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Inclusion body myositis: The interplay between ageing, muscle degeneration and autoimmunity

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A B S T R A C T

Inclusion body myositis (IBM) is a slowly progressive muscle disease affecting ageing individuals. IBM presents with a distinctive pattern of weakness involving the quadriceps and finger flexor muscles, although other muscles including pharyngeal muscles become affected over time. Pathological hallmarks of IBM include autoimmune features, including endomysial infiltration by highly differentiated T cells, as well as degenerative features marked by intramyofibre protein aggregates organised into inclusion bodies. Despite some progress in understanding the cellular pathways involved in IBM, it remains untreatable, and the progression of the disease leads to progressive weakness, disability, wheelchair dependency and loss of independence. Therefore, there is an urgent need to improve our understanding of the underlying mechanisms and pathways involved in this disease to identify new treatment targets. Here, we discuss the current understanding of aetiopathogenesis, the interrelationship between autoimmunity and degeneration, and how ageing is a major influencer of both these features.

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Introduction

Inclusion body myositis (IBM) is an untreatable progressive muscle disease that belongs to a heterogeneous group of muscle diseases called inflammatory myopathies. It is a disease of ageing, most commonly affecting individuals over the age of 45 years. The muscle weakness and wasting are quite selective initially, most severely affecting the quadriceps, hip flexors, tibialis anterior, finger and wrist flexors [1,2]. Pharyngeal muscles are often affected leading to dysphagia [3]. Creatine kinase (CK) levels are typically less than twelve times the upper level of normal (ULN), and *anti*-cN1A antibodies are detected in approximately half of the patients. MRI scans highlight a characteristic pattern of muscle involvement, but muscle biopsy remains the gold standard for diagnosis [2]. Histologically, IBM muscle displays a triad of changes, including degenerative, mitochondrial and inflammatory changes. The degenerative changes include congophilic inclusions, rimmed vacuoles and p62 accumulation seen on immunohistochemistry, as well as 15–18 nm filamentous inclusions seen on electron microscopy [4]. Many proteins, including β-amyloid [5] and TDP-43 [6], have been found to accumulate and form aggregates in IBM muscle as a result of disrupted proteostasis. There are increased numbers of cytochrome *c* oxidase (COX) negative fibres highlighting the mitochondrial dysfunction [7]. The inflammatory changes include endomysial infiltrates predominantly composed of $CD8^+$ T cells that invade non-necrotic muscle fibres, which diffusely overexpress the major histocompatibility complex I (MHC-I) molecules. There are currently no effective disease-modifying therapies, reviewed by Needham et al. [1]. The aetiopathogenesis of IBM is still largely unknown, but it is likely that in the ageing environment and with genetic susceptibility factors, both inflammation and misfolded protein accumulation due to impaired autophagy and proteasome systems contribute to myofibre breakdown and poor regeneration, causing progressive muscle loss, weakness and disability [8]. However, whether the inflammation is initially responsible for the degenerative changes, or that the degenerative changes precede and trigger autoimmunity, has not been fully elucidated. This review recapitulates our understanding of the relevant degenerative and inflammatory changes observed in IBM and discusses the interrelationship between autoimmunity and degeneration, as well as the contribution of ageing in the aetiopathology of IBM.

Degenerative pathomechanisms in IBM

Congophilic inclusion bodies were initially reported in the 1960s in patients with “chronic polymyositis,” but IBM was not recognised as a distinct entity until 1978 [9]. Early electron microscopic (EM) images described 15–18 nm tubulofilaments, and the identification of protein aggregates within muscle led to speculation that they could be viral particles, leading to a decade-long search for viruses that might cause IBM but were never proven. The finding of amyloid-β proteins (Aβ40 and Aβ42) using Congo red stains and “rimmed vacuoles” containing several ubiquitinated protein aggregates led to early hypotheses that the inclusion bodies in IBM muscle might be analogous to those seen in Alzheimer's disease and other neurodegenerative diseases [10]. Despite initial enthusiasm and work on the amyloid hypothesis, the fact amyloid is only seen in less than 1% of fibres [11] and that Aβ42 is one of a large number of proteins to accumulate in IBM muscle had led to scepticism as to whether it plays a significant role in the aetiopathogenesis [12].

