scheller, J., 2014. The interleukin-6 receptor Asp358Ala single nucleotide polymorphism rs2228145 confers increased proteolytic conversion rates by ADAM proteases. Biochim. Biophys. Acta - Mol. Basis Dis. 1842, 1485–1494. https://doi.org/10.1016/j.bbadis.2014.05.018.

Garbers, C., Heink, S., Korn, T., Rose-John, S., 2018. Interleukin-6: designing specific therapeutics for a complex cytokine. Nat. Rev. Drug Discov. 17, 395–412. https://doi.org/10.1038/nrd.2018.45.

Giacconi, R., Cipriano, C., Albanese, F., Boccoli, G., Saba, V., Olivieri, F., Franceschi, C., Mocchegiani, E., 2004. The −174G/C polymorphism of IL-6 is useful to screen old subjects at risk for atherosclerosis or to reach successful ageing. Exp. Gerontol. 39, 621–628. https://doi.org/10.1016/j.exger.2003.12.013.

Giovannini, S., Onder, G., Liperoti, R., Russo, A., Carter, C., Capoluongo, E., Pahor, M., Bernabei, R., Landi, F., 2011. Interleukin-6, C-reactive protein, and tumor necrosis factor-alpha as predictors of mortality in frail, community-living elderly individuals. J. Am. Geriatr. Soc. 59, 1679–1685. https://doi.org/10.1111/J.1532-5415.2011.03570.X.

Godbout, J.P., Johnson, R.W., 2004. Interleukin-6 in the aging brain. J. Neuroimmunol. 147, 141–144. https://doi.org/10.1016/J.JNEUROIM.2003.10.031.

Gonzalo, S., Kreienkamp, R., Askjaer, P., 2017. Hutchinson-gilford progeria syndrome: a premature aging disease caused by LMNA gene mutations. Ageing Res. Rev. 33, 18–29. https://doi.org/10.1016/j.arr.2016.06.007.

Gritti, G., Raimondi, F., Bottazzi, B., Ripamonti, D., Riva, I., Landi, F., Alborghetti, L., Frigeni, M., Damiani, M., Micò, C., Fagiuoli, S., Lorini, F.L., Gandini, L., Novelli, L., Morgan, J.P., Owens, B.M.J., Kanhai, K.J.K., Reljanovic, G.T., Rizzi, M., Di Marco, F., Mantovani, A., Rambaldi, A., 2021. Siltuximab downregulates interleukin-8 and pentraxin 3 to improve ventilatory status and survival in severe COVID-19. Leukemia 35, 2710–2714. https://doi.org/10.1038/s41375-021-01299-x.

Guaraldi, G., Meschiari, M., Cozzi-Lepri, A., Milic, J., Tonelli, R., Menozzi, M., Franceschini, E., Cuomo, G., Orlando, G., Borghi, V., Santoro, A., Di Gaetano, M., Puzzolante, C., Carli, F., Bedini, A., Corradi, L., Fantini, R., Castaniere, I., Tabbì, L., Girardis, M., Tedeschi, S., Giannella, M., Bartoletti, M., Pascale, R., Dolci, G., Brugioni, L., Pietrangelo, A., Cossarizza, A., Pea, F., Clini, E., Salvarani, C., Massari, M., Viale, P.L., Mussini, C., 2020. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. Lancet Rheuma 2, e474–e484. https://doi.org/10.1016/S2665-9913(20)30173-9.

Gubernatorova, E.O., Gorshkova, E.A., Polinova, A.I., Drutskaya, M.S., 2020. IL-6: relevance for immunopathology of SARS-CoV-2. Cytokine Growth Factor Rev. 53, 13–24. https://doi.org/10.1016/j.cytogfr.2020.05.009.

Gyengesi, E., Rangel, A., Ullah, F., Liang, H., Niedermayer, G., Asgarov, R., Venigalla, M., Gunawardena, D., Karl, T., Münch, G., 2019. Chronic microglial activation in the GFAP-IL6 mouse contributes to age-dependent cerebellar volume loss and impairment in motor function. Front. Neurosci. 13, 303. https://doi.org/10.3389/FNINS.2019.00303/BIBTEX.

Haddad, F., Zaldivar, F., Cooper, D.M., Adams, G.R., 2005. IL-6-induced skeletal muscle atrophy. J. Appl. Physiol. 98, 911–917. https://doi.org/10.1152/japplphysiol.01026.2004.

Hamczyk, M.R., del Campo, L., Andrés, V., 2018. Aging in the cardiovascular system: lessons from hutchinson-gilford progeria syndrome. Annu. Rev. Physiol. 80, 27–48. https://doi.org/10.1146/annurev-physiol-021317-121454.

Harris, T.B., Ferrucci, L., Tracy, R.P., Corti, M.C., Wacholder, S., Ettinger, W.H., Heimovitz, H., Cohen, H.J., Wallace, R., 1999. Associations of elevated Interleukin-6 and C-Reactive protein levels with mortality in the elderly**Access the "Journal Club" discussion of this paper at http:/www.elsevier.com/locate/ajmselect/. Am. J. Med. 106, 506–512. ⟨https://doi.org/10.1016/S0002–9343(99)00066–2⟩.

He, B., Yin, X., Hao, D., Zhang, X., Zhang, Z., Zhang, K., Yang, X., 2020. Blockade of IL-6 alleviates bone loss induced by modelled microgravity in mice. Can. J. Physiol. Pharmacol. 98, 678–683. https://doi.org/10.1139/CJPP-2019-0632/SUPPL_FILE/CJPP-2019-0632SUPPLA.DOCX.

Heink, S., Yogev, N., Garbers, C., Herwerth, M., Aly, L., Gasperi, C., Husterer, V., Croxford, A.L., Möller-Hackbarth, K., Bartsch, H.S., Sotlar, K., Krebs, S., Regen, T., Blum, H., Hemmer, B., Misgeld, T., Wunderlich, T.F., Hidalgo, J., Oukka, M., Rose-John, S., Schmidt-Supprian, M., Waisman, A., Korn, T., 2017. Trans-presentation of IL-6 by dendritic cells is required for the priming of pathogenic TH17 cells. Nat. Immunol. 18, 74–85. https://doi.org/10.1038/ni.3632.

Heinrich, P.C., Castell, J.V., Andus, T., 1990. Interleukin-6 and the acute phase response. Biochem. J. 265, 621–636. https://doi.org/10.1042/bj2650621.

Hershko, D.D., Robb, B.W., Luo, G., Hasselgren, P.O., 2002. Multiple transcription factors regulating the IL-6 gene are activated by cAMP in cultured Caco-2 cells. Am. J. Physiol. Regul. Integr. Comp. Physiol. 283, 1140–1148. https://doi.org/10.1152/AJPREGU.00161.2002/ASSET/IMAGES/LARGE/H61121439008.JPEG.

Hetzler, K.L., Hardee, J.P., Puppa, M.J., Narsale, A.A., Sato, S., Davis, J.M., Carson, J.A., 2015. Sex differences in the relationship of IL-6 signaling to cancer cachexia progression. Biochim. Biophys. Acta Mol. Basis Dis. 1852, 816–825. https://doi.org/10.1016/j.bbadis.2014.12.015.

Heymann, D., Rousselle, A.V., 2000. gp130 cytokine family and bone cells. Cytokine 12, 1455–1468. https://doi.org/10.1006/CYTO.2000.0747.

