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Metabolic pathways in immune senescence and inflammaging: Novel therapeutic strategy for chronic inflammatory lung diseases. An EAACI position paper from the Task Force for Immunopharmacology

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Abstract

The accumulation of senescent cells drives inflammaging and increases morbidity of chronic inflammatory lung diseases. Immune responses are built upon dynamic changes in cell metabolism that supply energy and substrates for cell proliferation, differentiation, and activation. Metabolic changes imposed by environmental stress and inflammation on immune cells and tissue microenvironment are thus chiefly involved in the pathophysiology of allergic and other immune-driven diseases. Altered cell metabolism is also a hallmark of cell senescence, a condition characterized by loss of proliferative activity in cells that remain metabolically active. Accelerated senescence can be triggered by acute or chronic stress and inflammatory responses. In contrast, replicative senescence occurs as part of the physiological aging process and has protective roles in cancer surveillance and wound healing. Importantly, cell senescence can also change or hamper response to diverse therapeutic treatments. Understanding the metabolic pathways of senescence in immune and structural cells is therefore critical to detect, prevent, or revert detrimental aspects of senescence-related immunopathology, by developing specific diagnostics and targeted therapies. In this paper, we review the main changes and metabolic alterations occurring in senescent immune cells (macrophages, B cells, T cells). Subsequently, we present the metabolic footprints described in translational studies in patients with chronic asthma and chronic obstructive pulmonary disease (COPD), and review the ongoing

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preclinical studies and clinical trials of therapeutic approaches aiming at targeting metabolic pathways to antagonize pathological senescence. Because this is a recently emerging field in allergy and clinical immunology, a better understanding of the metabolic profile of the complex landscape of cell senescence is needed. The progress achieved so far is already providing opportunities for new therapies, as well as for strategies aimed at disease prevention and supporting healthy aging.

KEYWORDS
cell metabolism, immune senescence, immunometabolism, inflammaging, senolytic drugs, senomorphic drugs

Abbreviations: 27-OHC, 27-hydroxycholesterol; AHR, airway hyperresponsiveness; AID, Activation-induced cytidine deaminase: involved in somatic hypermutation (SHM), gene conversion, and class-switch recombination (CSR) in B-lymphocytes by deaminating C to U during transcription of Ig-variable (V) and Ig-switch (S) region DNA; essential for B-cell terminal differentiation and efficient antibody responses.; AIM2, Absent in melanoma 2: recognizes cytosolic double-stranded DNA and inducing caspase-1-activating inflammasome formation in macrophages; acts as a mediator of pyro-/necro- and apoptosis in response to bacterial infection; Arg1, Arginase 1; key element of the urea cycle converting L-arginine to urea and L-ornithine, which is further metabolized into metabolites proline and polyamides that drive collagen synthesis and bioenergetic pathways critical for cell proliferation; oxidoreductase activity; Arg2, regulation of extra-urea cycle arginine metabolism and also in down-regulation of nitric oxide synthesis. Extrahepatic arginase functions to regulate L-arginine bioavailability to nitric oxide synthase (NOS); negative regulator for survival of activated T cells, promotes immune suppression; ATM, ATM serine/threonine kinase: activates checkpoint signaling upon double-strand breaks (DSBs), apoptosis and genotoxic stresses; ATP, adenosine triphosphate, a compound consisting of adenosine bonded to three phosphate groups. The breakage of one phosphate linkage (to form adenosine diphosphate, ADP) provides energy for physiological processes such as muscular contraction, nerve impulse propagation, condensate dissolution, and chemical synthesis.; ATR, ATR serine/threonine kinase: activates checkpoint signaling upon genotoxic stresses; BEC, bronchial epithelial cells; Cardiolipin, component of the inner mitochondrial membrane, part of complex IV, the cytochrome c oxidase in the OXPHOS process; Carnitine, essential cofactor that helps transport long-chain fatty acids into the mitochondria so that they can be oxidized to produce energy in the form of ATP; CD38, cyclic ADP ribose hydrolase, catalyzes the synthesis of ADP ribose (ADPR) and cyclic ADP-ribose (cADPR) from NAD+.; CDC25C, cell division cycle 25C (CDC25, PPP1R60), function as dosage-dependent inducer in mitotic control, triggers entry into mitosis; cGAS, Cyclic GMP-AMP synthase: Nucleotidyltransferase that catalyzes the formation of cyclic GMP-AMP (2′,3′-cGAMP) from ATP and GTP and plays a key role in innate immunity; key DNA sensor: directly binds dsDNA, inducing the formation of liquid-like droplets in which CGAS is activated, leading to synthesis of 2′,3′-cGAMP, a second messenger that binds to and activates STING1, thereby triggering type-I interferon production; CHEK1, checkpoint kinase 1: is required for checkpoint-mediated cell cycle arrest and activation of DNA repair.; CHEK2, checkpoint kinase 2: is required for checkpoint-mediated cell cycle arrest, activation of DNA repair and apoptosis in response to the presence of DNA double-strand breaks.; COPD, chronic obstructive pulmonary disease; CPT2, carnitine palmitoyl transferase 2: is essential for fatty acid oxidation to metabolize fats into energy.; CSR, class-switch recombination: DNA recombination process that replaces the immunoglobulin (Ig) constant region for the isotype for better protection against the pathogen; DAMP, danger associated molecular pattern; molecules that are released by stressed cells and activating innate immune cells via pattern recognition receptors; DDR, DNA damage response; EMT, epithelial-to-mesenchymal cell transition; ER, endoplasmatic reticulum; ETC, mitochondrial electron transport chain: site of oxidative phosphorylation, which uses NADH and succinate (generated in the citric acid cycle) and oxygen for ATP production; FAO, fatty acid oxidation = beta oxidation in the mitochondria, catabolic process by which fatty acid molecules are broken down to generate acetyl-CoA, which enters the citric acid cycle, and NADH and FADH2, which are co-enzymes used in the electron transport chain.; FFA, free fatty acids; FOXO1, Forkhead box O1: main target of insulin signaling and regulates metabolic homeostasis in response to oxidative stress, Required for the autophagic cell death induction in response to starvation or oxidative stress in a transcription-independent manner; FOXO3, Forkhead box O3: transcriptional activator for autophagy, triggers apoptosis in the absence of survival factors/presence of oxidative stress, promotes under metabolic stress mtDNA transcription; when lipid levels low represses FAO; GAPDH, Glyceraldehyde-3-phosphate dehydrogenase; key enzyme in glycolysis (catalyzes first step); promotes TNF-induced NF-kappa-B activation and type I interferon; GSTP, glutathione-S-transferase P: Conjugation of reduced glutathione to a wide number of exogenous and endogenous hydrophobic electrophiles; important for detoxification; HDAC2, histone deacetylase 2: catalyzes the deacetylation of lysine on the core histones (H2A, H2B, H3, and H4), thereby acting as epigenetic repressor and regulating in cell cycle progression and acting as transcriptional repressor with MAD, SIN3, YY1, and N-COR.; HDM, house dust mite; HIF-1a, hypoxia-inducible factor 1 alpha: master transcriptional regulator of the cellular and systemic homeostatic response to hypoxia by activating under hypoxic conditions the transcription of genes, including erythropoietin, glucose transporters, glycolytic enzymes, vascular endothelial growth factor, HILPDA, to increase oxygen delivery or facilitate metabolic adaptation to hypoxia. Activity is enhanced by interaction with NCOA1 and/or NCOA2; master regulator by activating transcription of many genes, including those involved in energy metabolism.; HMGB1, High mobility group box 1: redox sensitive protein that serves as biosensor for nucleic acids, acting as non-histone, nuclear DNA-binding protein chaperone and serving as DAMPS when released to extracellular environment.; HSF-1, Heat shock transcription factor 1: stress-inducible and DNA-binding transcription factor leading to expression of heat shock proteins; Ig, Immunoglobulin; IGF-1, Insulin-like growth factor: structurally and functionally related to insulin but have a much higher growth-promoting activity; enhances glucose uptake and stimulates glucose transport in bone-derived osteoblastic cells; IL, interleukin: cytokines regulating the immune response; iNOS, inducible nitric oxide synthase; alias NOS2, catalyzes the production of nitric oxide (NO) from L-arginine. In macrophages, NO mediates tumoricidal and bactericidal actions; involved in inflammation, enhances the synthesis of pro-inflammatory mediators such as IL6 and IL8.; KO, knock-out; LMNB1, nuclear lamina protein lamin B1: components of the nuclear lamina, a fibrous layer on the nucleoplasmic side of the inner nuclear membrane, which is thought to provide a framework for the nuclear envelope and may also interact with chromatin; LPC, lysophosphocholine; LPE, lysophosphoethanolamines; LPI, lysophosphatidylinositols; MIDAS, mitochondrial dysfunction-associated senescence: increased fragmented mitochondrial DNA acting as DAMP, decreased mitochondrial ETC complexes (I-III-IV) for OXPHOS; MK2, MAPK-activated protein kinase 2, MAPKAPK2: Stress-activated serine/threonine-protein kinase involved in cytokine production, endocytosis, reorganization of the cytoskeleton, cell migration, cell cycle control, chromatin remodeling, DNA damage response, and transcriptional regulation; regulates tumor necrosis factor (TNF) and IL6 production post-transcriptionally by phosphorylating AU-rich elements (AREs)-binding proteins ELAVL1, HNRNPA0, PABPC1, and TTP/ZFP36, leading to increased stability and translation of TNF and IL6 mRNAs.; MMPs, Matrix metalloproteinases are calcium-dependent zinc-containing endopeptidases; important role in tissue remodeling; mTORC1, protein complex that functions as a nutrient/energy/redox sensor and controls protein synthesis: composed of (1) mTOR protein complex, (2) regulatory-associated protein of mTOR (synonym raptor), mLST8 (short for mammalian lethal with SEC13 protein 8) and the non-core components PRAS40 and DEPTOR; mTORC1 is regulated by rapamycin, insulin, growth factors, phosphatidic acid, amino acids, and their derivatives such as l-leucine and β-hydroxy β-methylbutyric acid, mechanical stimuli, and oxidative stress.; NAD+, nicotinamide adenine dinucleotide, a coenzyme central to metabolism. NAD can be synthesized de novo from tryptophan or aspartic acid or from nutrients such as niacin (nicotinic acid).; NBN, nimbrin: modulate the DNA damage signal sensing by recruiting PI3/PI4-kinase family members ATM, ATR; NET, neutrophil extracellular traps: networks of extracellular fibers, primarily composed of DNA, which bind pathogens.; NF-kB, NF-kappa B is a pleiotropic transcription factor present in almost all cell types. It is activated by various intra- and extracellular stimuli such as cytokines, oxidant-free radicals, ultraviolet irradiation, and bacterial or viral products. Activated NFkB translocates into the nucleus and stimulates the expression of genes involved in a wide variety of biological functions. Inappropriate activation of NFkB has been associated with chronic inflammatory diseases while persistent inhibition of NFKB leads to inappropriate immune cell development or delayed cell growth.; NLRP1, NLR family pyrin domain containing 1: sensor component of the NLRP1 inflammasome, which mediates inflammasome activation in response to various pathogen-associated signals, leading to subsequent pyroptosis; binds ATP and shows ATPase activity; important role in antiviral immunity; NLRP3, NLR family pyrin domain containing 3, sensor component of the NLRP3 inflammasome; crucial role in innate immunity and inflammation; stimuli include extracellular ATP, reactive oxygen species, K(+) efflux, crystals of monosodium urate or cholesterol, amyloid-beta fibers, environmental or industrial particles and nanoparticles, cytosolic dsRNA, etc.; regulates Th2 differentiation; synonyms: AGTAVPRL, AII, AVP, C1orf7,