Phosphorylated Tau is another extensively studied aberrant protein that aggregates as paired-helical filaments (PHF) in IBM muscle fibres [13,14]. Likewise, several kinases known to phosphorylate Tau, such as extracellular signal-regulated kinase (ERK), cyclin-dependent kinase 5 (CDK5) and activated glycogen synthase kinase3β (GSK3β), are also increased and colocalise with Tau in IBM [14,15]. Many other proteins implicated in neurodegenerative diseases have also been found to be present in aggregates in IBM muscle, including p62/Sequestosome-1 (SQSTM1), Apolipoprotein E (ApoE), α-synuclein (α-syn), cellular prion protein (PrPC) [16,17] and Tar DNA-binding protein (TDP-43) [6]. TDP-43 is a ubiquitous DNA/RNA binding protein that plays a critical role in RNA processing and has been shown to form cytoplasmic aggregates in multiple neurodegenerative diseases, including Amyotrophic Lateral Sclerosis (ALS), Frontotemporal Dementia (FTD) and Alzheimer's disease [18,19]. Similar to that observed in ALS, IBM displays TDP-43 mislocalisation from the nucleus and aggregation within the sarcoplasm [19]. In these neurodegenerative diseases, frequently termed “TDP-43

proteinopathies", it remains unclear whether it is the cytoplasmic aggregates or the loss of nuclear TDP-43 that drives neurodegeneration. During pre-mRNA processing, TDP-43 recognises and prevents "cryptic exons" from being incorporated into mature RNA by binding to uracil and guanine (UG)-rich repeats [20]. Cryptic exon incorporation can lead to in-frame gain-of-function mutations or loss-of-function due to nonsense-mediated decay (NMD). A recent study by Britson et al. showed that cryptic exon incorporation was found in 84% of IBM muscle biopsies and in only 1.3% of control biopsies, suggesting that loss of TDP-43 function is specific to IBM compared to other inflammatory myopathies and appears independent of the inflammation [20] (Fig. 1). This may be important in understanding one of the mechanisms of myodegeneration.

Dysregulated autophagic and proteasomal machinery in IBM

A defect in protein homeostasis (proteostasis) may explain why so many aggregate-prone proteins have been identified in protein inclusions in IBM. A recent study from Ciryam and colleagues investigated this hypothesis using computational analyses of the proteome within and adjacent to rimmed vacuoles. They found that the proteins abundant in rimmed vacuoles tend to be those with unstructured domains and present at high concentrations in muscle [21]. This led to the hypothesis that there are aggregate-prone proteins that are saturated in muscle sarcoplasm, and that a slight imbalance or disruption in proteostasis can lead to aggregation.

Two primary pathways are known to mediate the degradation of aggregate-prone proteins, and both pathways have been implicated in IBM: autophagy and proteasome (Fig. 1). Autophagy is the process of removing accumulated cellular debris. During this process, debris such as aggregated proteins and damaged organelles are engulfed by a vesicle, known as an autophagosome. These autophagosomes fuse with lysosomes, and the debris is then degraded [22]. Though the nature of rimmed