Hirahara, K., Onodera, A., Villarino, A.V., Bonelli, M., Sciumè, G., Laurence, A., Sun, H.-W., Brooks, S.R., Vahedi, G., Shih, H.-Y., Gutierrez-Cruz, G., Iwata, S., Suzuki, R., Mikami, Y., Okamoto, Y., Nakayama, T., Holland, S.M., Hunter, C.A., Kanno, Y., O'Shea, J.J., 2015. Asymmetric action of STAT transcription factors drives transcriptional outputs and cytokine specificity. Immunity 42, 877–889. https://doi.org/10.1016/j.immuni.2015.04.014.

Hoffmann, S.C., Stanley, E.M., Darrin Cox, E., Craighead, N., DiMercurio, B.S., Koziol, D. E., Harlan, D.M., Kirk, A.D., Blair, P.J., 2001. Association of cytokine polymorphic inheritance and in vitro cytokine production in Anti-CD3/CD28-stimulated peripheral blood lymphocytes1. Transplantation 72, 1444–1450. https://doi.org/10.1097/00007890-200110270-00019.

Hoischen, S.H., Vollmer, P., März, P., Özbek, S., Götze, K.S., Peschel, C., Jostock, T., Geib, T., Müllberg, J., Mechtersheimer, S., Fischer, M., Grötzinger, J., Galle, P.R., Rose-John, S., 2000. Human herpes virus 8 interleukin-6 homologue triggers gp130 on neuronal and hematopoietic cells. Eur. J. Biochem 267, 3604–3612. https://doi.org/10.1046/J.1432-1327.2000.01389.X.

Honda, M., Yamamoto, S., Cheng, M., Yasukawa, K., Suzuki, H., Saito, T., Osugi, Y., Tokunaga, T., Kishimoto, T., 1992. Human soluble IL-6 receptor: its detection and enhanced release by HIV infection. J. Immunol. 148.

Jenny, N.S., French, B., Arnold, A.M., Strotmeyer, E.S., Cushman, M., Chaves, P.H.M., Ding, J., Fried, L.P., Kritchevsky, S.B., Rifkin, D.E., Sarnak, M.J., Newman, A.B., 2012. Long-term assessment of inflammation and healthy aging in late life: the cardiovascular health study all stars. J. Gerontol. Ser. A 67, 970–976. https://doi.org/10.1093/gerona/glr261.

Jones, S.A., Hunter, C.A., 2021. Is IL-6 a key cytokine target for therapy in COVID-19? Nat. Rev. Immunol. 21, 337–339. https://doi.org/10.1038/s41577-021-00553-8.

Jones, S.A., Jenkins, B.J., 2018. Recent insights into targeting the IL-6 cytokine family in inflammatory diseases and cancer. Nat. Rev. Immunol. 18, 773–789. https://doi.org/10.1038/s41577-018-0066-7.

Jones, S.A., Horiuchi, S., Topley, N., Yamamoto, N., Fuller, G.M., 2001. The soluble interleukin 6 receptor: mechanisms of production and implications in disease. FASEB J. 15, 43–58. https://doi.org/10.1096/fj.99-1003rev.

Jostock, T., Müllberg, J., Özbek, S., Atreya, R., Blinn, G., Voltz, N., Fischer, M., Neurath, M.F., Rose-John, S., 2001. Soluble gp130 is the natural inhibitor of soluble interleukin-6 receptor transsignaling responses. Eur. J. Biochem 268, 160–167. https://doi.org/10.1046/j.1432-1327.2001.01867.x.

Jylha, M., Paavilainen, P., Lehtimaki, T., Goebeler, S., Karhunen, P.J., Hervonen, A., Hurme, M., 2007. Interleukin-1 receptor antagonist, interleukin-6, and C-reactive protein as predictors of mortality in nonagenarians: the vitality 90+ study. J. Gerontol. Ser. A Biol. Sci. Med. Sci. 62, 1016–1021. https://doi.org/10.1093/gerona/62.9.1016.

Kemna, E., Pickkers, P., Nemeth, E., Van Der Hoeven, H., Swinkels, D., 2005. Time-course analysis of hepcidin, serum iron, and plasma cytokine levels in humans injected with LPS. Blood 106, 1864–1866. https://doi.org/10.1182/BLOOD-2005-03-1159.

Kennedy, S.A., Baerlocher, M.O., Baerlocher, F., Socko, D., Sacks, D., Nikolic, B., Wojak, J.C., Haskal, Z.J., 2016. Meta-analysis of local endovascular therapy for acute ischemic stroke. J. Vasc. Interv. Radiol. 27, 307–321. https://doi.org/10.1016/j.jvir.2015.11.053.

Kimura, A., Naka, T., Kishimoto, T., 2007. IL-6-dependent and -independent pathways in the development of interleukin 17-producing T helper cells. Proc. Natl. Acad. Sci. 104, 12099–12104. ⟨https://doi.org/10.1073/pnas.0705268104⟩.

Kistner, T.M., Pedersen, B.K., Lieberman, D.E., 2022. Interleukin 6 as an energy allocator in muscle tissue. Nat. Metab. 4, 170–179. https://doi.org/10.1038/s42255-022-00538-4.

Kokje, V.B.C., Gäbel, G., Koole, D., Northoff, B.H., Holdt, L.M., Hamming, J.F., Lindeman, J.H.N., 2016. IL-6: a Janus-like factor in abdominal aortic aneurysm disease. Atherosclerosis 251, 139–146. https://doi.org/10.1016/j.atherosclerosis.2016.06.021.

Korn, T., Hiltensperger, M., 2021. Role of IL-6 in the commitment of T cell subsets. Cytokine 146, 155654. https://doi.org/10.1016/j.cyto.2021.155654.

Kudo, O., Sabokbar, A., Pocock, A., Itonaga, I., Fujikawa, Y., Athanasou, N., 2003. Interleukin-6 and interleukin-11 support human osteoclast formation by a RANKL-independent mechanism. Bone 32, 1–7. https://doi.org/10.1016/S8756-3282(02)00915-8.

Kwak, K.S., Zhou, X., Solomon, V., Baracos, V.E., Davis, J., Bannon, A.W., Boyle, W.J., Lacey, D.L., Han, H.Q., 2004. Regulation of protein catabolism by muscle-specific and cytokine-inducible ubiquitin ligase E3alpha-II during cancer cachexia. Cancer Res 64, 8193–8198. https://doi.org/10.1158/0008-5472.CAN-04-2102.

Lee, J.H., Jun, H.S., 2019. Role of myokines in regulating skeletal muscle mass and function. Front. Physiol. 10, 42. https://doi.org/10.3389/FPHYS.2019.00042/BIBTEX.

Lee, J.W., Stone, M.L., Porrett, P.M., Thomas, S.K., Komar, C.A., Li, J.H., Delman, D., Graham, K., Gladney, W.L., Hua, X., Black, T.A., Chien, A.L., Majmundar, K.S., Thompson, J.C., Yee, S.S., O'Hara, M.H., Aggarwal, C., Xin, D., Shaked, A., Gao, M., Liu, D., Borad, M.J., Ramanathan, R.K., Carpenter, E.L., Ji, A., de Beer, M.C., de Beer, F.C., Webb, N.R., Beatty, G.L., 2019. Hepatocytes direct the formation of a pro-metastatic niche in the liver. Nature 567, 249–252. https://doi.org/10.1038/s41586-019-1004-y.