CIAS1, CLR1.1, DFNA34, FCAS, FCU, MWS, NALP3, and PYPAF1; NLRP6, NLR family pyrin domain containing 6: sensor component of the NLRP6 inflammasome, which mediates inflammasome activation in response to various pathogen-associated signals, leading to maturation and secretion of IL1B and IL18; during systemic bacterial infections, the NLRP6 inflammasome negatively regulates neutrophil recruitment and NET formation; NMN, nicotinamide mononucleotide, a precursor of nicotinamide adenine dinucleotide NAD+; Nrf2, Nuclear factor erythroid 2-related factor 2, NFE2L2: transcription factor and member of a small family of basic leucine zipper (bZIP) proteins; plays a key role in the response to oxidative stress and inflammation: binds to anti-oxidant response (ARE) elements in their promoters; suppresses macrophage inflammatory response by blocking pro-inflammatory cytokine transcription and the induction of IL6.; OVA, ovalbumin; OXPHOS, oxidative phosphorylation: nutrients are oxidized to gain energy in form of ATP; Oxylipin, oxylipins; class of biologically active lipids that arise from oxygenation of polyunsaturated fatty acids (PUFAs); p16, CDKN2a, cyclin-dependent kinase inhibitor 2a, negative regulator of the proliferation of normal cells inducing cell cycle arrest in G1 and G2 phases. Acts as a tumor suppressor. Synonyms: ARF, CDK4I, CDKN2, CMM2, INK4, INK4a, MLM, MTS1, p14, p14ARF, p16, p16INK4a, p19, and p19Arf; p21, CDKN1a, cyclin-dependent kinase inhibitor 1A, synonyms: CAP20, CDKN1, CIP1, P21, p21CIP1, p21Cip1/Waf1, SDI1, and WAF1; p53, tumor protein 53, acts as tumor suppressor, induces growth arrest and apotosis; synonyms: LFSA and TP53; PARP, poly(adenosine diphosphate-ribose) polymerase: Decreased NAD+ levels reduce SIRT1 function and reduce the mitochondrial unfolded protein response, which can be overcome by nicotinamide riboside NR supplementation. Decreased NAD+ levels cause NAD+-binding protein DBC1 to form a complex with PARP1, inhibiting poly(adenosine diphosphate-ribose) polymerase (PARP) catalytic activity; PAX5, paired box 5: transcription factor essential for B-cell lineage commitment; induces VDJ recombination, promotes mature B-cell differentiation.; PGC-1, PPARG coactivator 1 alpha, key regulator of gluconeogenesis, essential regulatory role in glucose and fatty acid metabolism; PGE2, prostaglandin E2; potent inflammatory mediator that is generated by cyclooxygenase 2 (COX2) conversion of arachidonic acid; PH, Pulmonary Hypertension; PI3K, phosphatidylinositol 3: family of intracellular enzymes phosphorylating the inositol ring of phosphatidylinositol. The pathway, with oncogene PIK3CA and tumor suppressor gene PTEN, is implicated in the sensitivity of cancer tumors to insulin and IGF1, and in calorie restriction.; pIgR, polymeric Immunoglobulin receptor: Mediates selective transcytosis of polymeric IgA and IgM across mucosal epithelial cells to the extracellular space; PML bodies, promyelocytic leukemia nuclear bodies: spheric matrix-associated domains up to 1 μm that are usually involved in DNA damage response, DNA repair, telomere homeostasis, and p53-associated apoptosis.; PPP, pentose phosphate pathway: branches from glucose 6-phosphate (G6P), rather anabolic, generates NADPH (reducing agent, prevents oxidative stress and for use in fatty acid synthesis), ribose 5-phosphate (for the synthesis of nucleotides), and erythrose-4-phosphate (for synthesis of aromatic amino acids). The pathway is especially important in red blood cells (erythrocytes); PTGERA4, Receptor for prostaglandin E2. The activity of this receptor is mediated by G(s) proteins that stimulate adenylate cyclase. Has a relaxing effect on smooth muscle, synonym EP4; pTregs, peripheral-derived T regulatory cells; PUFA, poly unsaturated fatty acids: have more than one double-bound; RIG 1, retinoic acid-inducible gene I, also named DDX58: is a putative RNA helicase which is implicated in a number of cellular processes involving RNA binding; senses cytoplasmic viral nucleic acids and activates a downstream signaling cascade leading to the production of type I interferons and pro-inflammatory cytokines; RNS, reactive nitrogen species: reaction of nitric oxide with superoxide to form peroxynitrite that can directly react with proteins containing transition metal centers, for example, hemoglobin, myoglobin, and cytochrome c; ROS, reactive oxygen species: highly reactive chemicals formed from oxygen, for example, peroxides, superoxide, and hydroxyl radical, are produced during respiration in mitochondria to gain ATP or by environmental stressors (e.g., drugs, UV, metals).; S1P, Sphingosine-1-phosphate: is a signaling sphingolipid, also known as lysosphingolipid; regulates angiogenesis, vascular stability, and permeability; major regulator for T- and B-cell trafficking.; SAHF, senescence-associated heterochromatic foci: specialized domains of facultative heterochromatin that contribute to silencing of proliferation-promoting genes in senescent cells; SAPD, senescence-associated protein degradation: selective degradation of proteins associated with cell cycle and RNA metabolism in senescent cells; SASP, senescence-associated secretory phenotype; SCD, Stearoyl-CoA desaturase; utilizes O2 and electrons from reduced cytochrome b5 to introduce the first double bond into saturated fatty acyl-CoA substrates; involved in fatty acid biosynthesis, primarily the synthesis of oleic acid; regulator of mitochondrial fatty acid oxidation; SHM, somatic hypermutation: provides the molecular basis for affinity maturation of antibodies in B cells; SIPS, stress-induced premature senescence; SIRT1, Sirtuin 1: NAD+-dependent deacetylase: regulator in cell cycle, response to DNA damage, metabolism, apoptosis, and autophagy, involved in DNA damage response, Involved in lipid metabolism; SIRT2, Sirtuin 2: NAD+-dependent deacetylase, which is a key regulator in the pentose phosphate pathway (PPP) by deacetylating and activating the glucose-6-phosphate G6PD enzyme, and therefore, stimulates the production of cytosolic NADPH to counteract oxidative damage; it maintains energy homeostasis in response to nutrient deprivation as well as energy expenditure by inhibiting adipogenesis and promoting lipolysis, high glucose leads to reduced NAD+/NADP+ ratio suppressing SIRT2. SIRT2 also inactivates NLRP3 inflammasome and suppresses NF-κB activation; Sirtuin, NAD-dependent deacetylase sirtuin, family of signaling proteins involved in metabolic regulation; possess either mono-ADP-ribosyltransferase or deacylase activity; SOD2, Superoxide dismutase 2, this protein belonging to the iron/manganese superoxide dismutase family binds to the superoxide by-products of OXPHOS and converts them to hydrogen peroxide and oxygen; STING, cyclic GMP-AMP synthase stimulator of interferon genes; SUCNR1, succinate receptor; G-protein-coupled receptor for succinate, an intermediate molecule of the citric acid cycle. It is involved in the promotion of hematopoietic progenitor cell development; TCA, tricarboxylic acid cycle, alias Krebs or citric acid cycle, is the main source of energy for cells and an important part of aerobic respiration.; TLR, toll like receptor: receptors on sentinel cells that recognize structurally conserved molecules and lead to immune activation.; TRM, Tissue-resident memory T cells; UPR, unfolded protein response is a cellular stress response related to the endoplasmatic reticulum; UPR is activated in response to an accumulation of unfolded or misfolded proteins and results in halting protein synthesis, degrading misfolded proteins and producing chaperones. If this objectives are not achieved until a certain time point, apoptosis is initiated.; UPRmt, mitochondrial unfolded protein response is a mitochondria stress response initiating the transcriptional of mitochondrial chaperone proteins and proteases to maintain proteostasis in mitochondria; promotes cell survival and mitochondrial recovery through metabolic adaptations and a precise mitochondrial biogenesis program.

1 | INTRODUCTION

The process of immune senescence is characterized by dynamic adjustments of the innate and adaptive arms of the immune system. The four recognized key hallmarks of cellular senescence include the presence of nonreversible cell cycle arrest, of macromolecular damage, of dysregulated metabolism and the establishment of senescence-associated secretory phenotype (SASP).[1] Importantly, senescence and aging from the biological standpoint are not synonyms. Replicative senescence represents age-related stable, nonreversible loss of proliferative activity in viable, metabolically active cells. In contrast, accelerated senescence or accelerated aging denotes that these responses can be triggered at any age and independently from replicative senescence, by stress responses induced by acute or chronic, extrinsic and intrinsic stimuli.[2] Accelerated senescence has its unique characteristics, but can also share some common features of replicative senescence.[3,4] The senescence phenotype fulfills important physiological roles in anti-cancer surveillance, tissue development, and wound healing, yet when deranged, it becomes central to the development of chronic inflammatory disorders, cancer, and many age-related diseases.

The innate and adaptive immune systems alter with age.[3,5] These changes are currently viewed as a process of immunoadaptation rather than an overall declining functional immune status.[6] This adaptation includes a low-grade inflammation that favors the aging host, as long as it is kept self-limiting by integrated anti-inflammatory brakes.[7] Increased environmental stressors and or/decreased protective pathways cause detrimental inflammation, defined as "inflammaging," due to immune cells undergoing senescence and by the subsequent response from the microenvironment. Accumulation of senescent cells, both age-dependent and due to inflammaging, are a common pathogenic hallmark of chronic non-communicable diseases with the development of multimorbidities in adults as they age. Indeed, severe phenotypes of chronic allergic and inflammatory lung diseases—especially atopic dermatitis, late-onset and severe asthma, chronic obstructive pulmonary disease (COPD)—display features of inflammaging, and

the signs of immune senescence are present even in childhood allergies and asthma.[8] This impacts on global health and has profound socioeconomic implications.[6]

Metabolic imbalance as a key feature of cell senescence is extensively present in dysregulated inflammation and together with altered epigenetic modifications; it constitutes an essential driver for pathogenic immune senescence.[4] Metabolic reprogramming is an integral part of immune cell regulation and function, providing the right substrates for energy supply according to changing demands in both homeostatic and stress conditions. Metabolic profiles and demands vary greatly among immune cell types; they also vary according to many contextual factors, such as cell differentiation and functional stage, the type of immune response, the microenvironment in which immune cells are acting and others.[9] Altered metabolic demands critically shape inflammatory responses, and accordingly, all features of cellular senescence—particularly growth arrest and SASP—are fueled by cellular metabolism. For these reasons in the last decade, immunometabolism has been recognized of major pathophysiological relevance and a key therapeutic target in chronic allergic and inflammatory skin and lung diseases.[10–12] In this context, the metabolic alterations related to cellular senescence and inflammaging constitute a relevant and specific therapeutic target.

This review will first summarize, from the pathophysiology standpoint, the features of altered metabolic demands related to cellular senescence and inflammaging that are particularly relevant to chronic allergic and inflammatory lung responses. Next, it will address how metabolic alterations related to senescence manifest in the clinical setting in exemplary diseases by affecting innate and adaptive responses, as well as tissue remodeling. From the pharmacological and therapeutic standpoint, metabolic targets and therapeutic approaches, tested so far in preclinical and clinical studies to control cellular senescence in these diseases, will be discussed. The actual and potential relationships of these therapeutic strategies with current therapies will be highlighted. Finally, through discussion of emerging unmet needs, potential developments and limitations we will propose the value of metabolic targeting of dysregulated cell senescence for the improvement of current therapies.

2 | PATHOPHYSIOLOGY. ALTERED METABOLIC DEMANDS IN CELL SENESCENCE, RELEVANT TO ALLERGIC AND LUNG INFLAMMATORY RESPONSES

2.1 | Metabolic alterations in cell senescence: general view

Cell senescence is often described as a double-edged sword. A protective edge promotes cancer surveillance, tissue remodeling, and regeneration through limited induction of senescence phenotype within a specific shift from homeostasis, followed by elimination of the affected cells. A physiologic, yet detrimental edge is associated with the aging process, when the ability of eukaryotic cells to restore homeostasis via proteasomal degradation, unfolded protein response (UPR) and autophagy decreases, resulting in a fragile state where cells lose proper function and either die or enter senescence. A pathological, detrimental aspect of senescence occurs regardless of age due to chronic injury and inflammation. Chronic inflammation promotes the development and long-term accumulation of senescent cells, further driving non-resolving inflammation, promoting impaired tissue function and organ failure. A causative relationship between the presence of senescent cells and elevated inflammation has been demonstrated in vitro and *in vivo*[9,13,14] with lifespan and function being curtailed by increased senescent-cell abundance.[15,16] In particular, intrinsic or extrinsic stress factors promote the accumulation of DNA damage, which initiates a perpetual DNA damage response (DDR) and ultimately leads to cell cycle arrest,[17,18] with other intracellular alterations (macromolecular damage, organelle dysfunction) occurring along with the nuclear damage.[16,19,20] Despite stable cell cycle arrest, senescent cells remain metabolically active through deregulated metabolic reprogramming,[20] which deeply influence the non-senescent neighboring resident cells through SASP. The senescence-mediated secretome is vast, complex and highly cell context- and cell type-dependent,[21] being excreted either directly or through microvesicle/exosome-mediated release. All these responses can be dependent or independent on the activation of p53–p21 and/or p16INK4a–pRB pathways, which cause cell cycle arrest.[22] Between these two entities, various shades and mixed forms are possible.[4] General features of cell senescence are discussed in major reviews[3,15,23] and summarized in Table 1.

Cell signaling, nutrient sensing, and biochemical pathways that physiologically provide energy and substrates can be affected by environmental and intracellular triggers of the senescence phenotype. In turn, metabolic imbalance affects nuclear, cytoplasmic, and organelle-related functions, brings damage to macromolecular species, metals accumulation and secretome alteration. Figure 1 and Table 2 summarize the main metabolic alterations of cell senescence, which are intricately linked.

2.1.1 | Alterations in glycolysis and oxidative phosphorylation (OXPHOS)

A healthy cell can regulate its energy needs and the balance between catabolism (production of energy in the form of ATP) and anabolism (synthesis of proteins, carbohydrates, nucleic acids, and lipids) during homeostasis or cell activation by functional metabolic reprogramming. These terms usually refer to shifting nutrients among main biochemical pathways of energy production including glycolysis, tricarboxylic acid (TCA or Krebs cycle), oxidative phosphorylation (OXPHOS), and fatty acid oxidation, depending on the energy needs, nutrients availability, activation, and proliferation stage of the cell.[12,24] In senescence, some of these processes become chronically

TABLE 1 Cellular senescence: main features. Refer to glossary for acronym description.

Cellular senescence		Refs
Definition	Irreversible cell cycle arrest driven by intrinsic and extrinsic stimuli, resistant to apoptosis, with conserved metabolic activity ("relative hyperfunction of aging")	1,15
Physiologic Function	• Tumor suppressive as cellular transformation is prevented • Contribute to wound healing	1,3,16
Pathologic function	• Accumulation of senescent cells contributes to decline of tissue and organ fitness • Protumorigenic	
Types of senescence		
Replicative	• Due to proliferative exhaustion: telomere shortening	1,286,287
Premature	Stress • Oncogenic (DNA damage, ongone activation) • Loss of tumor suppressor molecules • Mitogenic ➔ activation of mTORC1 • Extrinsic stress to environmental factors, for example, smoking, radiation, tissue damage • Delayed clearance of senescent cells by NK cells and macrophages • Inflammaging: pro-inflammatory outcome of accelerated aging	287
Characteristic of senescence		
Cell cycle arrest	• Growth arrest in G1 and possibly G2 phase (as opposed quiescence, G0 phase) by cyclin-dependent protein kinase inhibitors p16 (=CDKN2A) and $p21^{Cip1}$, which prevents phosphorylation of cyclin-dependent kinase CDK substrates and thereby of CDK activity and cell cycle progression	288
Persistent DNA damage response DDR	• Involved proteins are ATR, ATM, CHEK1, CHEK2, (NBN in macrophages) and p53. • Upon DNA damage: ATR and ATM, key protein kinases are activated and bind to damaged DNA sites, which subsequently activates Chek1, Chek2, and p53. Activated CHEK2 inhibit CDC25C phosphatase, preventing entry into mitosis, and stabilize the tumor suppressor protein p53, leading to cell cycle arrest in G1	288–290
SASP	• Increased release of multiple mediator classes with strong pro-inflammatory/remodeling functions: cytokines, chemokines, growth factors, enzymes, other molecules	291,292
Unfolded protein response (UPR)	• ↓ heat shock protein response via heat shock factor 1, HSF • ↓mitochondrial unfolded protein response UPR^{mt} • ↓endoplasmic reticulum unfolded protein response ER UPR, though enhanced ER sensing	293,294
Cellular changes		
Cell morphology	• Enlarged size with flattened shape • Multinucleated and/or nuclear enlargements with chromatin alterations: PML bodies, SAHF • Increased numbers of lysosomes and mitochondria • Altered plasma membrane composition	64,292,295
Biomarkers	• ↑ lysosomal ß-galactosidase • ↑ lipofuscin • ↑ tumor suppressor p16/CDKN2A • ↓ nuclear lamina protein lamin B1 (LMNB1) • Relocalization and secretion of HMGB1	1,296–298

dysregulated. Both replicative and accelerated senescence include decreased autophagy, dysregulated nutrient sensing, mitochondrial dysfunction, often suppressed OXPHOS, increased glycolysis, and critical increase in production of reactive oxygen species (ROS).[25,26] However, every cell type can have its own senescent metabolic signature, even with decreased glycolysis or increased OXPHOS.[26–28]