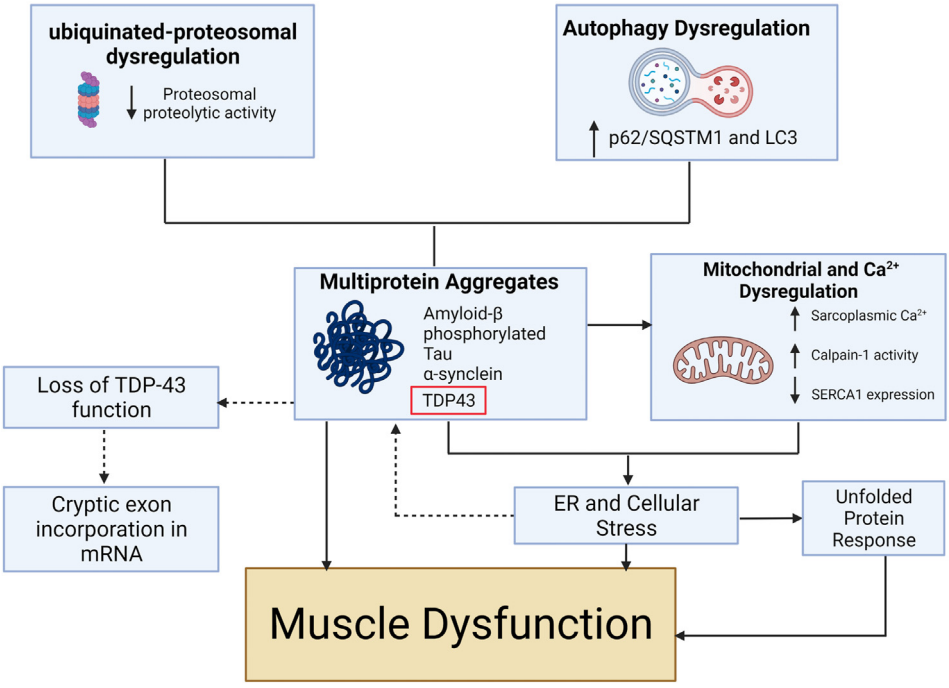

Fig. 1. Overview of the degenerative pathomechanisms in IBM. Disruptions in muscle proteostasis (autophagy and proteosome) can result in multiprotein aggregates, including amyloid β, phosphorylated Tau and TDP43. These protein aggregates can cause cellular stress, particularly ER stress pathways which can result in muscle dysfunction/atrophy.

vacuoles in IBM is incompletely understood, one common theory is that they represent an expanded autophagosomal structure. This might arise from either excessive autophagosome formation, a block in autophagosome fusion with lysosomes, or a failure of autophagolysosomes to degrade their contents [23]. This could potentially cause toxicity by slowing down the autophagic process, resulting in increased the accumulation of toxic cellular debris, or alternatively, the expanded autophagolysosomes may become damaged and release toxic lysosomal enzymes into the cytoplasm. Further evidence for disrupted autophagy in IBM comes from the identification of the critical autophagic proteins, p62/Sequestosome-1(SQSTM1) and LC3, which are some of the most sensitive and specific markers for identifying protein aggregates in IBM muscle [24,25]. The modification of LC3-I to LC3-II is one of the critical steps in the formation of the autophagosome, and p62/SQSTM1 binds to ubiquitinated cargo through its UBA domain and delivers them to the newly forming autophagosome through direct interaction with LC3-II [25]. Various studies have demonstrated that p62/SQSTM1 and LC3-II colocalise with protein aggregates in IBM myofibres. Interestingly, rare variants in the *SQSTM1* gene have been found at an increased in frequency in IBM patients, and a mutation in *SQSTM1* is known to cause a skeletal myopathy [26]. Similarly, rare variants in *FYCO1* may increase the risk for IBM [27]. *FYCO1* links autophagosomes to microtubule motors for transport to the lysosome. These findings suggest the possibility that variants in the autophagic machinery may predispose certain individuals to disrupted proteostasis and progressive supersaturation and aggregation of multiple proteins, as seen in IBM.

Similarly, mechanisms that govern the ubiquitin-proteasomal system have been shown to be dysregulated in IBM patients. The 26S proteasome degrades misfolded or ubiquitinated proteins into short polypeptides, thereby preventing their accumulation [28]. In IBM, proteasome components are increased in cultured muscle fibres of IBM patients; yet, proteasomal proteolytic activity was greatly reduced [28]. This reduction resulted in several multiprotein aggregates (amyloid-β, phosphorylates Tau and heat shock protein) which colocalised with the 26S proteasome [28]. Thus, the accumulation of ubiquitinated, misfolded, protein aggregates may cause proteasome inhibition and ultimately the myodegeneration that is seen in IBM.

Mitochondrial abnormalities and endoplasmic reticulum stress in IBM

Mitochondria are essential for ATP generation, and mitochondrial dysfunction has been linked to a large number of metabolic and muscle diseases. IBM muscle features mitochondrial abnormalities including a higher proportion of COX negative fibres, ragged red fibres and mitochondrial DNA (mtDNA) deletions compared to healthy aged-matched samples [7,29]. In many neurodegenerative diseases, cellular stress, such as that caused by protein aggregation, can lead to mitochondrial toxicity and activation of the mitochondrial permeability transition pore (mPTP) [30]. The activation of the mPTP can lead to the secretion of mitochondrial components, including mtDNA and calcium (Ca^{2+}) [31]. In IBM, mitochondrial Ca^{2+} regulatory proteins, such as the sarco/endoplasmic reticulum Ca^{2+} ATPase protein (SERCA1), are reduced, consistent with an elevation of cytosolic and mitochondrial Ca^{2+} concentrations [32]. This is further supported by post-translational altered the expression of Ca^{2+} protease calpain-1 which is markedly increased in IBM [32] (Fig. 1). Intracellular Ca^{2+} dysregulation can have a large impact on myofibre health due to the activation of reactive oxygen species (ROS), triggering endoplasmic reticulum (ER) stress and the activation of the unfolded protein response (UPR).