Lee, J.-Y., Hall, J.A., Kroehling, L., Wu, L., Najar, T., Nguyen, H.H., Lin, W.-Y., Yeung, S. T., Silva, H.M., Li, D., Hine, A., Loke, P., Hudesman, D., Martin, J.C., Kenigsberg, E., Merad, M., Khanna, K.M., Littman, D.R., 2020. Serum amyloid A proteins induce pathogenic Th17 cells and promote inflammatory disease. Cell 183, 2036–2039. https://doi.org/10.1016/j.cell.2020.12.008.

Li, X., Zhou, Z., Zhang, Y., Yang, H., 2016. IL-6 contributes to the defective osteogenesis of bone marrow stromal cells from the vertebral body of the glucocorticoid-induced osteoporotic mouse. PLoS One 11, e0154677. https://doi.org/10.1371/journal.pone.0154677.

Li, X., Yang, T., Sun, Z., 2019. Hormesis in Health and Chronic Diseases. Trends Endocrinol. Metab. 30, 944–958. https://doi.org/10.1016/j.tem.2019.08.007.

Li, Y., Lu, L., Xie, Y., Chen, X., Tian, L., Liang, Y., Li, H., Zhang, J., Liu, Y., Yu, X., 2021. Interleukin-6 knockout inhibits senescence of bone mesenchymal stem cells in high-fat diet-induced bone loss. Front. Endocrinol. (Lausanne) 11. https://doi.org/10.3389/fendo.2020.622950.

Lin, T., Liu, G.A., Perez, E., Rainer, R.D., Febo, M., Cruz-Almeida, Y., Ebner, N.C., 2018. Systemic inflammation mediates age-related cognitive deficits. Front. Aging Neurosci. 10 https://doi.org/10.3389/fnagi.2018.00236.

Linton, P.J., Dorshkind, K., 2004. Age-related changes in lymphocyte development and function. Nat. Immunol. 5, 133–139. https://doi.org/10.1038/ni1033.