2.1.2 | Disrupted NAD+/NADH levels and ratio

Nicotinamide adenine dinucleotide (NAD) is an electron acceptor during oxidative phosphorylation catalyzed by mitochondrial electron transport chain (ETC). NAD metabolism activate major signaling pathways regulating key molecules [such as sirtuins, Poly(ADP-ribosyl) transferases (PARP), CD38] that reprogram cellular metabolism using NAD+ as an effector substrate.[29] Dysfunction in the activity of mitochondrial ETC activity decreases the mitochondrial conversion of NADH to NAD+, thereby reducing the intracellular mitochondrial NAD+/NADH ratio.[30] Low NAD+/NADH ratio is a significant inducer of cellular senescence.[31] Poly(ADP-ribosyl) transferase (PARP1) activity, that uses NAD+ and detects DNA damage, increases and further impairs mitochondrial activity. Along with reduced NAD+/NADH levels, senescence mediated by mitochondrial dysfunction is also associated with sustained 5′-AMP-activated protein kinase (AMPK) activity.[32] Mitochondrial dysfunction and endoplasmic reticulum (ER) stress are associated with dysfunctional autophagic activation. NAD metabolism and mitochondria also provides a link to

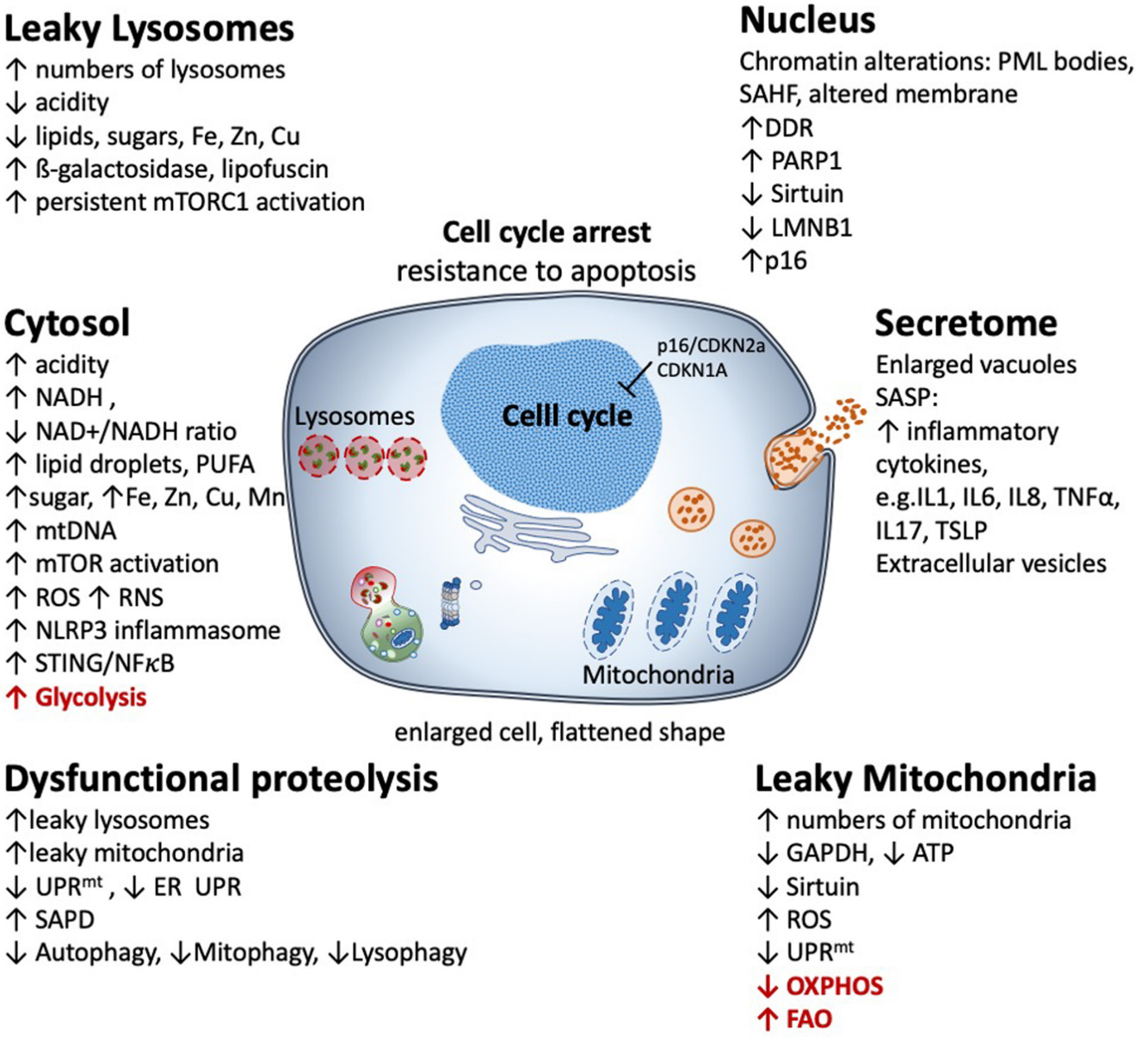

FIGURE 1 Main features of cellular senescence and of related metabolic alterations. Senescent cells are on an irreversible cell cycle arrest and are resistant to apoptosis, despite the presence of excessive oxidative stress. This results in "leaky," dysfunctional lysosomes and mitochondria, which further trigger DNA and protein damage and ultimately alters cellular metabolism. Lysosomal accumulation of ß-galactosidase serves as common marker for senescent cell identification. Despite being cell cycle arrested, senescent cells are metabolic active. They release multiple pro-inflammatory cytokines, termed senescent-associated secretory phenotype, SASP, which contribute to inflammaging.

inflammaging, as low NAD+ levels or oxidized mitochondrial DNA induce activation of NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome, a sensor of the damage-associated molecular patterns (DAMPs) that accumulate with aging.[33,34] The activation of NLRP3 inflammasomes by DAMPs triggers many intracellular events, such as NF-κB activation, NLRP3 inflammasome complex formation and caspase-1-dependent release of mature forms of IL-1β and IL-18, often leading to the inflammatory cell death called pyroptosis. Thus, activation of NLRP3 and any other inflammasomes, formed by other sensor pattern recognition receptors, including AIM2, NLRP1, NLRP6, and RIG-I need to be very tightly regulated to prevent excessive tissue damage and inflammation, which is not the case in chronic inflammatory diseases.[35-37] Other innate intracellular pathways are also important in cell senescence, such as cyclic GMP-AMP synthase (cGAS), which recognizes cytosolic chromatin fragments and activates STimulator of INterferon Genes (STING).[38]

TABLE 2 Cellular senescence: subcellular changes and related metabolic alterations. Refer to glossary for acronym description.

Cellular senescence: Subcellular changes	Refs
Nucleus • Increased DNA damage response (DDR) can be triggered by oxidative damage, telomere attrition, drug treatment, cell irradiation	5,8,17,18,59
Lysosomes • Increased numbers of dysfunctional lysosomes • Increased lysosomal permeability leads to loss of lysosomal acidity, loss of sugars, fatty acids and minerals (iron, zinc, copper)	3,19,59,299,300

Mitochondria
• Increased number of dysfunctional mitochondria
• Mitochondrial dysfunction-associated senescence (MiDAS):
  • Decreased nutrient transfer to mitochondria: results in GAPDH inhibition and ATP depletion
  • Decreased mitochondrial unfolded protein response (UPR^{mt}): → mitochondrial SIRT suppress senescent phenotype: a decline of sirtuin leads to increased IL6 secretion due to failure to activate anti-oxidative enzymes, despite dysfunctional mitochondria; also mitophagy declines
  • Decreased oxidative phosphorylation: OXPHOS
  • Increased ROS formation
  • Increased fatty acid oxidation (FAO)/beta oxidation
	3,19,20,53,54,281,293,300–303

Cytosol • Increased cytosolic acidity: leads to changes in the cellular redox state • Increased molecular species: NADH, lipid droplets, glucose, ferritin, free minerals: leads to increased ROS • Increased mitochondrial oxidized DNA and cardiolipin by damaged mitochondria • Decreased NAD+ • Increased glycolysis	3,19,20,64,279,296–300,304–307
Cellular senescence: Metabolic characteristics	
DNA damage response • DDR triggers persistent PARP1 activation consequent to DDR, initiates the repair of DNA breaks and adds ADP-D-ribosyl group of NAD+ to proteins, resulting in NAD+ depletion	31,308
NAD+ depletion • Decreased NAD+ or NAD+/NADH ratio leads to decreased rate of ATP production and supply • Decreased NAD+ or NAD+/NADH ratio leads to decline of efficient activity of sirtuins (SIRT)	309,310
NLRP3 inflammasome and downstream pathway activation, SASP and inflammaging • Impaired mitochondria release damage-associated molecular patterns (DAMPs) composed of oxidized mitochondrial DNA and cardiolipin into the cytoplasm with the subsequent activation of inflammatory pathways including NLRP3 inflammasome, cGAS/STING pathway and NF-kB. • Activation of NLRP3 inflammasome is also required for HMGB1 secretion. • SASP is regulated by inflammasome and IL-1 signaling, with some SASP factors themselves acting as DAMPs. • SASP alter NAD+ metabolism and stimulate the expression of CD38, a NADase on immune cells, which leads to further NAD reduction.	285,293,294,304–307,310–313
Sirtuins • Decreased expression • Reduced NAD+/NADP+ ratio (due to high intracellular glucose) leads to suppression of SIRT1, which acts as sensor of the cytosolic NAD+/NADH ratio and SIRT2, with inability to deacetylate and inactivate NLRP3 inflammasome and inactivate NF−κB functions	45–54
Decreased autophagy • Senescent cells express decreased levels of mitochondrial autophagy (mitophagy), that results in accumulation of dysfunctional mitochondria, increased ROS production and ROS-induced senescence	54,314

Altered antagonistic nutrient sensing: AMPK-mTOR
• Persistent activation of nutrient-sensor mTORC1 (mammalian target of rapamycin complex 1), resistant to nutrient starvation
  • Nutrient-repletion conditions favors mTORC1 activation, fatty acid synthesis, protein synthesis, nucleic acid synthesis
  • Nutritional restriction (methionine, leucin) inactivates mTORC1, increased autophagy to liberate nutrients and support cell survival
• Energy responsiveness via AMPK
  • Low-energy conditions (increased AMP/ADP) lead to AMPK activation and consequent increase of cytoplasmic glycolysis and mitochondrial FAO, (fatty acid are broken down), that generates Acetyl-CoA which enters TCA
• Resistance to apoptosis
	2,3,31,59,64,308,315–317

(Continues)

TABLE 2 (Continued)

Cellular senescence: Subcellular changes	Refs
Decreased proteostasis • Decreased unfolded protein response (UPR) in mitochondria and endoplasmic reticulum (ER) • Increased proteasome activity (Senescence-associated protein degradation, SAPD) • Decreased autophagy • Increased translation of IL-1 through activation of MK2	2–4,291,318
Altered lipid metabolism • Upregulation of FAO beta oxidation • Increased cytosolic PUFAs, fatty acids (lipid droplets)	3
Altered secretome • Nucleic acid secretion (leakage mtDNA) • Protein factors (cytokines, chemokines, growth factors, enzymes) • Metabolites (carnitine, LDL) • Extracellular vesicle secretion	4,292,311,319

2.1.3 | Senescence-associated secretory phenotype (SASP)

Inflammasome and IL-1β signaling are among the most common triggers that stimulate senescent cells to secrete a large and heterogeneous body of inflammatory factors, collectively known as SASP; in addition, some SASP factors themselves may function as DAMPs. NF-κB controls the SASP as many components are NF-κB target genes[39] and increased NF-κB phosphorylation has been detected in senescent cells of different origin.[39–43] An increase in secretory activity is driven by the high NAD+/NADH ratio produced by the high mobility group A proteins (HMGA)-nicotinamide phosphoribosyltransferase (NAMPT) axis, along with increased glycolysis and mitochondrial respiration. SASP factors in turn alter NAD+ metabolism and stimulate the expression on immune cells of CD38, a NADase which leads to NAD+ reduction.[44]

Sirtuins. Nuclear and mitochondrial sirtuins (SIRT) are NAD+-dependent deacetylases that play a fundamental role in DNA damage response, chromatin remodeling, transcription, metabolism, and mitochondrial biogenesis.[45–54] SIRT proteins also maintain energy homeostasis in response to both nutrient deprivation and energy expenditure by inhibiting adipogenesis and promoting lipolysis. A reduced NAD+/NADP+ ratio suppresses sirtuins. As a consequence, sirtuins ability to inactivate NLRP3 inflammasome and NFκB activation is hampered.[46] Hence, the reduction of sirtuins, with its related metabolic alterations, is a major characteristic in senescent cells and associated with the SASP phenotype.

2.1.4 | Oxidative stress

In homeostasis, controlled production of reactive oxygen species (ROS) functions as an important regulator of immune and structural cell differentiation, senescence, and apoptosis. Alterations in cellular redox status by chronic increase in ROS burden, as occurs in chronic inflammatory diseases,[55] contributes to accelerated senescence through altered redox-responsive gene regulation, signal transduction, and genomic stability. Altered ROS also affects also protein conformation, altering their function through loss of catalytic activities, protein–protein and protein-DNA or RNA interactions, or affecting protein transport and catabolism.[56,57]

2.2 | Senescence-related metabolic alterations in cell players in allergy and lung diseases

The occurrence of cell senescence is particularly common in keratinocytes and adipocytes, but also affects mesenchymal, immune (T cells, B cells, and NK cells), endothelial, epithelial, bone, and muscle cells.[58–60] Clearance of senescent cells have been particularly identified in macrophages, but is also described in NK cells, cytotoxic T cells and neutrophils. Mesenchymal stem cells are generally described as displaying a mostly anti-inflammatory phenotype,[61] but are programed toward a pro-tumorogenic, inflammatory phenotype that contributes to immunosenescence under hypoxic conditions and in nutrient-deficient environments.[62] Metabolic changes in immune cells have been increasingly characterized and thoroughly reviewed recently.[3,12,63–66] Herewith are briefly described the main metabolic changes related to senescence identified in macrophages (Figure 2), as well as in B cells and T cells (Figures 3 and 4) to represent innate and adaptive responses, respectively.