In addition, the accumulation of protein aggregates in the cytoplasm can activate ER stress pathways that likely contribute to myofibre dysfunction. The ER plays a pivotal role in the processing and folding of newly synthesised proteins, and the accumulation of misfolded proteins can activate the UPR [33]. The activation of the UPR leads to an increase in the transcription of ER chaperones that increases the folding capacity and helps reduce protein aggregation in the cells. There is an increase in chaperone proteins in IBM biopsies, which colocalise with amyloid-β [33]. While acute ER stress is believed to be cytoprotective, continuous UPR stimulation leads to the activation of ER transmembrane sensors, including activation transcription factor-6 (ATF6), inositol-requiring protein (IRE) 1α and protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK) and ultimately leads to UPR-associated degeneration [34].

Genetic associations and susceptibility in IBM

Although IBM is not an inherited disease, early candidate gene approach studies based on genes related to inflammatory and degenerative markers identified potential susceptibility genes associated with IBM [35]. In these studies, it was identified that IBM has one of the strongest disease associations with HLA genes located within the major histocompatibility complex region [36]. The HLA class I and II gene products are responsible for presenting antigenic peptides to CD8 and CD4 T cells, respectively. In IBM, the strongest risk association is with HLA-DRB1*03:01 and the extended 8.1 ancestral haplotype (AH) [36,37]. A comprehensive summary of IBM-associated HLA alleles outside the 8.1 AH was recently summarised in a review by Britson et al. [38] In addition, a polymorphism (rs10527454) within the 'translocase of outer mitochondrial membrane 40' (*TOMM40*) gene has been associated with disease and may play a disease-modifying effect on IBM by delaying the onset of symptoms; this effect could be enhanced by the APOE $\varepsilon 3/\varepsilon 3$ genotype characterised by a very long ($N \geq 30$) poly-T repeat motif [39]. Furthermore, genetic variants in *SQSTM1* and *FYCO1* genes may be a risk factor for developing IBM [27]. Interestingly, these genes are involved in autophagy and proteasomal degradation of misfolded proteins and, therefore, variants in these genes may cause a failure of autophagosome trafficking and contribute to inclusion body formation (see above).

Contribution of ageing in IBM

IBM very rarely occurs in patients younger than 40 years, with most patients being diagnosed after the age of 50 [1], strongly suggesting that changes associated with ageing are an important factor in developing disease. Normal ageing muscle is associated with a decline in muscle mass and function, due to physical inactivity, reduced anabolic hormones and metabolic changes known as sarcopenia [40]. Skeletal muscle is increasingly recognised as an endocrine organ and an important modulator of immunity through the secretion of soluble immunoregulatory mediators (myokines) in response to environmental stimuli. These sarcopenic changes affect the myokines released by skeletal muscle, inducing a chronic low-grade inflammatory environment which affects the recruitment of immune cells and enhances muscle catabolism [41]. Ageing not only directly affects skeletal muscle, but it is also a major factor in the decline in function and specificity of the immune cells [42]. Ageing causes a decline of regulatory T cells (Tregs) and naïve T cells, which are gradually replaced by effector-memory (T_{EM}) and T cell effector-memory re-expressing CD45RA (T_{EMRA}), demonstrating reduced proliferation and increased effector functions [43]. This shift in T cell compartment from naïve to late-differentiated effector cells contributes to reduced immune vigilance and progressive immune dysfunction. This phenomenon, referred to as immunosenescence, is a likely contributor of increased susceptibility to infections, reduced anti-tumoral immunity and the promotion of autoimmune diseases [44]. These immunosenescent changes can negatively affect skeletal muscles by further promoting a sustained inflammatory environment that impairs muscle regeneration [41]. Ageing is also associated with the accumulation of mtDNA deletions and mitochondrial dysfunction, although these are seen far more frequently in IBM patients than in age-matched controls [7,45]. Similar protein accumulation is observed in neurodegenerative disorders associated with ageing such as Alzheimer's suggesting the existence of common pathogenic pathways linked to impaired proteostasis [5,18].

Collectively, ageing-related changes affect the skeletal muscle and immune system, in both a direct and interdependent manner. The combined negative impact of ageing on mitochondrial function and proteostasis in muscle creates additive and self-amplifying pathological conditions when occurring in genetically predisposed individuals. These factors may combine to accelerate muscle atrophy, due to the inadequacy of older muscle to cope with the continuous cell stress caused by chronic inflammation and/or other degenerative mechanisms (Fig. 2). Therefore, the contribution of ageing is an important consideration in the pathogenesis of IBM.