Liu, H., Huang, Y., Lyu, Y., Dai, W., Tong, Y., Li, Y., 2021. GDF15 as a biomarker of ageing. Exp. Gerontol. 146, 111228 https://doi.org/10.1016/j.exger.2021.111228.
Luo, Y., Zheng, S.G., 2016. Hall of fame among pro-inflammatory cytokines: Interleukin-6 gene and its transcriptional regulation mechanisms. Front. Immunol. 7, 604. https://doi.org/10.3389/FIMMU.2016.00604/BIBTEX.
Martens, A.S., Bode, J.G., Heinrich, P.C., Graeve, L., 2000. The cytoplasmic domain of the interleukin-6 receptor gp80 mediates its basolateral sorting in polarized madin-darby canine kidney cells. J. Cell Sci. 113, 3593–3602. https://doi.org/10.1242/jcs.113.20.3593.
Martin, K.R., Barrett, J.C., 2002. Reactive oxygen species as double-edged swords in cellular processes: low-dose cell signaling versus high-dose toxicity. Hum. Exp. Toxicol. 21, 71–75. https://doi.org/10.1191/0960327102ht213oa.
Martucci, M., Ostan, R., Biondi, F., Bellavista, E., Fabbri, C., Bertarelli, C., Salvioli, S., Capri, M., Franceschi, C., Santoro, A., 2017. Mediterranean diet and inflammaging within the hormesis paradigm. Nutr. Rev. 75, 442–455. https://doi.org/10.1093/NUTRIT/NUX013.
Martucci, M., Conte, M., Ostan, R., Chiariello, A., Miele, F., Franceschi, C., Salvioli, S., Santoro, A., Provini, F., 2020. Both objective and paradoxical insomnia elicit a stress response involving mitokine production. Aging 12, 10497–10505. https://doi.org/10.18632/aging.103274.
Mauer, J., Chaurasia, B., Goldau, J., Vogt, M.C., Ruud, J., Nguyen, K.D., Theurich, S., Hausen, A.C., Schmitz, J., Brönneke, H.S., Estevez, E., Allen, T.L., Mesaros, A., Partridge, L., Febbraio, M.A., Chawla, A., Wunderlich, F.T., Brüning, J.C., 2014. Signaling by IL-6 promotes alternative activation of macrophages to limit endotoxemia and obesity-associated resistance to insulin. Nat. Immunol. 15, 423–430. https://doi.org/10.1038/ni.2865.
Mauer, J., Denson, J.L., Brüning, J.C., 2015. Versatile functions for IL-6 in metabolism and cancer. Trends Immunol. 36, 92–101. https://doi.org/10.1016/j.it.2014.12.008.
Maurel, S., Hamon, B., Taillandier, J., Rudant, E., Bonhomme-Faivre, L., Trivalle, C., 2007. Prognostic value of serum interleukin-6 (IL-6) levels in long term care. Arch. Gerontol. Geriatr. 45, 65–71. https://doi.org/10.1016/j.archger.2006.09.003.
Mihara, M., Hashizume, M., Yoshida, H., Suzuki, M., Shiina, M., 2012. IL-6/IL-6 receptor system and its role in physiological and pathological conditions. Clin. Sci. 122, 143–159. https://doi.org/10.1042/CS20110340.
Mikó, A., Pótó, L., Mátrai, P., Hegyi, P., Füredi, N., Garami, A., Illés, A., Solymár, M., Vincze, Á., Balaskó, M., Pár, G., Sarlós, P., Bajor, J., Tenk, J., Rostás, I., Pétervári, E., 2018. Gender difference in the effects of interleukin-6 on grip strength – a systematic review and meta-analysis. BMC Geriatr. 18, 107. https://doi.org/10.1186/s12877-018-0798-z.
Miller, P.D., Hattersley, G., Riis, B.J., Williams, G.C., Lau, E., Russo, L.A., Alexandersen, P., Zerbini, C.A.F., Hu, M., Harris, A.G., Fitzpatrick, L.A., Cosman, F., Christiansen, C., 2016. Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis. JAMA 316, 722. https://doi.org/10.1001/jama.2016.11136.
Minciullo, P.L., Catalano, A., Mandraffino, G., Casciaro, M., Crucitti, A., Maltese, G., Morabito, N., Lasco, A., Gangemi, S., Basile, G., 2016. Inflammaging and anti-inflammaging: the role of cytokines in extreme longevity. Arch. Immunol. Ther. Exp. 64, 111–126. https://doi.org/10.1007/s00005-015-0377-3.
Mladen, Jergovic, Heather, L.Thompson-Ryder, Arveen, Asghar, Janko, Nikolich-Zugich, 2020. The role of Interleukin-6 in age-related frailty syndrome. J. Immunol. 204.
Mocco, J., Zaidat, O.O., von Kummer, R., Yoo, A.J., Gupta, R., Lopes, D., Frei, D., Shownkeen, H., Budzik, R., Ajani, Z.A., Grossman, A., Altschul, D., McDougall, C., Blake, L., Fitzsimmons, B.-F., Yavagal, D., Terry, J., Farkas, J., Lee, S.K., Baxter, B., Wiesmann, M., Knauth, M., Heck, D., Hussain, S., Chiu, D., Alexander, M.J., Malisch, T., Kirmani, J., Miskolczi, L., Khatri, P., 2016. Aspiration thrombectomy after intravenous alteplase versus intravenous alteplase alone. Stroke 47, 2331–2338. https://doi.org/10.1161/STROKEAHA.116.013372.
Müller-Newen, G., Küster, A., Hemmann, U., Keul, R., Horsten, U., Martens, A., Graeve, L., Wijdenes, J., Heinrich, P.C., 1998. Soluble IL-6 receptor potentiates the antagonistic activity of soluble gp130 on IL-6 responses. J. Immunol. 161, 6347–6355.
Muñoz-Cánoves, P., Scheele, C., Pedersen, B.K., Serrano, A.L., 2013. Interleukin-6 myokine signaling in skeletal muscle: a double-edged sword? FEBS J. 280, 4131–4148. https://doi.org/10.1111/febs.12338.
Murakami, M., Kamimura, D., Hirano, T., 2019. Pleiotropy and specificity: insights from the interleukin 6 family of cytokines. Immunity 50, 812–831. https://doi.org/10.1016/j.immuni.2019.03.027.
Murthy, L., Duque, G., 2021. Parathyroid hormone levels and aging: Effect on balance. pp. 173–184. ⟨https://doi.org/10.1016/bs.vh.2020.12.009⟩.
Narazaki, M., Yasukawa, K., Saito, T., Ohsugi, Y., Fukui, H., Koishihara, Y., Yancopoulos, G.D., Taga, T., Kishimoto, T., 1993. Soluble forms of the interleukin-6 signal-transducing receptor component gp130 in human serum possessing a potential to inhibit signals through membrane-anchored gp130. Blood 82, 1120–1126. https://doi.org/10.1182/BLOOD.V82.4.1120.1120.
Neipel, F., Albrecht, J.-C., Ensser, A., Huang, Y.-Q., Li, J.J., Friedman-Kien, A.E., Fleckenstein, B., 1997. Human herpesvirus 8 encodes a homolog of interleukin-6. J. Virol. 71, 839–842. https://doi.org/10.1128/JVI.71.1.839-842.1997.
Nelke, C., Dziewas, R., Minnerup, J., Meuth, S.G., Ruck, T., 2019. Skeletal muscle as potential central link between sarcopenia and immune senescence. EBioMedicine 49, 381–388. https://doi.org/10.1016/J.EBIOM.2019.10.034.
Nolte, A.A., Movin, M., Lundin, H., Salminen, H., 2015. IGFBP-1 predicts all-cause mortality in elderly women independently of IGF-I. Growth Horm. IGF Res 25, 281–285. https://doi.org/10.1016/j.ghir.2015.09.001.
Novick, D., Engelmann, H., Wallach, D., Rubinstein, M., 1989. Soluble cytokine receptors are present in normal human urine. J. Exp. Med. 170, 1409–1414. https://doi.org/10.1084/JEM.170.4.1409.
Olivieri, F., Bonafè, M., Cavallone, L., Giovagnetti, S., Marchegiani, F., Cardelli, M., Mugianesi, E., Giampieri, C., Moresi, R., Stecconi, R., Lisa, R., Franceschi, C., 2002. The −174C/G locus affects in vitro/in vivo IL-6 production during aging. Exp. Gerontol. 37, 309–314. https://doi.org/10.1016/S0531-5565(01)00197-8.
Patterson, C.C., Smith, A.E., Yarnell, J.W.G., Rumley, A., Ben-Shlomo, Y., Lowe, G.D.O., 2010. The associations of interleukin-6 (IL-6) and downstream inflammatory markers with risk of cardiovascular disease: the Caerphilly study. Atherosclerosis 209, 551–557. https://doi.org/10.1016/j.atherosclerosis.2009.09.030.
Payette, H., Roubenoff, R., Jacques, P.F., Dinarello, C.A., Wilson, P.W.F., Abad, L.W., Harris, T., 2003. Insulin-like growth factor-1 and interleukin 6 predict sarcopenia in very old community-living men and women: the Framingham Heart Study. J. Am. Geriatr. Soc. 51, 1237–1243. https://doi.org/10.1046/J.1532-5415.2003.51407.X.
Pedersen, B.K., Steensberg, A., Schjerling, P., 2001. Muscle-derived interleukin-6: possible biological effects. J. Physiol. 536, 329–337. https://doi.org/10.1111/j.1469-7793.2001.0329c.xd.
Pedersen, B.K., Steensberg, A., Fischer, C., Keller, C., Keller, P., Plomgaard, P., Febbraio, M., Saltin, B., 2003. Searching for the exercise factor: is IL-6 a candidate? J. Muscle Res. Cell Motil. 24, 113–119. https://doi.org/10.1023/A:1026070911202.
Pelosi, L., Berardinelli, M.G., Forcina, L., Spelta, E., Rizzuto, E., Nicoletti, C., Camilli, C., Testa, E., Catizone, A., De Benedetti, F., Musarò, A., 2015. Increased levels of interleukin-6 exacerbate the dystrophic phenotype in mdx mice. Hum. Mol. Genet 24. https://doi.org/10.1093/hmg/ddv323.
Pelosi, L., Forcina, L., Nicoletti, C., Scicchitano, B.M., Musarò, A., 2017. Increased circulating levels of interleukin-6 induce perturbation in redox-regulated signaling cascades in muscle of dystrophic mice. Oxid. Med. Cell. Longev. 2017 https://doi.org/10.1155/2017/1987218.
Pelosi, L., Berardinelli, M.G., Forcina, L., Ascenzi, F., Rizzuto, E., Sandri, M., De Benedetti, F., Scicchitano, B.M., Musarò, A., 2021. Sustained systemic levels of IL-6 impinge early muscle growth and induce muscle atrophy and wasting in adulthood. Cells 10. https://doi.org/10.3390/CELLS10071816.
Pelosi, M., De Rossi, M., Barberi, L., Musarò, A., 2014. IL-6 impairs myogenic differentiation by downmodulation of p90RSK/eEF2 and mTOR/p70S6K axes, without affecting AKT activity. Biomed. Res. Int. 2014, 206026 https://doi.org/10.1155/2014/206026.
Perry, V.H., Newman, T.A., Cunningham, C., 2003. The impact of systemic infection on the progression of neurodegenerative disease. Nat. Rev. Neurosci. 4, 103–112. https://doi.org/10.1038/nrn1032.
Petersen, A.M.W., Pedersen, B.K., 2005. The anti-inflammatory effect of exercise. J. Appl. Physiol. 98, 1154–1162. https://doi.org/10.1152/japplphysiol.00164.2004.
Petrillo, S., Pelosi, L., Piemonte, F., Travaglini, L., Forcina, L., Catteruccia, M., Petrini, S., Verardo, M., D'Amico, A., Musaró, A., Bertini, E., 2017. Oxidative stress in Duchenne muscular DYSTROPHY: focus on the NRF2 redox pathway. Hum. Mol. Genet. 26 https://doi.org/10.1093/hmg/ddx173.
Petruzzelli, M., Schweiger, M., Schreiber, R., Campos-Olivas, R., Tsoli, M., Allen, J., Swarbrick, M., Rose-John, S., Rincon, M., Robertson, G., Zechner, R., Wagner, E.F., 2014. A switch from white to brown fat increases energy expenditure in cancer-associated cachexia. Cell Metab. 20, 433–447. https://doi.org/10.1016/j.cmet.2014.06.011.
Poli, V., Balena, R., Fattori, E., Markatos, A., Yamamoto, M., Tanaka, H., Ciliberto, G., Rodan, G.A., Costantini, F., 1994. Interleukin-6 deficient mice are protected from bone loss caused by estrogen depletion. EMBO J. 13, 1189–1196. https://doi.org/10.1002/j.1460-2075.1994.tb06368.x.
Poljsak, B., Šuput, D., Milisav, I., 2013. Achieving the balance between ROS and antioxidants: when to use the synthetic antioxidants. Oxid. Med. Cell. Longev. 2013, 1–11. https://doi.org/10.1155/2013/956792.
Ponti, G., Maccaferri, M., Ruini, C., Tomasi, A., Ozben, T., 2020. Biomarkers associated with COVID-19 disease progression. Crit. Rev. Clin. Lab. Sci. 57, 389–399. https://doi.org/10.1080/10408363.2020.1770685.
Puzianowska-Kuźnicka, M., Owczarz, M., Wieczorowska-Tobis, K., Nadrowski, P., Chudek, J., Slusarczyk, P., Skalska, A., Jonas, M., Franek, E., Mossakowska, M., 2016. Interleukin-6 and C-reactive protein, successful aging, and mortality: The PolSenior study. Immun. Ageing 13, 1–12. https://doi.org/10.1186/S12979-016-0076-X/FIGURES/2.
Qiu, Z., Sweeney, D.D., Netzeband, J.G., Gruol, D.L., 1998. Chronic interleukin-6 alters NMDA receptor-mediated membrane responses and enhances neurotoxicity in developing CNS neurons. J. Neurosci. 18, 10445–10456. https://doi.org/10.1523/JNEUROSCI.18-24-10445.1998.
Quaglia, L.A., Freitas, W.M., Soares, A.A., Santos, R.D., Nadruz, W., Blaha, M., Coelho, O. R., Blumenthal, R., Agatston, A., Nasir, K., Sposito, A.C., 2014. C-reactive protein is independently associated with coronary atherosclerosis burden among octogenarians. Aging Clin. Exp. Res. 26, 19–23. https://doi.org/10.1007/s40520-013-0114-x.
Quinn, L.B.S., Anderson, B.G., Strait-Bodey, L., Wolden-Hanson, T., 2010. Serum and muscle interleukin-15 levels decrease in aging mice: Correlation with declines in soluble interleukin-15 receptor alpha expression. Exp. Gerontol. 45, 106–112. https://doi.org/10.1016/J.EXGER.2009.10.012.
Ranucci, M., Ballotta, A., Di Dedda, U., Baryshnikova, E., Dei Poli, M., Resta, M., Falco, M., Albano, G., Menicanti, L., 2020. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. J. Thromb. Haemost. 18, 1747–1751. https://doi.org/10.1111/jth.14854.
Reeh, H., Rudolph, N., Billing, U., Christen, H., Streif, S., Bullinger, E., Schliemann-Bullinger, M., Findeisen, R., Schaper, F., Huber, H.J., Dittrich, A., 2019. Response to IL-6 trans- and IL-6 classic signalling is determined by the ratio of the IL-6 receptor α to gp130 expression: fusing experimental insights and dynamic modelling. Cell Commun. Signal 17. https://doi.org/10.1186/S12964-019-0356-0.