2.2.1 | Energy metabolism in cell senescence affects macrophage polarization and inflammatory response

Activation, polarization, and energy metabolism are closely related to macrophages' inflammatory function.[12,67,68] A vast heterogeneity in macrophage phenotypes is comprised between two distinct phenotypes with different metabolic patterns: the pro-inflammatory, glycolytic M1-macrophages and the anti-inflammatory, pro-resolving oxidative M2 macrophages (Figure 2). Inflammatory M1 macrophages can be distinguished metabolically from M2 macrophages as they meet their acute energy demand—in a usually hypoxic environment—by glycolysis. In this setting, hypoxia-inducible factor 1 alpha (HIF-1a) is stabilized

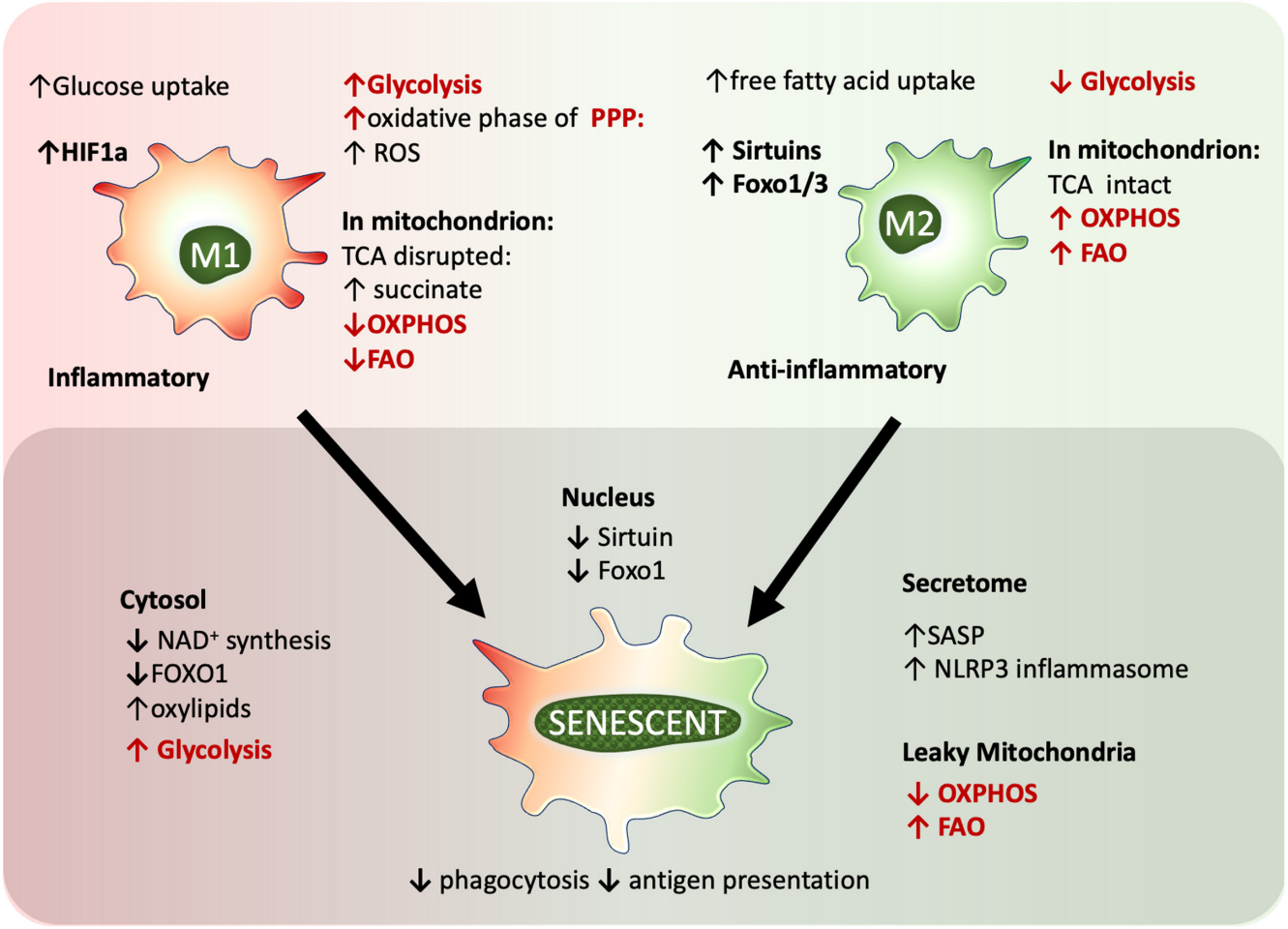

FIGURE 2 Main features of cellular senescence and related metabolic alterations in macrophages. M1 macrophages can be overall described as glycolytic compared to the oxidative M2 macrophages.[393] In M1 macrophages, AKT activity promotes glucose uptake and activates glycolysis and lipid biosynthesis via upregulation of HIF1—as inflamed site are usually characterized by low oxygen levels. In addition, OXPHOS is inhibited and M1 macrophages display an iron retention phenotype. In contrast, in M2 macrophages sirtuins promote OXPHOS and FAO and inhibit glucose uptake and glycolysis. In senescent M2 macrophages, the accumulation of leaky mitochondria disrupts ATP generation, shifting M2 macrophages toward a more pro-inflammatory phenotype, where energy is provided by anaerobic glycolysis. Also the function of M1 macrophages is compromised upon senescence, with lysosomal leakage of lipids, trace elements into the cytosol leading to a reduced phagocytosis and microbicidal capacities, an ineffective mounting of an immune response despite the presence of a constant basal inflammatory activity.

by succinate, which accumulates in M1 cells from the disrupted TCA cycle, which leads to the transcription of glycolytic genes, for example, the glucose transporter Glut1,[69] and is responsible for sustaining the production of pro-inflammatory cytokines.[69] As such, inhibition of glycolysis inhibits HIF-1α-mediated responses and an M1- phenotype with pro-inflammatory cytokines.[70] Conversely, anti-inflammatory M2-macrophages rely predominantly on aerobic respiration via OXPHOS as an ATP source[68] and usually also of fatty acid oxidation (FAO),[64,68,71–74] though for FAO the precise contribution in the M2 metabolism is still debated.[68,75] Interestingly, M1 and M2 macrophages have also distinct fatty acid and eicosanoid profile, which may depend on or activate distinct metabolic reprogramming. M1 macrophages produce higher amounts of prostaglandins (PGE_2/PGD_2) and lower anti-inflammatory lipoxins (LXA4) after stimulation than M2 macrophages.[76,77]

The canonical decline in NAD+ occurring due to the senescence process has been well documented in murine and human macrophages, in vitro and in vivo.[78–84] With aging, decreased NAD+ in murine macrophages goes along with the decline in sirtuins (e.g., SIRT2) and an increased inflammatory phenotype,[46] with NLRP3 inflammasome assembly[78,84,85] and more ER stress.[86] The NAD^+-dependent SIRT1 inhibits NF-κB-mediated inflammation in human epithelial cells,[87] with a recent study identifying a role for CD9 and CD81 in maintaining SIRT1 activity and protecting macrophages from aged-induced inflammation.[88] Sirtuin 1 and AMPK stimulate peroxisome proliferator-activated receptor gamma coactivator-1 (PGC-1) and drive M2 polarization and mitochondrial function,[65] with its activity being linked to longevity.[65,89] Supplementing NAD with nicotinamide mononucleotide

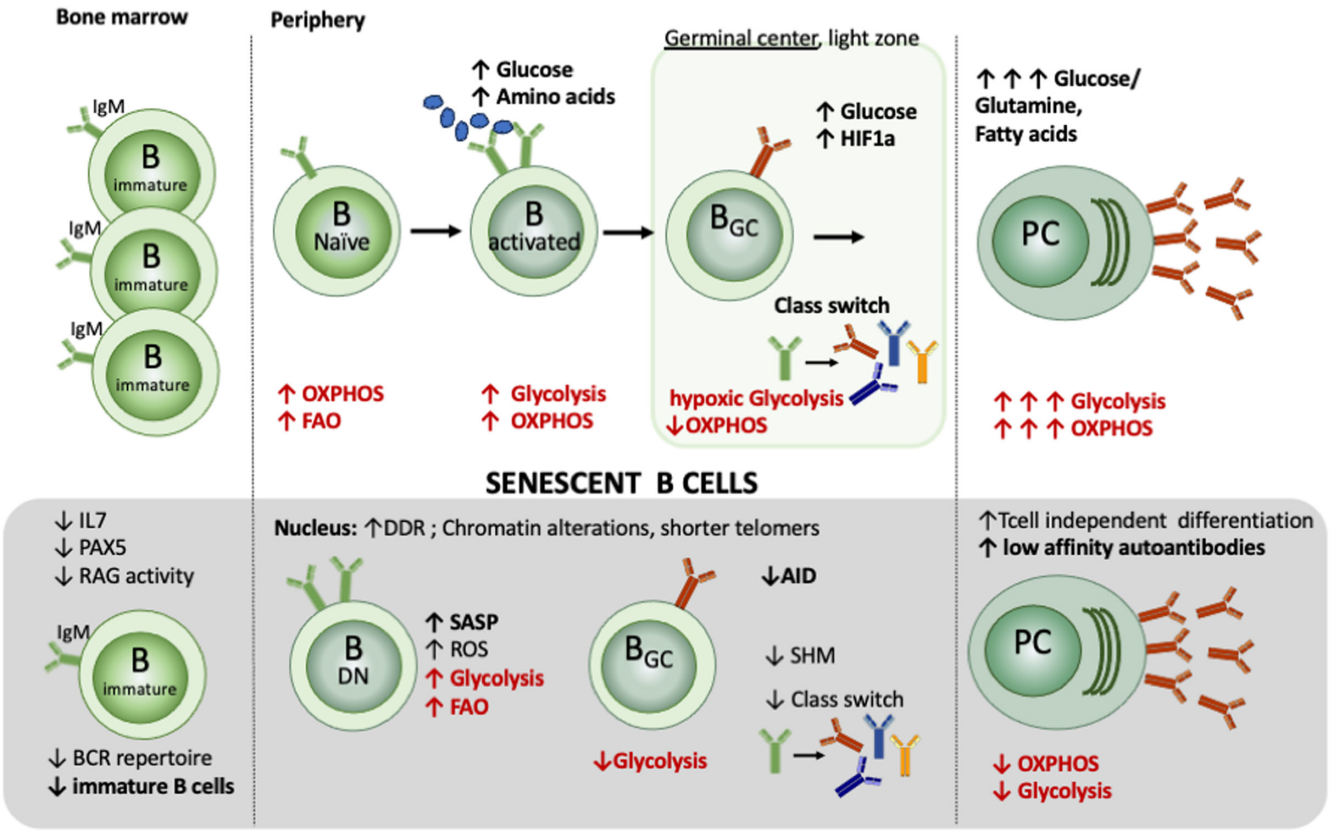

FIGURE 3 Metabolism and main alterations in B cells upon senescence. The metabolic activity of B cells changes during the different development and maturation stages. Upon antigen stimulation, B cells fuel their energy requirements by aerobic glycolysis and importing glucose and amino acids. Once they migrate in the germinal centers, they pass from the normoxic dark zone, in which FAO and aerobic glycolysis prevails to the light zone. The light zone is hypoxic, consequently B-cell metabolism switches to anaerobic glycolysis and undergo class switch and somatic hypermutation. Particularly, plasma cells due to their antibody synthesis have a very high nutritional demand, with the specific nutrient uptake (glucose, glutamine, fatty acids) associated with specific antibody classes. With aging of the B cells, the output of B cells from the bone marrow declines partly due to IL7. Also, the transcription factor PAX5 is decreased leading to reduced recombination by RAGs and a reduced BCR repertoire. In the periphery, the characteristic alterations of senescent cells become evident with a higher frequency of pro-inflammatory double-negative B cells (B_{DN}) releasing inflammatory cytokines (SASP) and increased ROS and showing chromatin alterations. In the light zone of the germinal center, AID activity is reduced resulting in a decreased ability for somatic hypermutation and class switch, meaning that the ability to produce high-affinity antibodies is impaired in senescent B cells. As also class-switch is compromised, aged B cells have also lower ability to combat pathogens effectively, while simultaneously due to SASP more (in a T-cell independent manner) of autoantibodies are produced (with low-affinity antibodies and of the same class).

(NMN) has been reported to counteract metabolic defects in aging macrophages.[90]

Senescence also leads to mitochondrial dysfunction affecting OXPHOS and drives the senescent-associated inflammatory phenotype in macrophages, which cannot be reprogramed into an anti-inflammatory phenotype due to the dysfunctional mitochondria.[68] Aging macrophages also show a reduced phagocytosis and antigen presentation capacity.