Evidence of an autoimmune pathogenesis in IBM

Historically, there has been much debate over the classification of IBM as an autoimmune disease, based in part because of the resistance of IBM to traditional immunosuppression combined with the

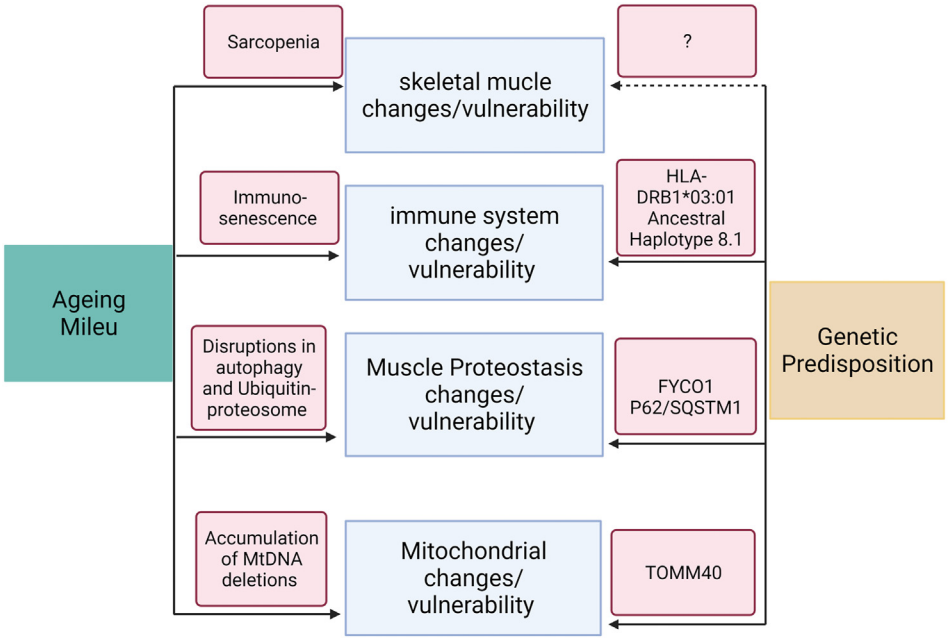

Fig. 2. Schematic depicting the contribution of ageing and genetics on the pathogenesis of IBM. Ageing sees a variety of changes including sarcopenic changes, shifting towards a pro-inflammatory profile with impaired immune functions/immunosenescence, altered proteostasis and mitochondrial abnormalities. These changes in combination with host genetics may ultimately lead to some of the autoimmune and degenerative changes seen in IBM.

plethora of research into degenerative protein accumulations that dominated much of the early literature. However, a previous study by Pruitt et al. reported that muscle fibres showing immune infiltrates are several fold more common than those with congo red positive protein aggregates [11]. Additionally, IBM is often associated with other autoimmune comorbidities such as Sjogren's disease and seems to be able to result from chronic viral infections such as HIV-1, HTLV-1 and Hepatitis C [46–48,101]. Moreover, the strong HLA association points to an important role played by the immune system [36,37]. Increasing evidence suggests that IBM may be primarily an autoimmune disease, mediated by terminally differentiated effector (TEMRA) T cells, with secondary degenerative changes that once established, can progress even in the absence of ongoing inflammation [20,49]. Detailed characterisation of the underlying immune-mediated mechanisms of IBM is crucial, as this will provide a critical step towards the identification of cellular and molecular targets for future therapies.

Pathomechanisms involving innate immunity in IBM

The early events of immune responses are mediated by non-specific innate immune cells that detect pathogens via danger-associated molecular patterns (DAMPS) and pathogen-associated molecular patterns (PAMPS). Initiation of these activation pathways is augmented through pattern recognition receptors including toll-like receptor (TLR) signalling and NOD-like receptor (NLR) inflammasome signalling and leads to the production of pro-inflammatory cytokines and chemokines that promote the initiation of adaptive immune responses, reviewed by Bonomo et al. [50]. Although in IBM professional antigen-presenting cells such as macrophages and dendritic cells (DCs) constitute a minor proportion of the muscle infiltrating mononuclear cells, their role in facilitating the pro-inflammatory milieu has significant implications on the pathogenesis of this disease. DCs are potent antigen-presenting cells that initiate T cell responses [50]. In IBM, DCs are found surrounding and invading

healthy myofibres in a similar pattern to infiltrating T cells [51]. Furthermore, the abundance of pro-inflammatory cytokines from DCs including IL-12 and IL-18 in IBM muscle likely polarises T cells towards a Th1 (interferon-gamma producing) phenotype [49,52] (Fig. 3).