Reich, D., Patterson, N., Ramesh, V., De Jager, P.L., McDonald, G.J., Tandon, A., Choy, E., Hu, D., Tamraz, B., Pawlikowska, L., Wassel-Fyr, C., Huntsman, S., Waliszewska, A., Rossin, E., Li, R., Garcia, M., Reiner, A., Ferrell, R., Cummings, S., Kwok, P.-Y., Harris, T., Zmuda, J.M., Ziv, E., 2007. Admixture Mapping of an Allele Affecting Interleukin 6 Soluble Receptor and Interleukin 6 Levels. Am. J. Hum. Genet. 80, 716–726. https://doi.org/10.1086/513206.

Resliany, Rachim, Agus, Sudarso, Shanti Pricillia, Makagiansar, Syakib, Bakri, Haerani, Rasyid, A Makbul, Aman, Hasyim, Kasim, Arifin, Seweng, 2020. Expression of interleukin-6 levels in elderly sarcopenia. Eur. J. Mol. Clin. Med. 7, 2837–2844.

Reuben, D.B., Ferrucc, L., Wallace, R., Tracy, R.P., Corti, M.C., Heimovitz, H., Harris, T. B., 2000. The prognostic value of serum albumin in healthy older persons with low and high serum interleukin-6 (IL-6) levels. J. Am. Geriatr. Soc. 48, 1404–1407. https://doi.org/10.1111/j.1532-5415.2000.tb02629.x.

Ridker, P.M., Luscher, T.F., 2014. Anti-inflammatory therapies for cardiovascular disease. Eur. Heart J. 35, 1782–1791. https://doi.org/10.1093/eurheartj/ehu203.

Riethmueller, S., Somasundaram, P., Ehlers, J.C., Hung, C.-W., Flynn, C.M., Lokau, J., Agthe, M., Düsterhöft, S., Zhu, Y., Grötzinger, J., Lorenzen, I., Koudelka, T., Yamamoto, K., Pickhinke, U., Wichert, R., Becker-Pauly, C., Rädisch, M., Albrecht, A., Hessefort, M., Stahnke, D., Unverzagt, C., Rose-John, S., Tholey, A., Garbers, C., 2017. Proteolytic origin of the soluble human IL-6R in vivo and a decisive role of N-glycosylation. PLOS Biol. 15, e2000080 https://doi.org/10.1371/journal.pbio.2000080.

Rodríguez-Hernández, M.Á., Carneros, D., Núñez-Núñez, M., Coca, R., Baena, R., López-Ruiz, G.M., Cano-Serrano, M.E., Martínez-Tellería, A., Fuentes-López, A., Praena-Fernandez, J.M., Garbers, C., Hernández-Quero, J., García, F., Rose-John, S., Bustos, M., 2022. Identification of IL-6 signalling components as predictors of severity and outcome in COVID-19. Front. Immunol. 13. https://doi.org/10.3389/fimmu.2022.891456.

Rong, Y.-D., Bian, A.-L., Hu, H.-Y., Ma, Y., Zhou, X.-Z., 2018. Study on relationship between elderly sarcopenia and inflammatory cytokine IL-6, anti-inflammatory cytokine IL-10. BMC Geriatr. 18, 308. https://doi.org/10.1186/s12877-018-1007-9.

Roodman, G.D., Kurihara, N., Ohsaki, Y., Kukita, A., Hosking, D., Demulder, A., Smith, J. F., Singer, F.R., 1992. Interleukin 6. A potential autocrine/paracrine factor in Paget's disease of bone. J. Clin. Invest 89, 46–52. https://doi.org/10.1172/JCI115584.

Rosas, I.O., Bräu, N., Waters, M., Go, R., Hunter, B.D., Bhagani, S., Skiest, D., Aziz, M.S., Cooper, N., Douglas, I.S., Savic, S., Youngstein, T., Del Sorbo, L., Cubillo Gracian, A., De La Zerda, D.J., Ustianowski, A., Bao, M., Dimonaco, S., Graham, E., Matharu, B., Spotswood, H., Tsai, L., Malhotra, A., Peters, J.J., 2020. Tocilizumab in hospitalized patients With COVID-19 pneumonia. medRxiv. https://doi.org/10.1101/2020.08.27.20183442.