Further potential targets to counteract macrophage immune senescence are the transcription factors FOXO1 and FOXO3. FOXO1 regulates gluconeogenesis and glycogenolysis by insulin signaling and both FOXO1 and 3 are regulators during starvation or oxidative stress.[71,91,92] FOXO1 is upregulated in M2 macrophages[93] and its activity is linked to a prolonged life span.[70,91,94] In contrast, its expression is reduced in senescent cells.[66,94–96]

2.2.2 | Metabolic alterations and senescence affecting B cells

The cellular metabolism and nutritional requirements of B cells change during development and also, significantly, with age[97] (Figure 3). Profound changes occur in aging B cells already in the bone marrow, with limited IL7 availability[98] and decreased PAX5 expression, which reduce the overall production of B cells.[99] Reduced PAX5 also leads to lower activity of the recombination-activating genes (RAG),[100] resulting in an overall reduced BCR repertoire[101,102] and lower output of mature B cells.[103] Simultaneously, there is an increase in frequency of pro-inflammatory B cells, named age-associated B cells in mice[104] and corresponding to double-negative (DN) B cells in humans,[105,106] which release high amounts of TNF-α.[107,108] The DN B cells are considered to be

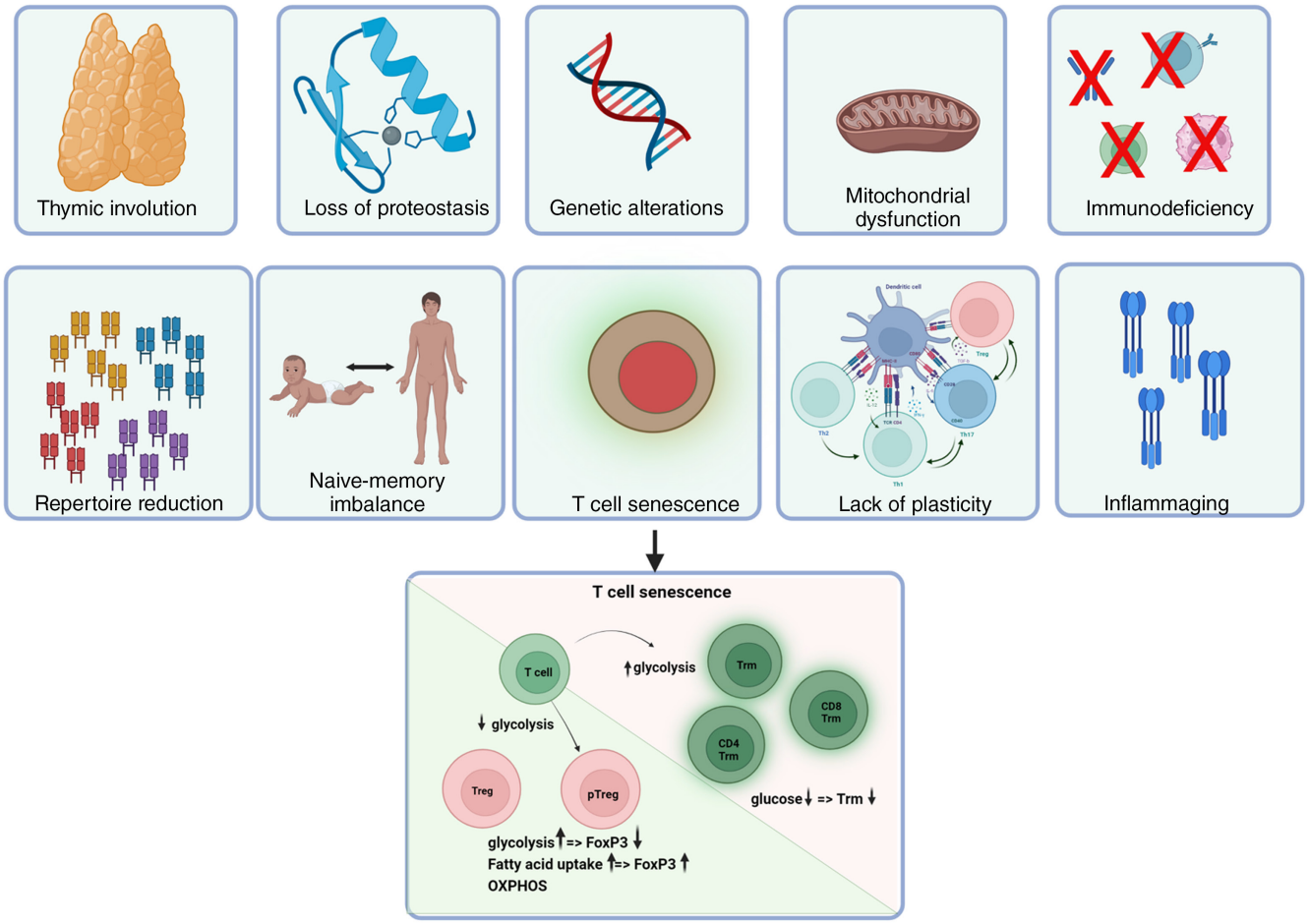

FIGURE 4 Mechanisms in T-cell aging, including senescence. During T-cell aging, many T-cell functions become impaired. Due to inflammation, or in tumor microenvironments, these processes can be initiated even independent of the aging process. This is most dramatically demonstrated by metabolic alterations causing differential effects on regulatory T cells (Treg) versus effector T cells, mostly in the tissue-resident memory T cells (Trm). Created with BioRender.com. Part of figure adapted from Mittelbrunn M et al[394]; Gerriets VA et al.[395]; and Wang H et al.[396]

the most pro-inflammatory B-cell subset, releasing autoantibodies.[97,109,110] They are expanded with age in both mice and humans as a result of chronic inflammation[111] and have been compared to exhausted B cells due to their lack of response to BCR stimulation.[112] They have a senescent phenotype with sustained AMPK and sestrin activity, showing increased glycolysis and fatty acid oxidation.[113]

Upon senescence, in the germinal center (GC) of the peripheral lymph organs there is also a decrease in levels of Activation-induced cytidine deaminase (AID),[114] which is a key protein initiating class-switch recombination (CSR)[115] and somatic hypermutation (SHM) of B cells. Consequently, also the generation of high-affinity antibodies is impaired. The CSR and SHM effects occur in GCs in response to both T cell-dependent and T cell-independent stimuli. Thus, upon senescence there is an increased amount of low-affinity antibodies that lack specificity, leading to a general weaker and inefficient antibody response to vaccination and infections.

2.2.3 | Metabolic alterations and senescence affecting adaptive/Treg response

The cellular metabolism of T cells not only meets the energetic demands of each T cell but also provides critical substrates for their development and function. Among metabolic pathways to T-cell differentiation and function, particularly relevant appear those involving glycolysis and mitochondria,[116,117] lipid and cholesterol synthesis,[89,117,118] mTOR pathway,[116–118] enzymes involved in the cellular redox balance,[119] and pathways related to amino acids (including glutamine and serine).[118,119]

In immune-related pathologies such as inflammatory skin and lung diseases, a central role is played by regulatory T cells (Treg) and tissue-resident memory T cells (TRM).[12] Treg subsets, most of which express the transcription factor Foxp3, are important for maintaining homeostasis. In particular, during inflammation and allergy, activated conventional CD4+ T cells differentiate in peripherally derived Treg (pTreg) and contribute to the resolution of immune

responses. Tregs have metabolic requirements distinct from the other T cells.[120] Mice with T cells lacking phosphatase and tensin homolog (PTEN), a tumor suppressor and metabolic regulator,[121] develop an auto-immune lymphoproliferative disease[122,123]; PTEN-deficient Tregs display elevated glycolytic activity, which correlates with the loss of Foxp3 stability and functional capacity. Along the same lines, inhibition of serine/threonine kinase Akt enhances Treg differentiation,[124] as phosphatidylinositol 3-kinase (PI3K)-AKT signaling broadly controls cellular metabolism through activation of transcription factors, nutrient transporters, and metabolic enzymes.[125] Forced expression of Foxp3 suppresses glycolysis-related genes while inducing expression of genes associated with lipid and oxidative metabolism, the latter of which is required for their maximal suppressive ability[126] (Figure 4). The utilization of OXPHOS is presumed to be dependent on FAO.[127] However, the picture is not so clear considering that in human Tregs, glycolysis ensures the maintenance of the enzyme enolase-1 and is tightly linked to suppressive activity.[128] It remains unclear whether proliferation and suppression in Tregs are invariably mutually exclusive or exceptions to this dichotomy exist in specific Treg subsets.[117]

TRM represent a relevant T-cell subset, considering that an adult human being holds about twice T cells in the skin than in the entire blood volume.[129,130] In immune-related diseases, TRM may be inappropriately and chronically activated in the tissue/organ in which the disease is observed. For example, in experimental allergic inflammation induced by repetitive house dust mite exposure, the Th2 TRM present in the lungs of mice are pathogenetic.[131] Interestingly, it has been demonstrated that allergen-specific CD4+ T cells can survive for over 70 days in the lung[132] and it is thought that they are nearly impossible to dislodge from their tissue sites of residence, so that they may be responsible for recurrence after treatment. Skin CD8+ TRM utilize lipid metabolism of exogenous free fatty acids (FFAs) internalized by overexpressing molecules [such as fatty acid-binding proteins 4 and 5 (Fabp4/5), CD36, and lipoprotein lipase (LPL] facilitating exogenous FFAs acquisition and metabolism.[133–135] The senescence environment provokes the accumulation of malfunctional CD8+ TRM in the lung, as suggested by the severe morbidity in elderly COVID-19 patients.[136] The mTOR pathway also may be involved in TRM differentiation.[137] The uniqueness of TRM in their dependence on lipid metabolism of FFAs from the external environment could be exploited therapeutically.[138,139]

With further clarification of the links between metabolism and function of relevant T-cell subsets, it may become possible to modulate metabolic pathways to facilitate T-cell development and activation. Thus, a better understanding of metabolic pathway regulation in T cells may offer novel opportunities to improve immunotherapies for a broad spectrum of inflammatory disorders, including asthma, COPD, and atopic diseases.

In view of such complexity, a more coherent understanding of energy metabolism as determinant of senescence will likely emerge by integration of multiple omics data and using functional genomics. This will enable tracking of how key "omic" factors related to cell metabolism, in both immune and structural cells, change with aging.[1,140–142]

3 | CLINICAL DATA. ALTERED METABOLISM IN SENESCENCE: FOCUS ON ASTHMA AND COPD

3.1 | Senescence-related metabolic alterations in asthma

The main hallmarks of cell senescence and related metabolic changes identified in asthma are listed in Table 3.

3.1.1 | Metabolic alterations in innate immunity in asthma

Studies in this area for asthma are relatively limited and generally focused on non-eosinophilic phenotype. Mitochondrial dysfunction, oxidative stress, and epigenetic changes[143] have been chiefly implicated.[12,144] Non-eosinophilic asthma can be characterized by airway neutrophil, alveolar macrophages, and decreased Th2-cells which all share hallmarks of senescence such as telomere shortening, genomic instability, epigenetic changes, increased protein misfolding, mitochondrial dysfunction, and dysregulated nutrient sensing.[23,91,145,146] These innate immune cell changes are characterized by increased intracellular PI3K signaling and reduced histone deacetylase 2 (HDAC2) activity, leading to reduced sensitivity to the anti-inflammatory effects of glucocorticoids.[147–151] PI3K signaling is further activated by ROS[145] derived from neutrophils and by neutrophil extracellular traps (NETs).[152] Oxidative stress impairs mitochondrial function leading to increased glycolysis and OXPHOS suppression, which is linked to increased NLRP3 inflammasome activation,[14,63] pro-inflammatory mediator release[153] and to altered killing and phagocytic capacity. Moreover, increased ROS correlated with impaired autophagy, although the link with cellular senescence in asthma is unclear.[14,63] Thus, in this setting senescent innate immune cells engage in a vicious circle of SASP activation, NLRP3 activation, and pro-inflammatory mediator release. While T2 asthma is characterized by increased alveolar macrophages with M2 polarization, M1 polarization is present in non-eosinophilic asthma and severe asthma associated with enhanced pro-inflammatory mediator release, including cytokines, reactive nitrogen species (RNS), and specific profile of eicosanoids.[76,154,155]

3.1.2 | Asthma studies

Asthma in elderly is generally characterized by an increase in sputum neutrophils, lower airway caliber variability, and air trapping.[156] Lung tissues from elderly asthmatics have an increased expression of multiple senescent markers such as phospho-p53 and p21, and they show greater airway fibrosis compared with age-matched elderly persons without asthma and young age controls.[157] In patients with stable and oral corticosteroid (OCS)-independent asthma, urinary metabotype is characterized by reduced carnitine expression and in

TABLE 3 Hallmarks of senescence and related metabolic features in T2 and non-eosinophilic asthma. Refer to glossary for acronym description.

Senescence features and metabolic components		Ref
• Genomic and epigenetic alterations: • Leaky lysosomes • Leaky mitochondria • Dysbalance of the cytosolic content • Dysfunctional proteolysis • SASP	Telomere shortening, increased DDR, PARP1 activation, apoptosis resistance • Defective nutrient sensing: decreased NAD+, loss of sirtuin • Decreased OXPHOS, increased glycolysis and FAO • Decreased UPR^{mt} • Decreased autophagy • Increased NLRP3 inflammasome: IL1β, IL6, IL17, IL18, TNFα, TSLP	65,66,74,80–84,88,117,126,133,143,153,198,202,225,302
Glucocorticoid resistance • Increased PI3K signaling leading to HDAC2 inhibition, glucocorticoid resistance • Glucocorticoid treatment associated with anemia, adrenal suppression and fatigue (T2 asthma) • Decreased steroid metabolites in T2 asthma • Decreased leucocyte redistribution		147–150,152,165,167,272,320
Immune senescence hallmarks in asthma associated with metabolic alterations		
Neutrophils		
• Numbers increased • Reduced chemotaxis • Reduced phagocytosis • Impaired intracellular killing	• Decreased release of cytokines and granules • Reduced NET formation • Elevated PI3K signaling • Decreased TLR1 signaling	145,147,148,150,152
Monocytes/macrophages		
• Increased number • Inflammatory macrophage phenotype in T2 asthma	• Pro-inflammatory signature: increased basal cytokine production, decreased efficiency against infecting pathogens • M1 phenotype due to increased RNS NO radicals in non-eosinophilic asthma, IL1ß, TNFα	76,145,147,148,150,152,15572,74,75,77,79
Bronchial epithelial cells		113,115,116,118,120
• Reduced OXPHOS metabolites	• Higher levels of genes in fatty acid metabolism pathway correlated with asthma severity • Elevated phosphatidylcholines, lysophosphatidylcholine and bis- (monoacylglycerol)phosphate lipids	95

those with severe asthma by the carnitine transporter SLC22A5.[158] Carnitine aids transport of fatty acids into the mitochondrial matrix, enabling energy to be generated from fat reserves. Bronchial smooth muscle (BSM) cells from asthmatic patients had increased mitochondrial respiration and beta oxidation due to increased fatty acid consumption.[159] Increased fatty acid consumption was linked to increased expression of low-density lipoprotein (LDL) receptor and carnitine palmitoyl transferase (CPT)2, which enhance fatty acid cell and mitochondrial import.[159]

Analysis of transcriptomic databases of bronchial biopsies from U-BIOPRED and the Australian NOVocastrian Asthma cohorts identified 36 common significantly differentially expressed genes and four common pathways.[160] These genes and pathways were associated with tissue remodeling/repair including SUMOylation, NRF2 pathway, and oxidative stress pathways.

Higher levels of glutathione-S-transferase P (GSTP) and of pyruvate kinase M2 (PKM2) have been reported in the sputum of asthmatics compared to healthy controls and correlate with increased glycolysis.[161] Pharmacological and genetic suppression of GSTP attenuates house dust mite (HDM)-induced airway remodeling and airway hyperresponsiveness (AHR) and restored normal glycolysis levels.