Circulating monocytes and tissue macrophages are prominent phagocytic cells that engulf dead cells and process proteins into antigenic peptides presented to T cells; they also produce ROS, nitric oxide (NO) and secrete cytokines and chemokines [50]. Furthermore, macrophages can exhibit a pro-inflammatory (M1) or an anti-inflammatory (M2) profile, depending on the milieu. In IBM, the predominance of pro-inflammatory cytokines highlights the participation of M1 macrophages in the disease pathogenesis [52]. The sustained elevation of pro-inflammatory cytokines parallels the predominance of the M1 subset within the muscle-infiltrating macrophages and may participate in IBM pathogenesis. The M1 macrophages play a key regulatory role in muscle homeostasis; they contribute towards either myofibre regeneration or myofibre injury depending on the inflammatory environment [50]. For instance, during acute muscle repair, M1 macrophages contribute to the activation of satellite cells and promote muscle regeneration through the production of IL-1β [53]. Alternatively, during chronic inflammation, the constantly elevated concentrations of pro-inflammatory cytokines, such as

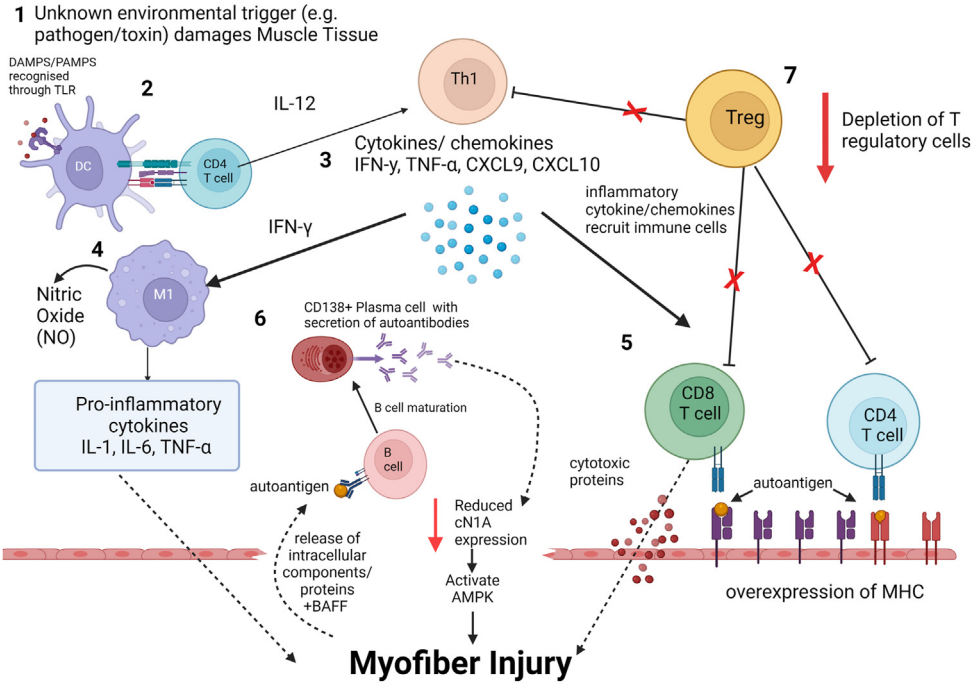

Fig. 3. Model of autoimmune manifestations within IBM muscle. 1. Unknown environmental triggers (e.g., viruses, pathogens and toxins) may cause skeletal muscle damage and release of DAMPS or PAMPS. Macrophages and DCs phagocytose damaged cells and recognize DAMPS/PAMPS via the toll-like receptors (TLR). **2.** Macrophages and DCs migrate to muscle draining lymph nodes where they prime adaptive immune cells CD8 and CD4 T cells via antigen presentation on MHC-I and MHC-II, respectively**. 3**. In IBM, the cytokine milieu differentiates CD4 T cells into Th1 cells [52] releasing pro-inflammatory cytokines IFN-γ and TNF-α and promotes M1 macrophages. **4.** M1 macrophages secrete pro-inflammatory cytokines, (including IL-1, IL-6 and TNF-α) [50,53,54] which further contributes to muscle degeneration and activates several signalling cascades, thereby perpetuating chronic inflammation. **5.** Antigen presentation to autoreactive $CD8^+$ T cells triggers perforin and granzymes release which contributes to the myofibre destruction. **6.** Ageing leads to a depletion of Treg; reduced Tregs likely contribute to the dysregulated inflammatory environment and promote the unrestricted autoimmune response [52,63]. **7.** B cells react to motifs displayed on molecules/proteins; activated B cells become antibody-secreting plasma cells. In approximately half of IBM patients, antibodies directed against cN1A are produced, although their exact pathogenic effect is unknown [74,80]. Autoantibodies against cN1A lead to a reduction in cN1A protein expression. Reduction in cN1A is shown to activate AMPK and cause muscle atrophy [81]. Peptides derived from proteins released by damaged myocytes may also be presented to autoreactive T cells.