Rose-John, S., 2012. IL-6 trans-signaling via the soluble IL-6 receptor: importance for the pro-inflammatory activities of IL-6. Int. J. Biol. Sci. 8, 1237–1247. https://doi.org/10.7150/ijbs.4989.

Rose-John, S., 2018. Interleukin-6 family cytokines. Cold Spring Harb. Perspect. Biol. 10, a028415 https://doi.org/10.1101/CSHPERSPECT.A028415.

Rothaug, M., Becker-Pauly, C., Rose-John, S., 2016. The role of interleukin-6 signaling in nervous tissue. Biochim. Biophys. Acta Mol. Cell Res. https://doi.org/10.1016/j.bbamcr.2016.03.018.

Rupert, J.E., Narasimhan, A., Jengelley, D.H.A., Jiang, Y., Liu, J., Au, E., Silverman, L.M., Sandusky, G., Bonetto, A., Cao, S., Lu, X., O'Connell, T.M., Liu, Y., Koniaris, L.G., Zimmers, T.A., 2021. Tumor-derived IL-6 and trans-signaling among tumor, fat, and muscle mediate pancreatic cancer cachexia. J. Exp. Med. 218 https://doi.org/10.1084/jem.20190450.

Sabaka, P., Koščálová, A., Straka, I., Hodosy, J., Lipták, R., Kmotorková, B., Kachlíková, M., Kušnírová, A., 2021. Role of interleukin 6 as a predictive factor for a severe course of Covid-19: retrospective data analysis of patients from a long-term care facility during Covid-19 outbreak. BMC Infect. Dis. 21, 308. https://doi.org/10.1186/s12879-021-05945-8.

Sacks, D., Baxter, B., Campbell, B.C.V., Carpenter, J.S., Cognard, C., Dippel, D., Eesa, M., Fischer, U., Hausegger, K., Hirsch, J.A., Shazam Hussain, M., Jansen, O., Jayaraman, M.V., Khalessi, A.A., Kluck, B.W., Lavine, S., Meyers, P.M., Ramee, S., Rüfenacht, D.A., Schirmer, C.M., Vorwerk, D., 2018. Multisociety consensus quality improvement revised consensus statement for endovascular therapy of acute ischemic stroke. Int. J. Stroke 13, 612–632. https://doi.org/10.1177/1747493018778713.

Salvarani, C., Dolci, G., Massari, M., Merlo, D.F., Cavuto, S., Savoldi, L., Bruzzi, P., Boni, F., Braglia, L., Turrà, C., Ballerini, P.F., Sciascia, R., Zammarchi, L., Para, O., Scotton, P.G., Inojosa, W.O., Ravagnani, V., Salerno, N.D., Sainaghi, P.P., Brignone, A., Codeluppi, M., Teopompi, E., Milesi, M., Bertomoro, P., Claudio, N., Salio, M., Falcone, M., Cenderello, G., Donghi, L., Del Bono, V., Colombelli, P.L., Angheben, A., Passaro, A., Secondo, G., Pascale, R., Piazza, I., Facciolongo, N., Costantini, M., 2021. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia. JAMA Intern. Med. 181, 24. https://doi.org/10.1001/jamainternmed.2020.6615.

Sang, E.R., Tian, Y., Miller, L.C., Sang, Y., 2021. Epigenetic evolution of ACE2 and IL-6 genes: non-canonical interferon-stimulated genes correlate to COVID-19 susceptibility in vertebrates. Genes 12. https://doi.org/10.3390/genes12020154.

Saver, J.L., Goyal, M., Bonafe, A., Diener, H.-C., Levy, E.I., Pereira, V.M., Albers, G.W., Cognard, C., Cohen, D.J., Hacke, W., Jansen, O., Jovin, T.G., Mattle, H.P., Nogueira, R.G., Siddiqui, A.H., Yavagal, D.R., Baxter, B.W., Devlin, T.G., Lopes, D.K., Reddy, V.K., du Mesnil de Rochemont, R., Singer, O.C., Jahan, R., 2015. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N. Engl. J. Med 372, 2285–2295. https://doi.org/10.1056/NEJMoa1415061.

Sayed, N., Huang, Y., Nguyen, K., Krejciova-Rajaniemi, Z., Grawe, A.P., Gao, T., Tibshirani, R., Hastie, T., Alpert, A., Cui, L., Kuznetsova, T., Rosenberg-Hasson, Y., Ostan, R., Monti, D., Lehallier, B., Shen-Orr, S.S., Maecker, H.T., Dekker, C.L., Wyss-Coray, T., Franceschi, C., Jojic, V., Haddad, F., Montoya, J.G., Wu, J.C., Davis, M.M., Furman, D., 2021. An inflammatory aging clock (iAge) based on deep learning tracks multimorbidity, immunosenescence, frailty and cardiovascular aging. Nat. Aging 1, 598–615. https://doi.org/10.1038/s43587-021-00082-y.

Scambia, G., Testa, U., Panici, P.B., Martucci, R., Foti, E., Petrini, M., Amoroso, M., Masciullo, V., Peschle, C., Mancuso, S., 1994. Interleukin-6 serum levels in patients with gynecological tumors. Int. J. Cancer 57, 318–323. https://doi.org/10.1002/IJC.2910570305.

Schaap, L.A., Pluijm, S.M.F., Deeg, D.J.H., Visser, M., 2006. Inflammatory markers and loss of muscle mass (Sarcopenia) and strength. Am. J. Med. 119, 526.e9–526.e17. https://doi.org/10.1016/J.AMJMED.2005.10.049.

Schaper, F., Rose-John, S., 2015. Interleukin-6: biology, signaling and strategies of blockade. Cytokine Growth Factor Rev. 26, 475–487. https://doi.org/10.1016/J.CYTOGFR.2015.07.004.

Scheller, J., Chalaris, A., Schmidt-Arras, D., Rose-John, S., 2011. The pro- and anti-inflammatory properties of the cytokine interleukin-6. Biochim. Biophys. Acta Mol. Cell Res. https://doi.org/10.1016/j.bbamcr.2011.01.034.

Schumacher, N., Meyer, D., Mauermann, A., Von Der Heyde, J., Wolf, J., Schwarz, J., Knittler, K., Murphy, G., Michalek, M., Garbers, C., Bartsch, J.W., Guo, S., Schacher, B., Eickholz, P., Chalaris, A., Rose-John, S., Rabe, B., 2015. Shedding of endogenous interleukin-6 receptor (IL-6R) is governed by a disintegrin and metalloproteinase (ADAM) proteases while a full-length IL-6R isoform localizes to circulating microvesicles. J. Biol. Chem. 290, 26059–26071. https://doi.org/10.1074/JBC.M115.649509.

Schumacher, N., Schmidt, S., Schwarz, J., Dohr, D., Lokau, J., Scheller, J., Garbers, C., Chalaris, A., Rose-John, S., Rabe, B., 2016. Circulating soluble IL-6R but Not ADAM17 activation drives mononuclear cell migration in tissue inflammation. J. Immunol. 197, 3705–3715. https://doi.org/10.4049/jimmunol.1600909.