Asthma treatments, level of asthma control, and severity of the disease significantly affect central metabolism and cellular immunometabolism. Severe uncontrolled patients with asthma as well as patients treated with inhaled corticosteroids have unique serum metabolic fingerprints with upregulation of lysophosphocholines (LPC), lysophosphoethanolamines (LPE), lysophosphatidylinositols (LPI), leucine, arginine, arachidonic acid, sphingosine-1-phosphate (S1P), and retinol in uncontrolled asthma.[162] Galectin-3 is an immunomodulatory factor[163] and high expression of galectin-3 in bronchial biopsies from severe asthmatic patients predicted a good response to omalizumab therapy after 3 years, and it is also associated with significantly reduced airway remodeling.[164] Both inhaled CS (ICS) and OCS therapy have dose-dependent effects on metabolite profiles.[165] The levels of 17-steroid metabolites in plasma were significantly reduced in asthma, but differences in metabolic profiles were not studied in relation to airway remodeling. The differences in circulating metabolites might further reflect the behavior and immune functions of circulating cells, as their energy needs might be not met in the changed environment.[166] Various populations of peripheral leukocytes including T cells, B cells, eosinophils, and neutrophils respond differently to intravenous treatment with corticosteroids in severe asthma patients with corticosteroid resistance.[167]

Bronchial epithelial cell (BEC) transcriptomic analysis showed significant suppression of OXPHOS genes and increases in fatty acid metabolism pathway genes with increasing asthma severity.[168] Furthermore, metabolomic and lipidomic analysis of cultured BECs from severe asthma patients confirmed elevated levels of phosphatidylcholines, lysophosphatidylcholine, and bis(monoacylglycerol) phosphate lipids with reduced OXPHOS metabolites. Bronchial thermoplasty resulted in significantly increased OXPHOS pathway and decreased fatty acid metabolism genes in BECs.[168] The distribution of saturated and unsaturated fatty acids is dysregulated in serum of patients with asthma, and the expression of stearoyl-coenzyme A desaturase (SCD) enzyme is decreased in human BECs and in the lungs of mice with OVA and HDM-induced asthma.[169]

Furthermore, reduced blood levels of ceramides and sphingomyelins at 6 months of age predicted a greater risk of developing asthma before age 3.[170] In another study, there were significantly higher serum levels of methionine, glutamine, histidine, and succinate in asthma compared to healthy controls.[171] The succinate receptor (SUCNR1) is highly expressed on human mast cells, and pretreatment with succinate enhances IgE-mediated human mast cell activation and antigen-induced airway contraction.[172] The expression of itaconate, a mitochondrial metabolite with antimicrobial and anti-inflammatory functions that accumulates when the Krebs cycle is disrupted, is upregulated in murine models of asthma[173] where it suppresses both pro-inflammatory (M1) and alternatively activated (M2) macrophages.[174] The effect on M2 macrophages is through suppression of Janus kinase (JAK)1 activity.[174] Patients with asthma have also specific eicosanoid profile.[175,176]

3.2 | Senescence-related metabolic alterations in COPD

The main hallmarks of cell senescence and related metabolic changes found in COPD are listed in Table 4.

3.2.1 | Metabolic alterations in innate immunity for COPD

COPD is a slow-progressing disease mostly in elderly patients.[23] Impaired innate immune cell activation in COPD is correlated to their altered metabolism induced by an increased oxidative stress.[11,177] Macrophages accumulate in the lower airways with a prevalent iNOS+ M1-phenotype which is pro-inflammatory, but in some patients dual positive-M1-M2-type (arginase+) macrophages, which are more anti-inflammatory, are abundant too.[178] Lung macrophages of COPD patients have a typical signature of senescent cells, with reduced phagocytosis and bactericidal capacities (that facilitate lower airways colonization by bacteria), reduced clearance (efferocytosis) of senescent and apoptotic cells, reduced autophagy activation (including mitophagy), mitochondrial dysfunction (contributing to increasing endogenous oxidative stress), and increased SASP. Furthermore, activation of the cellular energy sensor, AMPK, decreases glycolysis and the production of pro-inflammatory cytokines, such as interleukin-6.[179] Metformin activates AMPK and in animal models decreases lung inflammation, airspace enlargement, and small airway remodeling. Metformin use over 5 years in the COPD Gene cohort was associated with reduced progression of pulmonary emphysema.[180] Moreover, COPD macrophages release greater levels of elastolytic proteases (e.g., MMP-12).[181] Their accumulation of iron (trapped intracellularly as bound to ferritin) and lipids may further facilitate oxidative damage and lower airways inflammation.[182–184]

Neutrophils also accumulate in the lower airways of COPD patients and show signs of senescence with decreased phagocytosis and bacterial killing, chemotaxis and apoptosis (thus with longer survival) and increased release of elastolytic proteases.[185] The cells display a diminished glycolytic activity, lower lactate levels, a diminished capacity to utilize glutamine for gluconeogenesis with significantly lower ATP levels and impaired NADH generation.[186] Mediators in serum from COPD patients but not healthy controls are also able to induce the expression of cellular senescence marker in human bronchial epithelial cells such as senescence-associated β-galactosidase (SA-β-Gal) and p21.[187]

3.2.2 | COPD studies

Airway smooth muscle cells (ASMCs) from COPD patients have abnormal mitochondrial function with increased mitochondrial synthesis, release of oxidants, and enhanced levels of the glycolytic product lactate, glutamine, fatty acids, and amino acids metabolism, along with hyperproliferation and alterations in morphology.[188,189] Dysregulated amino acid metabolism, energy production pathway, and lipid metabolism are detectable also in lung tissues, likely contributing to the pathogenesis of COPD.[190]

In primary human ASMCs, overexpression of Hedgehog interacting protein (HHIP)1, a gene for which polymorphisms are associated with COPD risk by GWAS, attenuates their glycolysis, proliferation, and cell metabolic reprogramming via modulation of pyruvate kinase M1/2 (PKM2) activity.[191] PKM2 is linked to epithelial-to-mesenchymal cell transition (EMT) in COPD.[13] Cigarette smoke-enhanced lung PKM2 expression correlated with induced EMT and EMT changes was abolished by the PKM2 inhibitor shikonin.[13] Cigarette smoke also induced PKM2 expression in BEAS-2B bronchial epithelial cells and PKM2 knockdown attenuated smoke-enhanced expression of N- and E-cadherin mRNAs, and reduced CS-induced mitophagy.[13] Lower airways epithelium, including alveolar cells, of COPD patients also show a SASP phenotype and mitochondrial dysfunction.[12,120] Epithelial cell and macrophage senescence is important in COPD pathophysiology and in systemic disease, via release of airway epithelial cell-derived senescence factor-containing microvesicles.[11,192] In addition, COPD lungs are characterized by three variant distal airway progenitor cells (which are minor constituents of healthy smoker control subjects and fetal lungs and may contribute to the

TABLE 4 Hallmarks of senescence and associated metabolic features in COPD.

Senescence features and metabolic components		Refs
• Genomic and epigenic alterations: • Leaky lysosomes • Leaky mitochondria • Dysbalance of the cytosolic content • Dysfunctional proteolysis • SASP:	Epigenetic changes, telomere shortening, increased DDR, apoptosis resistance • Defective nutrient sensing: increased cytoplasmic lipids, metals, sugars leading to increased ROS/RNS • Decreased NAD+ and loss of sirtuin function • Decreased OXPHOS, increased AMPK, glycolysis and FAO, decreased SOD • Decreased UPR^{mt}, decreased autophagy • Increased NLRP3 inflammasome: IL1β, IL6, TNFα, Activation of JAK/STATs, MAPKs, RAS/PI3K/Akt-mTOR • Increased proteases (neutrophil elastase and MMPs) • Increased extracellular vesicles and/or change in content	3,19,52,64,299,315,321–333
Immune senescence hallmarks related to metabolic alterations in COPD		
• Increased basal activity despite reduced cytotoxicity/killing capacity[281]		
Neutrophils		
• Numbers increased • Reduced chemotaxis • Reduced NET formation • Elevated PI3K signaling	• Reduced phagocytosis, impaired intracellular killing • Reduced glycolysis and glycogenesis upon stimuli • Reduced release of cytokines and granules • Decreased TLR1 signaling	150,186,192,334
Monocytes/macrophages		
• Numbers increased • Reduced TLR1/2/4/7/8 signaling • Increased levels of MMPs	• Increased basal cytokine production • Decreased efficiency against infecting pathogens • Inflammatory macrophages due to increased RNS NO radicals, IL1ß, TNFα, IL6	46,177,325,335,336
Bronchial epithelial cells		
• Epithelial mesenchymal transition, foci of preneoplasia • Epithelial barrier damage with decreased tight junction proteins, • Stem cells exhaustion • Reduced OXPHOS • Increased SASP signature	• Elevated phosphatidylcholines, lysophosphatidylcholines and bis (monoacylglycerol)phosphate lipids • Higher levels of fatty acid metabolism pathway genes correlated with asthma severity • Increased TLR4 and MUC5AC/MUC5B expression • Increased microRNA-34a, miR-21, miR-494-3p and miR-570-3p expression • Increased HSP60 expression • Reduced polymeric Ig receptor (pIgR) and secretory IgA	335,337–342
Smooth muscle cells of the lower airways and pulmonary arteries		
• Increased proliferation • Cell hypertrophy	• Increased SASP signature • Increased ↑miR-101–3p and decreased ↓miR126 expression	299,323,332,343–345
Endothelial cells of the pulmonary arteries and lung capillaries		
• Defective angiogenesis • Increased SASP signature	• Blood stem cell progenitors exhaustion • Increased miR-181b-3p, miR-429 and miR-23c expression	198,345,346
Lung fibroblast		
• SASP signature • Dysfunctional mitochondria	• Reduced OXPHOS, reduced PGE2 receptor PTGERA4 • Increased 27-hydroxycholesterol	199,202,204,206–208

immune surveillance) epigenetically committed to distinct metaplastic lesions. When transplanted to immunodeficient mice, these variant clones induced pathology akin to the mucous and squamous metaplasia, neutrophilic inflammation, and fibrosis as seen in COPD.[193,194] Skeletal muscle from COPD patients also demonstrate mitochondrial dysfunction (due to changes in their succinate dehydrogenase subunit C) compared to healthy controls.[195–197] Inhaled corticosteroids reduce senescent endothelial progenitor cell numbers in COPD;[198] however, the impact of corticosteroids on senescence needs further investigation in this context.

Repeated exposure of lung fibroblasts to cigarette smoke induces senescence,[199] regulated by anti-aging and anti-oxidant molecules such as Klotho.[200,201] Long-term exposure to cigarette smoke is essential for this effect, as senescent fibroblasts are seen in the lung, but not skin, of emphysema patients.[202] Lung fibroblast senescence correlates with disease severity[203,204] and is prevented by mitochondrial anti-oxidants in vitro.[205] Enhanced matrix stiffness seen in disease may also affect fibroblast senescence and the release of functional SASP.[206] Elevated 27-hydroxycholesterol (27-OHC) levels seen in COPD airways enhance fibroblast senescence via the prostaglandin E2 (PGE2) pathway.[207] Activators of the PGE2 receptor (EP4) reversed senescence of alveolar organoids.[208] Subtypes of airway structural cells may be more susceptible to senescence than immune cells.[209] Changes in pulmonary tissues pH as a result of inflammation and calcifications could also contribute to COPD pathogenesis.[210]

Bronchoalveolar lavage (BAL) fluid and plasma metabolomics data from a COPD cohort have shown 792 metabolites in BAL and

2 in plasma associated with the degree of emphysema.[211] Using multi-omics analysis combining blood proteomic and metabolomic data, a network of 13 proteins and 10 metabolites was significantly correlated with emphysema.[203,212] Furthermore, by integrating peripheral blood mononuclear cells (PBMC) transcriptomics and plasma metabolomics, the degree of airflow obstruction and the number and severity of COPD exacerbations were associated with glycerophospholipid and sphingolipid metabolism.[213] Pairing metabolomic and microbiome results from a COPD cohort indicated that lower lung function, or greater symptoms were linked to colonization with *Veillonella*, *Streptococcus*, and *Neisseria*. Lower lung function was also linked to glycosphingolipids, glycerophospholipids, polyamines, and xanthine. In contrast, colonization with *Prevotella*, along with adenosine, 5′-methylthioadenosine, sialic acid, tyrosine, and glutathione correlated with better lung function and fewer symptoms.[214]

Analyzing the metabolites as groups or clusters rather than as single entities or pathways may help to understand better the role of the immunometabolism in COPD.[215] However, using 129 plasma metabolites to generate a metabolomic severity score (metSS) no specific metabolic pathways were associated with the degree of pulmonary emphysema.[215,216]

Instead of linking metabolomic data and metabolic pathways in a COPD cohort, 17 metabolic pathways (including ABC transporters, β-alanine metabolism, neuroactive ligand–receptor interaction pathway, glycine, serine, threonine, and histidine metabolism) were associated with the degree of pulmonary emphysema.[217] Protein–protein interaction pathway analysis in COPD highlighted the potential role of immunomodulatory pathways—including glucose transport, regulation of lipid metabolism and oxidative stress—as being common to both asthma and COPD.[218] Many studies using urine, serum, plasma, and sputum metabolomics and lipidomics have been able to differentiate COPD patients from controls. Urinary metabolomics profiles of 86 metabolites may distinguish asthma from COPD.[219] In addition, 23 serum metabolites, including myoinositol, glycerophosphoinositol, fumarate, cysteine sulfonic acid, and a modified version of fibrinogen peptide B (mFBP), are able to discriminate COPD from controls.[220]

A profile of 50 serum lipid metabolites, including phospholipids, sphingolipids, glycerophospholipid, and cholesterol esters, can distinguish COPD from healthy subjects: COPD can be considered a systemic hypometabolic state with reduced levels of N-acetylglycoprotein, lipoprotein, polyunsaturated fatty acid (pUFA), and lactate but with increased levels of diacylglycerols, branched chain amino acids, palmitoleic, oleic and linoleic acids.[221–228]

Females with non-severe COPD have less pulmonary emphysema but more small airways disease than males, but this difference disappears as lung function decreases. How sex-related metabotypes may affect airway remodeling is unknown, but there is evidence for sex-related differences in the metabolites lysoPA (16:0) and lysoPA (18:2) in COPD.[229] In COPD cohorts, acyl carnitines and phosphatidylethanolamines are more abundant in women while sphingomyelins are higher in men.[230]

4 | IMMUNOPHARMACOLOGY: SHIFTING METABOLIC DEMANDS TO ANTAGONIZE CELL SENESCENCE

4.1 | Senescence-related metabolic targets and therapeutic approaches

Senescence is intricately linked with metabolism and inflammation. Therefore, strategies that impact metabolism and/or inflammation could in theory influence the accumulation or properties of senescent cells.[3] Interventions focused on lifestyle include dietary modification and regular exercise. Dietary effects may be mediated in part via microbiota metabolism, and specifically designed consortia of microbes can be deliberately targeted to replace microbes that are lost with age.[231,232] In addition, drugs that selectively kill senescent cells (senolytics) or drugs that prevent the senescence growth arrest (e.g., statins) are being explored.[233,234] Lastly, it is not known whether the use of biologics to successfully control chronic inflammatory responses might also diminish the senescence march in the long term.