IL-1, IL-6 and TNF-α, may tip the balance towards catabolic processes leading to myofibre injury and ultimately degeneration rather than repair [54]. Therefore, both through their antigen presentation capacity to T cells and their pro-inflammatory role, macrophages may play a critical for the initiation of muscle damage and autoimmune processes in IBM.

Pathomechanisms involving adaptive immunity in IBM

In contrast to innate immunity, adaptive immunity is initially a slow-onset antigen-specific response that upon primary activation develops memory features. It includes cell and antibody-mediated responses generated by T and B cells, respectively.

T cell responses in IBM

One of the distinctive characteristics of IBM pathology is the intense endomysial infiltration of $CD8^+$ T cells surrounding and invading non-necrotic muscle fibres demonstrating diffuse overexpression of MHC class I molecules expressed on sarcolemma [55]. $CD8^+$ T cells co-localise with MHC-I along with the costimulatory molecule inducible co-stimulator-ligand (ICOS-L), highlighting the capacity of IBM muscle fibres to act as antigen-presenting cells [56]. A large proportion of infiltrating $CD8^+$ T cells exhibit a terminally differentiated (T_{EMRA}) phenotype characterised by the loss of the co-stimulatory molecule CD28 and an upregulation of natural killer cell receptors such as Killer cell lectin-like receptor G1 (KLRG1) and CD57 [49] that arise due to chronic antigen exposure driven by unknown autoantigens [43,57]. T_{EMRA} cells are significant in the context of IBM given their strong cytotoxic potential (increased perforin, granulysin and granzyme content); and their limited proliferative capacity which is believed to render these cells refractory towards traditional immunosuppressant therapies [49,58].

A T cell disorder called T cell large granular lymphocytic (T-LGL) leukaemia arises from clonally expanded $CD57^{hi}CD8^+$ T cells and is commonly associated with several autoimmune and haematological conditions, reviewed by Lamy et al. [59]. It has been reported to be associated with IBM in 58% of patients, and the T-LGL cells are highly abundant within the muscle immune infiltrates [60]. Additionally, Greenberg and colleagues later reported that the cytokine IL-15 was consistently up-regulated in the muscle of IBM patients [49]. IL-15 plays an essential role in immune cell development and regulation and may, therefore, have significant implications for the promotion of T-LGL leukaemia as IL-15 is known as an important survival mechanism in the pathogenesis of these cells [61]. It is still unclear whether T-LGLs directly participate in the autoreactive attack against the myofibres or are recruited to the muscle as a secondary event and contribute to immune dysregulation.

$CD4^+$ T cells are less commonly seen than $CD8^+$ T cells in immune infiltrates. Like their $CD8^+$ counterparts, they lack CD28, possess intracellular cytotoxic granules and produce inflammatory cytokines (such as IFN-γ and TNF-α) contributing to the overall inflammatory environment [57]. Additionally, IBM muscle fibres also express MHC-II and ICOS-L, indicating that they are also capable of presenting antigens and triggering $CD4^+$ T cell function [55,62]. Furthermore, a distinct subset of $CD4^+$ T cells, known as Tregs, is found to be markedly diminished in IBM patients compared to healthy controls [52]. Tregs play a critical role in maintaining peripheral tolerance to self-antigens and suppressing excessive immune responses. Treg reduction or dysregulation is linked to autoimmunity and is associated with immunosenescence [63]. In IBM, reduced Tregs likely contribute to the overall dysregulated inflammatory environment and promote the unrestricted autoimmune response (Fig. 3).