Senchenkova, E.Y., Komoto, S., Russell, J., Almeida-Paula, L.D., Yan, L.-S., Zhang, S., Granger, D.N., 2013. Interleukin-6 mediates the platelet abnormalities and thrombogenesis associated with experimental colitis. Am. J. Pathol. 183, 173–181. https://doi.org/10.1016/j.ajpath.2013.03.014.

Serrano, A.L., Baeza-Raja, B., Perdiguero, E., Jardí, M., Muñoz-Cánoves, P., 2008. Interleukin-6 is an essential regulator of satellite cell-mediated skeletal muscle hypertrophy. Cell Metab. 7, 33–44. https://doi.org/10.1016/j.cmet.2007.11.011.

Skiniotis, G., Boulanger, M.J., Garcia, K.C., Walz, T., 2005. Signaling conformations of the tall cytokine receptor gp130 when in complex with IL-6 and IL-6 receptor. Nat. Struct. Mol. Biol. 12, 545–551. https://doi.org/10.1038/NSMB941.

Smits, S.L., de Lang, A., van den Brand, J.M.A., Leijten, L.M., van IJcken, W.F., Eijkemans, M.J.C., van Amerongen, G., Kuiken, T., Andeweg, A.C., Osterhaus, A.D. M.E., Haagmans, B.L., 2010. Exacerbated innate host response to SARS-CoV in aged non-human primates. PLoS Pathog. 6, e1000756 https://doi.org/10.1371/journal.ppat.1000756.

Sommer, J., Garbers, C., Wolf, J., Trad, A., Moll, J.M., Sack, M., Fischer, R., Grötzinger, J., Waetzig, G.H., Floss, D.M., Scheller, J., 2014. Alternative intronic polyadenylation generates the interleukin-6 trans-signaling inhibitor sgp130-E10. J. Biol. Chem. 289, 22140–22150. https://doi.org/10.1074/jbc.M114.560938.

Squarzoni, S., Schena, E., Sabatelli, P., Mattioli, E., Capanni, C., Cenni, V., D'Apice, M.R., Andrenacci, D., Sarli, G., Pellegrino, V., Festa, A., Baruffaldi, F., Storci, G., Bonafè, M., Barboni, C., Sanapo, M., Zaghini, A., Lattanzi, G., 2021. Interleukin-6 neutralization ameliorates symptoms in prematurely aged mice. Aging Cell 20. https://doi.org/10.1111/ACEL.13285.

Storci, G., De Carolis, S., Papi, A., Bacalini, M.G., Gensous, N., Marasco, E., Tesei, A., Fabbri, F., Arienti, C., Zanoni, M., Sarnelli, A., Santi, S., Olivieri, F., Mensà, E., Latini, S., Ferracin, M., Salvioli, S., Garagnani, P., Franceschi, C., Bonafè, M., 2019. Genomic stability, anti-inflammatory phenotype, and up-regulation of the RNAseH2 in cells from centenarians. Cell Death Differ. 269 (26), 1845–1858. https://doi.org/10.1038/s41418-018-0255-8.

Strohbehn, G.W., Heiss, B.L., Rouhani, S.J., Trujillo, J.A., Yu, J., Kacew, A.J., Higgs, E.F., Bloodworth, J.C., Cabanov, A., Wright, R.C., Koziol, A.K., Weiss, A., Danahey, K., Karrison, T.G., Edens, C.C., Bauer Ventura, I., Pettit, N.N., Patel, B.K., Pisano, J., Strek, M.E., Gajewski, T.F., Ratain, M.J., Reid, P.D., 2021. COVIDOSE: a phase II clinical trial of low-dose tocilizumab in the treatment of noncritical COVID-19 pneumonia. Clin. Pharmacol. Ther. 109, 688–696. https://doi.org/10.1002/cpt.2117.

Tanaka, T., Narazaki, M., Kishimoto, T., 2014. IL-6 in inflammation, immunity, and disease. Cold Spring Harb. Perspect. Biol. 6, a016295 https://doi.org/10.1101/cshperspect.a016295.

Terry, C.F., Loukaci, V., Green, F.R., 2000. Cooperative influence of genetic polymorphisms on interleukin 6 transcriptional regulation. J. Biol. Chem. 275, 18138–18144. https://doi.org/10.1074/JBC.M000379200.

Toulmond, S., Vige, X., Fage, D., Benavides, J., 1992. Local infusion of interleukin-6 attenuates the neurotoxic effects of NMDA on rat striatal cholinergic neurons. Neurosci. Lett. 144, 49–52. https://doi.org/10.1016/0304-3940(92)90713-h.

Trichopoulos, D., Psaltopoulou, T., Orfanos, P., Trichopoulou, A., Boffetta, P., 2006. Plasma C-reactive protein and risk of cancer: a prospective study from Greece. Cancer Epidemiol. Biomark. Prev. 15, 381–384. https://doi.org/10.1158/1055-9965.EPI-05-0626.

Tsujinaka, T., Fujita, J., Ebisui, C., Yano, M., Kominami, E., Suzuki, K., Tanaka, K., Katsume, A., Ohsugi, Y., Shiozaki, H., Monden, M., 1996. Interleukin 6 receptor antibody inhibits muscle atrophy and modulates proteolytic systems in interleukin 6 transgenic mice. J. Clin. Invest. 97, 244–249. https://doi.org/10.1172/JCI118398.

Tu, Y.-F., Chien, C.-S., Yarmishyn, A.A., Lin, Y.-Y., Luo, Y.-H., Lin, Y.-T., Lai, W.-Y., Yang, D.-M., Chou, S.-J., Yang, Y.-P., Wang, M.-L., Chiou, S.-H., 2020. A review of SARS-CoV-2 and the ongoing clinical trials. Int. J. Mol. Sci. 21, 2657. https://doi.org/10.3390/ijms21072657.

Tumu, V.R., Govatati, S., Guruvaiah, P., Deenadayal, M., Shivaji, S., Bhanoori, M., 2013. An interleukin-6 gene promoter polymorphism is associated with polycystic ovary syndrome in South Indian women. J. Assist. Reprod. Genet. 30, 1541–1546. https://doi.org/10.1007/S10815-013-0111-1.

Ulhaq, Z.S., Soraya, G.V., 2020. Interleukin-6 as a potential biomarker of COVID-19 progression. Médecine Mal. Infect. 50, 382–383. https://doi.org/10.1016/j.medmal.2020.04.002.

Vanden Berghe, W., Vermeulen, L., De Wilde, G., De Bosscher, K., Boone, E., Haegeman, G., 2000. Signal transduction by tumor necrosis factor and gene regulation of the inflammatory cytokine interleukin-6. Biochem. Pharmacol. 60, 1185–1195. https://doi.org/10.1016/S0006-2952(00)00412-3.

Vasan, R.S., Sullivan, L.M., Roubenoff, R., Dinarello, C.A., Harris, T., Benjamin, E.J., Sawyer, D.B., Levy, D., Wilson, P.W.F., D'Agostino, R.B., 2003. Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: the Framingham Heart Study. Circulation 107, 1486–1491. https://doi.org/10.1161/01.CIR.0000057810.48709.F6.

Velavan, T.P., Meyer, C.G., 2020. Mild versus severe COVID-19: laboratory markers. Int. J. Infect. Dis. 95, 304–307. https://doi.org/10.1016/j.ijid.2020.04.061.

Veldhoen, M., Hocking, R.J., Atkins, C.J., Locksley, R.M., Stockinger, B., 2006. TGFβ in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells. Immunity 24, 179–189. https://doi.org/10.1016/j.immuni.2006.01.001.