4.1.1 | Approach by non-pharmacological interventions

Slowing down and even prevention of the complex processes of immunosenescence by various non-pharmacological interventions and strategies, especially in the context a "healthy lifestyle," has been extensively discussed and studied for many years. Non-pharmacological strategies against immunosenescence include physical activity and sporting activities, dietary interventions (e.g., vitamins, minerals, polyunsaturated fatty acids, and anti-oxidants), modulation of the gut microbiome, sleep (quality), and relaxation. However, real evidence and clear recommendations about the "dosing" of these measures and interventions are currently lacking as many studies brought inconclusive outcomes, probably due to differences across methods and interindividual variability. On the other hand, it is evident that all such interventions should comprise long-term changes in lifestyle with reprogramming of the metabolic processes leading to heathy aging.[235,236]

Several studies and observations indicated that regular physical activity and exercise (in combination with a healthy diet) can help reduce the incidence of both communicable and non-communicable diseases in older age and can positively impact the processes of immune aging. Specifically, positive effects have been observed of regular physical activity and high-intensity interval training, which are beneficial for immunological health in older age.[235] Positive ("anti-aging") effects of exercise on the immunological profile include decreased numbers of senescent memory and naive $CD8^+$ and $CD4^+$ T lymphocytes[237] improvement in immune cells reactivity and cytokine signaling,[238] increased repertoire of naive T cells and exclusion of dysregulated apoptosis-resistant T cells, increased ratio of $CD4^+$/$CD8^+$, increased T-cell proliferation and expression of costimulatory molecules on T cells, increased maturation of dendritic cells,

increased neutrophil phagocytic activity, greater NK-cell cytotoxic activity, resolution of chronic viral infections and lowered inflammatory response to bacterial challenge, and increased post-vaccination immune response.[239–241] Several underlying mechanisms have been suggested and described, for example, the decrease in low-grade chronic inflammation, modulation of cytokine microenvironment, restoration of the anti-oxidant mechanisms, improvement in immune defense against pathogens, increase in telomerase length and activity, modulation of cytokine signaling, and increase in autophagy-induced mitochondrial functions.[238] Regular physical activity showed both preventive and restoring effects against immunosenescence and could possibly support longevity as well as promote quality of life in older age. In general, we can conclude that physical activity as part of lifestyle can promote rejuvenation of the immune system.[239,240,242]

Nutrition, dietary interventions, and modulation of microbiome: nutritional interventions have already shown great potential to positively influence aging of the immune system. Among dietary supplements with the highest capacity to modulate immune functions and decrease susceptibility to infections are vitamins (vitamin A, C, D, E, carotenoids), minerals (iron, zinc, selenium),[243,244] probiotics and prebiotics (modulation of gastrointestinal microbiome), polyphenols, and polyunsaturated fatty acids.[245–247] Whole diet approaches, for example, the Mediterranean diet, consisting of fruits and vegetables (containing vitamins and anti-oxidants) as well as gut microbiome-stimulating fibers and polyunsaturated fatty acids (fish and olives), could also yield beneficial effects on the immune system and hence protect against several age-related diseases.[248–251] Understanding metabolic changes induced by different nutrition-based interventions is necessary to optimize cell senescence antagonism, both for chronic non transmissible diseases treatment and to favor healthy aging.

Sleep, both the quality and the duration include other factors with a positive effect on immune functions. During aging, the duration of sleep is decreasing which leads to dysregulation of circadian rhythm. Sleep deprivation is associated with altered protein synthesis and increased pro-inflammatory signaling and low-grade systemic inflammation. As such, insomnia was associated with increased epigenetic age, higher counts of late differentiated $CD8^+$ and decline in naive T cells.[252] In contrast, sufficient sleep duration in elderly individuals[253] as well as meditation associated with the maintenance or increased telomerase length.[254] In general, enough sleep positively affects antibody titers and post-vaccination immune responses.[254–256] Not unexpectedly, several of the abovementioned non-pharmacological interventions may provide superimposed benefits: for example, lifelong physical activity and exercise may serve as a possible tool for improvement of sleep quality.[257]

Also, the microbiome may delay or accelerate immune senescence. Throughout life, the microbiome—consisting of several species of commensal, symbiotic, and pathogenic bacteria, fungi and viruses—closely interacts with the host-immune system[258–260] and can offer protection against detrimental assaults.[261,262] Under normal conditions, beneficial microbes are capable of producing short-chain fatty acids (SCFAs) including acetate, butyrate, and propionate, that promote a healthy gut environment.[236] Several factors including physical and psychological stress, lifestyle, diet, and xenobiotics (e.g., food additives and medications, especially antibiotics)[263] can alter the microbial composition and lead to dysbiosis. With age, a marked loss of beneficial commensals and a greater prevalence of pathogenic and pro-inflammatory species,[236] promoting leaky gut syndrome and systemic inflammation observed in chronic inflammatory, allergic, infectious and auto-immune or degenerative diseases[264] is observed. Dysbiosis also linked to a reduced responsiveness to immunotherapeutic interventions such as vaccinations.[262,265–267] In this context, also a potential link between the microbiome and late-onset asthma has been suggested.[268]

Therefore, targeting the dysbiosis of the aging microbiome may help to restore the host-immune function. So far, several approaches have been proposed including lifestyle and diet improvements, as well as food supplements (e.g., butyrate), prebiotics and probiotics and fecal microbial transplantation (FMT).[269] However, most approaches await further investigation of longer term outcomes, especially in the elderly, with many authors suggesting a personalized approach for restoring the imbalanced gut microbiome.[270]

On a more general level, studies in invertebrate species, such as *Drosophila melanogaster* and *Caenorhabditis elegans*, point toward possible effects of microbiota on several aspects of aging including the promotion of host longevity by genome modulation.[266] Genes found to be involved in "healthy aging" include the insulin growth factor (IGF)-1 signaling pathway, mechanistic target of rapamycin (mTOR), and AMP-activated protein kinase (AMPK). Although much still needs to be uncovered, but if these initial observations also apply to humans, this may have a major impact on our future view on therapeutic approaches in the elderly. Within this new paradigm, the "microbiome-preserving" approach may serve as a solid (preventive and general health promoting) cornerstone on top of which any disease-centered interventions can be applied.

4.1.2 | Approach by pharmacological intervention

Different pharmacological approaches to contrast senescence have been investigated. Senolytic and senomorphic drugs are promising approaches for targeting the aging process, and they are currently being investigated in preclinical and clinical studies. Senolytic drugs are compounds that selectively induce death in senescent cells. Senomorphic drugs, on the other hand, do not directly kill senescent cells but instead alter the SASP of these cells. Main approaches are either the introduction of potent radical scavenger/anti-inflammatory agents, such as fisetin and quercetin; or blocking signaling pathways for inflammatory cytokine synthesis with agents such as dasinitb, or improving respiration (OXPHOS) in mitochondria and ATP synthesis with sulforaphane. These compounds are Nrf2 activators, thereby promoting glucose and lipid utilization.[271–273] Nrf2 is a transcription factor important to maintain the cellular redox balance. Reduction of Nrf2 levels is associated with the induction of a senescent phenotype, and Nrf2 activators were found to reduce pulmonary oxidative stress in several in vitro and in vivo models. In Table 5 and

TABLE 5 (a) Metabolic targets antagonizing accelerated aging/pulmonary inflammation: preclinical studies in in vitro/animal models. (b). Metabolic targets antagonizing accelerated aging/pulmonary inflammation: preclinical studies in in vitro/animal models.(c) Metabolic targets antagonizing accelerated aging/pulmonary inflammation: preclinical studies in in vitro/animal models.

Compound	Mechanism of action/Target	Biological activity	In vitro/in vivo model	Disease	Refs
(a) Senolytic action with Anti-oxidants					
AEOL 10150	SOD mimetic	Decreased oxidative stress and monocyte/macrophage infiltration	Non-human primates	Radiation-induced inflammation	193
Ebselen	Glutathione peroxidase (GPx) mimetics		In vivo animal models of lung inflammation	COPD	347
GKT137831	NOX4-Nrf2	↓ apoptosis	Myofibroblast	Fibrosis	348
	NOX1 NOX2 inhibitor, p53	↓ apoptosis			349
BC-1901S	DCAF1/NRF2 axis			Inflammation	350
Berberine	AMPK and Nrf2	Macrophages		Inflammation	351
Astaxanthin (ATX)-Carotenoid	Stimulating Nrf2 pathway/HO-1 expression		Inflammation-oxidative stress	COPD	352
Astaxanthin (ATX)-Carotenoid	Decreasing NFkb	↓ Emphysema and BAL inflammation	In vivo and in vitro	COPD, IPF	353,354
Thymoquinone (TQ, 2-methyl-5-isopropyl-1, 4-benzoquinone)	(Nrf2), (PI3K/AKT), n (NF-Kβ).	Bronchial inflammation and edema	In vivo lung model		352
Thymoquinone		Anti-inflammatory	Allergic asthma model	Asthma	355
Resveratrol		↓ cytokine release Alveolar macrophages	in vitro	COPD	356
Resveratrol		↓ lung neutrophilia, reduction inflammatory cytokines	In vivo: LPS induced pulmonary neutrophilic inflammation	COPD	357
AZD 5904	Myeloperoxidase inhibitors		Animal model	COPD	347
Bardoxolone methyl	Nrf2 activators		Animal model	COPD	358
Dimethylfumarate (BG-12)	Nrf2 activators	Reduced oxidative stress, inflammation and fibrosis	Animal model	Lung fibrosis and pulmonary arterial hypertension	359,360
L-NIL	iNOS inhibitor	Inhibition of NO production	Animal model	Asthma	347,361
Fisetin	Anti-oxidant	Reduced senescent markers in multiple organs	Accelerated aged Ercc1□/Δ mice	Organ aging	362
Fisetin	Anti-oxidant		Animal model	Pulmonary fibrosis	363

Compound	Mechanism of action/ Target	Biological activity	In vitro/in vivo model	Disease	Refs
(b) Senolytic action via mTOR pathway and SASP					
Rapamycin, metformin and dimethyl fumarate	PI3K and mTOR	Metabolic dysregulation occurs in T cells.	T cells	COVID-19	364

TABLE 5 (Continued)

Compound	Mechanism of action/ Target	Biological activity	In vitro/in vivo model	Disease	Refs
GSK2126458	PI3K inhibitor	↓ fibrosis in lung slides	Lung slides	IPF	365
Rapamycin, PP42	PI3K/AKT/mTOR pathway		IPF-derived fibroblasts	IPF	366
miR-200b	Downregulating ZEB2 EMT		COPD mouse model, MLE cells	COPD	367
Rapamycin	mTOR dependent	↓ collagen deposition in murine lung	Myofibroblasts	IPF	368
Rapamycin	MAPKAPk2	↓ SASP			291
Rapamycin	PI3K, mTOR	↓ SASP IL-1 in vitro			369
Azithromycin	↑ Autophagy	↓ Viability of human senescent lung and skin fibroblasts in vitro	Fibroblast cell lines MRC-5 BJ	IPF	370
Roxithromycin	↑ Autophagy	↓ Viability of human senescent lung and skin fibroblasts in vitro		IPF	370
Metformin	↓ NF-κB, ↑ DICER1, ↓ Akt	↓ SASP in human lung fibroblasts in vitro	In vitro	IPF	371
PAI-1 inhibitor	Protease inhibitor PAI-1	Eliminated the aging-related apoptosis resistance and TGF-β1 sensitivity of human fibroblasts	Inhibition PAI-1 and TGFβ sensitivity-knock-down PAI-1	IPF	372
PAI1 inhibitor (TM5275)	↑ p53, ↑ apoptosis	↓ fibrosis in mice with bleomycin mouse model; protected AEC2s from senescence		IPF	373
MiR-34a	PI3K, mTOR,(miR-34a)	Sirtuin −1 and Sirtuin-6, mTOR		COPD/IPF	326,374
Inhibition of MiR-494-3p	p38MAPK pathway	SIRT-3	Epithelial cells of COPD patients	COPD	375
Melatonin		Reducing SASP SIRT-1		Anti-inflammatory	376
SIRT activator SRT1720	TPP/Sirt-1	Improves CS-induced lung cellular senescence	Animal model and human lung tissue	Pulmonary Emphysema	377
Senolytic action: Mitochondria-targeted (ubiquinone)					
DRP1 inhibitor Mdivi-1				COPD	301
MitoQ		↓ airway hyperresponsiveness, and lung inflammatory mediators	Animal model for chronic oxidative stress	Asthma/COPD	188
pyrroloquinoline quinone	p16, p21, jagged 1	Delays TNF-α -induced cellular senescence	Inflammaging model in human embryonic lung fibroblasts		378
Mito-tempo	Inhibitor of mitochondrial ROS	Reduced ozone-induced emphysema	Epithelial cells	COPD	379

Compound	Mechanism of action/Target	Biological activity	In vitro/in vivo model	Disease	Refs
(c) Senolytics: Removal of senescent cells (apoptosis)					
Mitochondrial outer membrane permeabilization (MOMP) = caspase cascade					
Navitoclax	BCL-2 family	No effect	Human Lung	IPF	380
Navitoclax-ABT263	BCL-2, BCL-xl, bcl-w		IMR human lung fibroblasts	IPF	381

(Continues)

TABLE 5 (Continued)

Compound	Mechanism of action/Target	Biological activity	In vitro/in vivo model	Disease	Refs
TW37	Bcl-2	No effect	IMR cell (human lung fibroblasts)	IPF	381
Dasatinib + Quercetin	↓ SASP factors, fibrosis		Alveolar epithelial cells (AT II), 3D lung	IPF	382
Dasatinib + Quercetin	↓ Bcl-xL, ↓ PI3K/Akt, ↓ p16, ↓ p21, ↑ cleaved caspase-3, ↑ apoptosis	↓ Senescent human cells in vitro; ↑ exercise capacity and ↓ SASP in mice; ↑ lifespan of progeroid and wildtype mice; ↓ physical dysfunction in human IPF patients	In vitro, in vivo, clinics	Alzheimer, IPF, Aging	16,383–385
ABT-737 siRNA's	↓ Bcl-XL, ↓ Bcl-W, ↑ apoptosis	↓ Senescent cells in lungs and epidermis	Lung, epidermis, in vivo		386
DNA damage signals					
Dasatinib + Quercetin	p16Ink4a, p53, cyclin-dependent kinases	↓ expression p16 and SASP mediators Mcp1, Il6, Mmp12 and Tgfβ.	Primary human fibroblasts-	IPF	380
Tenovin-6 (TnV6)	↑p21	Increases ↑SASP	Primary human fibroblasts-		387
HSP90 inhibitor 17-DMAG	↓p16Ink4a	↓Aging	Primary mouse embryonic fibroblasts rom DNA repair-deficient Ercc1−/− mice	Fibrosis	384
FOXO4-DRI peptide	p53 nuclear exclusion	↓ Apoptosis	Senescent human lung fibroblasts		388
Metformin	↓ p16, ↓ p21	↓ senescent human lung fibroblasts in vitro			389
Depolarization senescent cells					
Cardiac glycosides (Digoxin)	Na+/K+ATPase pump	↓ Senescent cells and fibrosis in a mouse model of lung fibrosis	Lung Fibrosis		390

Abbreviations: Q Quercetin, D Dasatinib, KO knock-out, IPF idiopathic pulmonary fibrosis.