Veverka, V., Baker, T., Redpath, N.T., Carrington, B., Muskett, F.W., Taylor, R.J., Lawson, A.D.G., Henry, A.J., Carr, M.D., 2012. Conservation of functional sites on interleukin-6 and implications for evolution of signaling complex assembly and therapeutic intervention. J. Biol. Chem. 287, 40043–40050. https://doi.org/10.1074/JBC.M112.405597.

Von Linsingen, R., Bompeixe, E.P., Da Graca Bicalho, M., 2005. A case-control study in *IL6* and *TGFB1* gene polymorphisms and recurrent spontaneous abortion in southern brazilian patients. Am. J. Reprod. Immunol. 53, 94–99. https://doi.org/10.1111/j.1600-0897.2005.00250.x.

Wang, Y., Fuller, G.M., 2017. Phosphorylation and internalization of gp130 occur after IL-6 activation of Jak2 kinase in hepatocytes. https://doi.org/10.1091/mbc.5.7.819 5, 819–828. ⟨https://doi.org/10.1091/MBC.5.7.819⟩.

Warren, K.N., Beason-Held, L.L., Carlson, O., Egan, J.M., An, Y., Doshi, J., Davatzikos, C., Ferrucci, L., Resnick, S.M., 2018. Elevated markers of inflammation are associated with longitudinal changes in brain function in older adults. J. Gerontol. Ser. A 73, 770–778. https://doi.org/10.1093/gerona/glx199.

Wassel, C.L., Barrett-Connor, E., Laughlin, G.A., 2010. Association of circulating C-reactive protein and interleukin-6 with longevity into the 80s and 90s: the rancho bernardo study. J. Clin. Endocrinol. Metab. 95, 4748. https://doi.org/10.1210/JC.2010-0473.

Weaver, J.D., Huang, M.-H., Albert, M., Harris, T., Rowe, J.W., Seeman, T.E., 2002. Interleukin-6 and risk of cognitive decline: MacArthur Studies of Successful Aging. Neurology 59, 371–378. https://doi.org/10.1212/WNL.59.3.371.

Weidle, U.H., Klostermann, S., Eggle, D., Krüger, A., 2010. Interleukin 6/interleukin 6 receptor interaction and its role as a therapeutic target for treatment of cachexia and cancer. Cancer Genom. Proteom. 7, 287–302.

Weinstein, D.A., Roy, C.N., Fleming, M.D., Loda, M.F., Wolfsdorf, J.I., Andrews, N.C., 2002. Inappropriate expression of hepcidin is associated with iron refractory anemia: implications for the anemia of chronic disease. Blood 100, 3776–3781. https://doi.org/10.1182/BLOOD-2002-04-1260.

Weisel, J.W., Litvinov, R.I., 2013. Mechanisms of fibrin polymerization and clinical implications. Blood 121, 1712–1719. https://doi.org/10.1182/BLOOD-2012-09-306639.

Wells, J.C.K., 2011. The thrifty phenotype: an adaptation in growth or metabolism? Am. J. Hum. Biol. 23, 65–75. https://doi.org/10.1002/ajhb.21100.

Weng, N., 2006. Aging of the immune system: how much can the adaptive immune system adapt? Immunity 24, 495–499. https://doi.org/10.1016/j.immuni.2006.05.001.

Wilkinson, A.N., Gartlan, K.H., Kelly, G., Samson, L.D., Olver, S.D., Avery, J., Zomerdijk, N., Tey, S.-K., Lee, J.S., Vuckovic, S., Hill, G.R., 2018. Granulocytes are unresponsive to IL-6 due to an absence of gp130. J. Immunol. 200, 3547–3555. https://doi.org/10.4049/jimmunol.1701191.

Wolf, J., Waetzig, G.H., Chalaris, A., Reinheimer, T.M., Wege, H., Rose-John, S., Garbers, C., 2016a. Different soluble forms of the interleukin-6 family signal transducer gp130 fine-tune the blockade of interleukin-6 trans-signaling. J. Biol. Chem. 291, 16186–16196. https://doi.org/10.1074/jbc.M116.718551.

Wolf, J., Waetzig, G.H., Reinheimer, T.M., Scheller, J., Rose-John, S., Garbers, C., 2016b. A soluble form of the interleukin-6 family signal transducer gp130 is dimerized via a C-terminal disulfide bridge resulting from alternative mRNA splicing. Biochem. Biophys. Res. Commun. 470, 870–876. https://doi.org/10.1016/j.bbrc.2016.01.127.

Wu, X., Zheng, W., Jin, P., Hu, J., Zhou, Q., 2019. Role of IGFBP1 in the senescence of vascular endothelial cells and severity of aging-related coronary atherosclerosis. Int. J. Mol. Med. https://doi.org/10.3892/ijmm.2019.4338.

Wyczalkowska-Tomasik, A., Czarkowska-Paczek, B., Zielenkiewicz, M., Paczek, L., 2016. Inflammatory markers change with age, but do not fall beyond reported normal ranges. Arch. Immunol. Ther. Exp. (Warsz.). 64, 249–254. https://doi.org/10.1007/s00005-015-0357-7.

Yang, M.-L., Wang, C.-T., Yang, S.-J., Leu, C.-H., Chen, S.-H., Wu, C.-L., Shiau, A.-L., 2017. IL-6 ameliorates acute lung injury in influenza virus infection. Sci. Rep. 7, 43829. https://doi.org/10.1038/srep43829.

Ye, S.M., Johnson, R.W., 1999. Increased interleukin-6 expression by microglia from brain of aged mice. J. Neuroimmunol. 93, 139–148. https://doi.org/10.1016/S0165-5728(98)00217-3.

Zhai, P., Ding, Y., Wu, X., Long, J., Zhong, Y., Li, Y., 2020. The epidemiology, diagnosis and treatment of COVID-19. Int. J. Antimicrob. Agents 55, 105955. https://doi.org/10.1016/j.ijantimicag.2020.105955.

Zhang, C., Wu, Z., Li, J.-W., Zhao, H., Wang, G.-Q., 2020. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int. J. Antimicrob. Agents 55, 105954. https://doi.org/10.1016/j.ijantimicag.2020.105954.

Zhang, J.G., Zhang, Y., Owczarek, C.M., Ward, L.D., Moritz, R.L., Simpson, R.J., Yasukawa, K., Nicola, N.A., 1998. Identification and characterization of two distinct truncated forms of gp130 and a soluble form of leukemia inhibitory factor receptor α-chain in normal human urine and plasma *. J. Biol. Chem. 273, 10798–10805. https://doi.org/10.1074/JBC.273.17.10798.

Zhang, Y., Zhang, Z., Wei, R., Miao, X., Sun, S., Liang, G., Chu, C., Zhao, L., Zhu, X., Guo, Q., Wang, B., Li, X., 2020. IL (Interleukin)-6 contributes to deep vein thrombosis and is negatively regulated by miR-338-5p. Arterioscler. Thromb. Vasc. Biol. 40, 323–334. https://doi.org/10.1161/ATVBAHA.119.313137.

Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Xiang, J., Wang, Y., Song, B., Gu, X., Guan, L., Wei, Y., Li, H., Wu, X., Xu, J., Tu, S., Zhang, Y., Chen, H., Cao, B., 2020. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395, 1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3.