Figure 5, preclinical studies on different classes of drugs that have been investigated for their potential to target airway diseases have been summarized. Strategies to remove senescent cells include compounds that increase anti-oxidant status, inhibit kinases or interfere with pro-survival or pro-apoptotic pathways. Other studies have shown that treatment with a number of different compounds results in reduction of pro-survival factors of the Bcl family and leading to a reduction in senescent cells and/or improvement of lung function. Furthermore, drugs targeting, for example, the p53/p21 pathway, mTOR, and sirtuins also appear promising to reduce the number of senescent cells in tissue and regulate the production of SASP. Much more research is needed to fully understand the mechanisms by which these drugs work, and to determine their safety and efficacy in humans. Currently, a number of clinical trials are ongoing to investigate the safety and efficacy of various senotherapeutics such as dasatinib, quercetin, and fisetin and combinations of these drugs in human disease (Table 6).

4.1.3 | Combination of metabolic targeting with current therapies

As mentioned above, senescent cells and the systemic metabolism display dynamic interplay. Several studies have pointed out different alterations of metabolic pathways such as mitochondrial dysfunction, hyperglycemia, or disrupted NAD+ metabolism as key metabolic drivers of senescence.[3] Emerging data indicate that age-related metabolic phenotypes or biomarkers might well be considered as potential therapeutic targets.[4] Recent studies are starting to delineate how current therapies for allergic inflammatory diseases could interfere with metabolic pathways to restore proper immune responses and tissue homeostasis. At this regard, it was shown that allergoid-mannan conjugates, which are next-generation vaccines for allergen-specific immunotherapy, are able to imprint tolerance through metabolic rewiring.[274] Also, the currently used allergen immunotherapy vaccines are able to induce trained tolerance in innate lymphoid cells, monocytes, and dendritic cells in allergic patients,[275] possibly through the immune reprograming and epigenetic modifications.[276,277] Human monocyte-derived dendritic cells (hmoDCs) from nonatopic and allergic subjects differentiated in the presence of this vaccine display increased expression of genes related to tricarboxylic acid cycle and OXPHOS compared to conventional hmoDCs. They have shown an increased glycolysis with a shift toward OXPHOS and ROS production, essential for the generation of FOXP3$^+$ Treg cells.[274]

Other proposed molecules to antagonize accelerated aging by shifting metabolism are Sestrins. Sestrins are a classical family of stress-inducible proteins known to have an anti-aging effect affecting cellular metabolism by counteracting oxidative stress.[278,279] Sestrins may improve elderly health by suppressing ROS production, regulating autophagy activity, and preventing metabolic dysfunction, which confers tissue-specific protective roles in muscle, heart, and brain.[280–282] Sesn-A, the N-terminal domain of Sestrin2, has a conserved Cys125 residue that reduces alkylhydroperoxide radicals

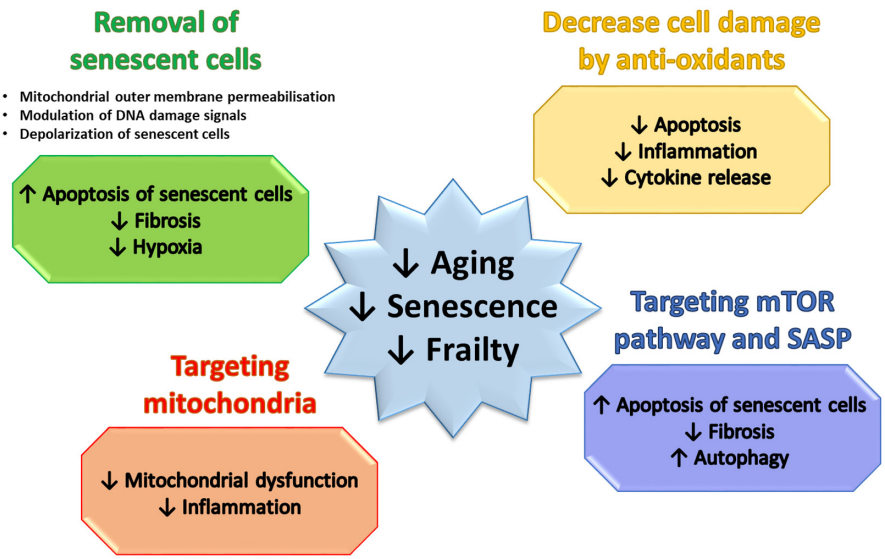

FIGURE 5 Pharmacological approaches to antagonize metabolic reprogramming in senescence. The effect of treatments on metabolism (cell damage and mTOR pathway, senescence-associated secretory phenotype-SASP, mitochondrial disfunctions, inflammation) and senescent cells is summarized. ↓, decrease; ↑, increase. As summarized in Table 5, strategies to remove senescent cells include compounds that increase anti-oxidant status, kinase inhibitors or interfere with pro-survival or pro-apoptotic pathways. For instance, Nrf2 is a transcription factor important to maintain the cellular redox balance. Reduction of Nrf2 levels is associated with the induction of a senescent phenotype and Nrf2 activators were found to reduce pulmonary oxidative stress in several cellular and in vivo models. Other studies showed that treatment with a number of different compounds resulted in reduction of pro-survival factors of the Bcl family and lead to a reduction of senescent cells and/or improvement of lung function. Also other drugs targeting, for example, the p53/p21 pathway, mTOR, and sirtuins appear promising to reduce the number of senescent cells in tissue and regulate production of SASP.

TABLE 6 Senolytic therapy in human disease: selected clinical trials registered at ClinicalTrials.gov[a].

Clinical trial	Trial subject	Disease/Condition	Senolytics	Status	Phase
NCT04476953	Pilot in SARS-CoV-2 of Fisetin to Alleviate Dysfunction and Inflammation	COVID-19	Fisetin	Enrollment by invitation	2
NCT04537299	Pilot in COVID-19 (SARS-CoV-2) of Fisetin in Older Adults in Nursing Homes	COVID-19	Fisetin	Enrollment by invitation	2
NCT04771611	COVID-19 Pilot Study of Fisetin to Alleviate Dysfunction and Decrease Complications	COVID-19	Fisetin	Enrollment by invitation	2
NCT04476953	COVID-FISETIN: Pilot in SARS-CoV-2 of Fisetin to Alleviate Dysfunction and Inflammation	COVID-19	Fisetin	Enrollment by invitation	2
NCT05593588	Senolytics Treatment of Interstitial Lung Disease in Common Variable Immunodeficiency	Interstitial Lung Disease Due to Systemic Disease	Fisetin and Quercetin	Not yet recruiting	2
NCT04733534	An Open-Label Intervention Trial to Reduce Senescence and Improve Frailty in Adult Survivors of Childhood Cancer	Frailty	Fisetin/Dasatinib and Quercetin	Active recruiting	2
NCT03989271	Biological Effects of Quercetin in COPD	COPD	Quercetin	Active recruiting	2
NCT01708278	Beneficial Effects of Quercetin in Chronic Obstructive Pulmonary Disease (COPD)	COPD	Quercetin	Completed	1
NCT05601180	Evaluation of the Efficacy of Respicure® in the Management of Respiratory Conditions Including Asthma, COPD and Long COVID	COPD/Asthma	Resveratrol and Quercetin	Active recruiting	n/a
NCT00994604	The Effects of Broccoli Sprout Extract on Obstructive Lung Disease	COPD/Asthma	Sulforaphane	Completed[391]	n/a
NCT01335971	Broccoli Sprout Extracts Trial to See if NRF2 is Enhanced by Sulforaphane Treatment in Patients With COPD (BEST)	COPD	Sulforaphane	Completed[392]	2
NCT03865927	GKT137831 in IPF Patients With Idiopathic Pulmonary Fibrosis (GKT137831)	IPF	Setanaxib GKT137831	Recruiting	2

[a]Selected trials registered on ClinicalTrials.gov at February 14, 2023; n/a not applicable.

and ROS accumulation.[283,284] In addition, sestrins stimulate autophagy by inhibiting mTORC1 encompassing mTOR and Raptor, either through activating AMPK or binding with GATOR2 via Sesn-B, the C-terminal domain.[284] Interestingly, autophagy induction also contributes to abrogate ROS production by eliminating dysfunctional mitochondria that produce the pathogenic level of ROS.[285] Inhaled corticosteroids reduce senescent endothelial progenitor cell numbers in COPD;[198] however, the impact of glucocorticoid treatment on senescence needs further investigation.

5 | CONCLUSIONS

Our knowledge of alterations in cell metabolism shaping all disease aspects from pathophysiology to response to therapy has increased dramatically in the last decade and is still being defined. Considering the central role, now well recognized, to the process of cell senescence—and the ensuing immune response—in cancer and all nontransmissible diseases (NTDs), it was only logical that a major research effort would be devoted in seeking how altered metabolism fuels cell senescence in all its physiological and pathological aspects. For allergic and chronic inflammatory lung diseases, the understanding of metabolic shifts carried by cell senescence is still in its early development. Many elements related to the metabolic profile of cell senescence in specific disease mechanisms, cellular players, disease phenotypes, and response to current therapies are open fields of research from the basic, clinical/translational, and pharmacological standpoint (Table 7). Based on the presented current knowledge in preclinical and disease settings, this rapidly advancing research field is already providing, as shown by the listed clinical trials, promising novel therapeutic approaches targeting cell metabolism to slow or revert pathogenic senescence. These could be working as main intervention, or by partnering with other current pharmacological approaches. Interventions must also ensure, as critical feature, to preserve the protective edge of the senescence sword, preserving this biological response for the immune response as a way to control cancer, xenobiotic stress, and wound healing, thus aiming to globally lower the NTD burden and to promote healthy aging.

TABLE 7 Current research gaps and needs for metabolic targeting of senescence in allergy and clinical immunology.

Basic
Single-cell metabolic pathway analysis of lung senescent cells
Single-cell resolution of SASP metabolism
Definition of metabolic changes in individual senescent lung cell types
Specificity of metabolic changes by senescence triggers
Epithelial senescence and metabolism in airway barrier dysfunction
Modulation of immune senescence-related metabolic changes by tissue environment
Cell senescent metabolic crosstalk through microvescicles and exosomes
Clinical
Understanding of disease-specific, senescence-related metabolic profiles
Contribution of senescence-driven metabolic reprogramming to disease phenotype
Identification of senescence-related metabolic signatures by combined –omics in large population cohort studies
Development of point-of-care diagnostics to detect metabolic hallmarks of senescence
Pharmacology
Identification of specific, upstream druggable metabolic targets in immune senescence
Understanding and correcting metabolic effects of senescence affecting current drug efficacy
Understanding metabolic changes in senescence-targeting brought by non-pharmacological interventions
Understanding metabolic changes in senescence-targeting brought by biologics, immunotherapy, CS therapy
Understanding hidden risks of senescence antagonization: preserving role of senescence in physiological lung immune response to inhaled and endogenous insults

AUTHOR CONTRIBUTIONS

The topic for this third TIPCO paper was chosen unanimously; specific parts were drafted by authors' subgroups: abstract, introduction, conclusion: CS; basic pathophysiology: FRW, LOM, RB, KG, KFC GC, GN, LC, MS, EFK; COPD and asthma: IMA, KFC, IEG, GC, RB, MS; pharmacology: MJ, ZD, LB, IMA, FLS, OP, CBV, LOM, FR, BvE, IEG; glossary, Tables 1 and 2, Figure 1–3: FRW; Tables 3 and 4: FRW, IMA, CS; Table 5a–c, Table 6: FR, BVE; Table 7: CS, FRW; Figure 4: EFK, Figure 5: CBV, OP. The first draft was assembled during an ad-hoc hybrid meeting (Naples, Italy, November 2022), edited by FRW and CS and submitted after final read and approval by authors. CS coordinated and structured the manuscript and assembled the first draft. All authors contributed to writing and critically revised the manuscript for the intellectual content. All authors approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

IMA, CBV, RB, LB, OB, LC, EK, AK, GN, FAR, FRW, CS, and FLS have no conflicts of interest regarding the subject of this manuscript. GC has received unrestricted educational and/or research grants and/or Lecture fees and/or grants for travel and accommodation to participate to scientific meetings from Astra Zeneca, Biofutura, Boehringer Ingelheim, Chiesi, Enfarma, GSK, and Menarini Group. ZD has received honoraria or consultancy fees from the following pharmaceutical companies: Antabio, Boehringer Ingelheim, Foresee Pharmaceuticals, GlaxoSmithKline, QPS-Netherlands, Sanofi-Genzyme-Regeneron, all outside the submitted work. IEG received advisory fees from ALK and Novartis, lectures fees from Astra-Zeneca, Novartis, Chiesi and Diater; FRW is lead inventor of EP2894478 (applicant Biomedical International R+D, Austria), has served as an investigator, speaker, and/or advisor for Biomedical Int R&D, Allergy Therapeutics and Bencard and is founder of Vialym; OP received lecture fees from AstraZeneca, GSK, Inmunotek, Novartis, Pfizer, Sanofi-Genzyme, and Regeneron and participated in advisory boards from AstraZeneca, GSK, Novartis, Pfizer, Sanofi-Genzyme, and Regeneron. CBV received the FPU fellowship from MINECO. KFC has received honoraria for participating in Advisory Board meetings of the pharmaceutical industry regarding treatments for asthma and chronic obstructive pulmonary disease and has also been renumerated for speaking engagements. BvE is partly employed by Nutricia Research. MS has received speaker's fee from AstraZeneca.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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