An unresolved question is what antigen triggers the $CD8^+$ and $CD4^+$ T cell autoreactivity. Several studies analysing the highly specific T cell receptor (TCR) variable (V) segment revealed that $CD8^+$ T cells invading IBM muscles display a TCR repertoire less diverse (more clonal) compared to peripheral blood T cells [64–66]. Further sequence analysis of the antigen-specific TCR's CDR3 region confirmed the shared specificity of these muscle-infiltrating T cells which were observed across different muscle groups of individual patients and persisted for years [65,67]. These results highlight a continuous, antigen-driven T-cell response that is prominent in the muscle of patients with IBM, but further studies using modern techniques are required to further elucidate T cell specificity.

B cell-mediated autoimmunity in IBM

The first strong evidence of humoral response in IBM came from Greenberg et al., who found marked upregulation of immunoglobulin gene transcripts within patients' muscles [68]. The origin of the transcripts was traced to infiltrating $CD138^+$ plasma cells that had clonally expanded, class-switched and undergone somatic hypermutation [69,70]. Moreover, the analysis of the plasma cell clonality after cell isolation by laser capture microdissection revealed the presence of identical or highly related clones within adjoining muscle sections suggesting that B cell maturation was occurring within the tissue rather than in secondary lymphoid organs [69,71]. Indeed, under chronic inflammatory conditions such as autoimmunity, infiltrating B and T cells can organise themselves into structures resembling secondary lymphoid organs within the affected tissues in a process termed lymphoid neogenesis [72]. Such structures have been detected in joints of rheumatoid arthritis, thyroid gland of autoimmune thyroiditis, salivary gland of Sjogren's syndrome and other autoimmune conditions [73]. Similar structures have been observed in 57% of IBM tissues [71]. The nodules found were composed primarily of $CD4^+$ T cells, myeloid dendritic cells and $CD138^+$ plasma cells [71]. Combined with a highly upregulated B cell-activating factor (BAFF), the presence of these immune structures provides further evidence for the local B cell activation [71].

The presence of antibodies that target cytosolic 5′-nucleotidase 1A (cN1A) – an intracellular enzyme highly expressed in skeletal muscles – has been reported in 33–72% of patients in various IBM cohorts [74–76]. While strongly associated with IBM, these antibodies have also been reported in other autoimmune conditions, such as Sjogren's syndrome and systemic lupus erythematosus, but not in other inflammatory myopathies [77]. The primary cellular function of cN1A is the dephosphorylation of adenosine monophosphate (AMP) into adenosine and inorganic phosphate [78]. In a healthy state, intracellular adenosine is transported to the extracellular environment, where it exerts effects through its receptors found on almost all cell types [79]. The molecular mechanisms by which *anti*-cN1A antibodies arise and subsequently contribute to IBM pathogenesis remain under investigation. A study by Tawara and colleagues assessed the pathogenic role of these antibodies in vivo using an experimental mouse model where healthy mice received patient-derived *anti*-cN1A IgG [80]. This led to a significant decrease in cN1A. Furthermore, the reduction in cN1A correlated with increased sarcoplasmic aggregation of proteins p62 and LC3 – hallmarks of defective autophagy present in IBM muscle [24]. Additional studies investigating cN1A knockdown in mouse models reported increased phosphorylation of AMP-activated protein kinase (AMPK); a metabolic stress-sensing protein kinase capable of activating catabolic pathways in muscle [81]. Thus, autoantibodies against cN1A are important in the pathogenesis of IBM, specifically in relation to muscle atrophy.

In summary, it is evident that responses of both innate and adaptive arms of immunity are actively involved in IBM. Understanding how they interact and integrate into skeletal muscle biology may uncover previously unexplored mechanisms that can direct future studies towards novel therapeutic targets. Additionally, the complexity of these inter-related systems could provide a reasonable explanation as to why therapeutic interventions targeting the adaptive immune system may be insufficient at stopping further muscle breakdown.

Interactions between autoimmune and degenerative processes in IBM

Due to the presence of both inflammatory and degenerative pathological features in IBM, there has been a long-standing question as to whether one aspect of this disease drives the other, or if they are acting independently in an additive manner. There are multiple potential links between inflammation and cellular stress (see Fig. 4), and both likely contribute ultimately to muscle atrophy but understanding how these two processes interact and what drives them is critical to developing specific therapies.

Mechanisms underpinning muscle atrophy are complex but essentially involve an imbalance between the rate of protein degradation and muscle regeneration. Furthermore, studies in muscle atrophy emphasise the important role of inflammatory mediators such as cytokines and myokines (muscle-derived cytokines). Cytokines typically function as immunomodulating agents that direct intracellular signalling cascades altering gene expression profiles and reshaping cell function. Early

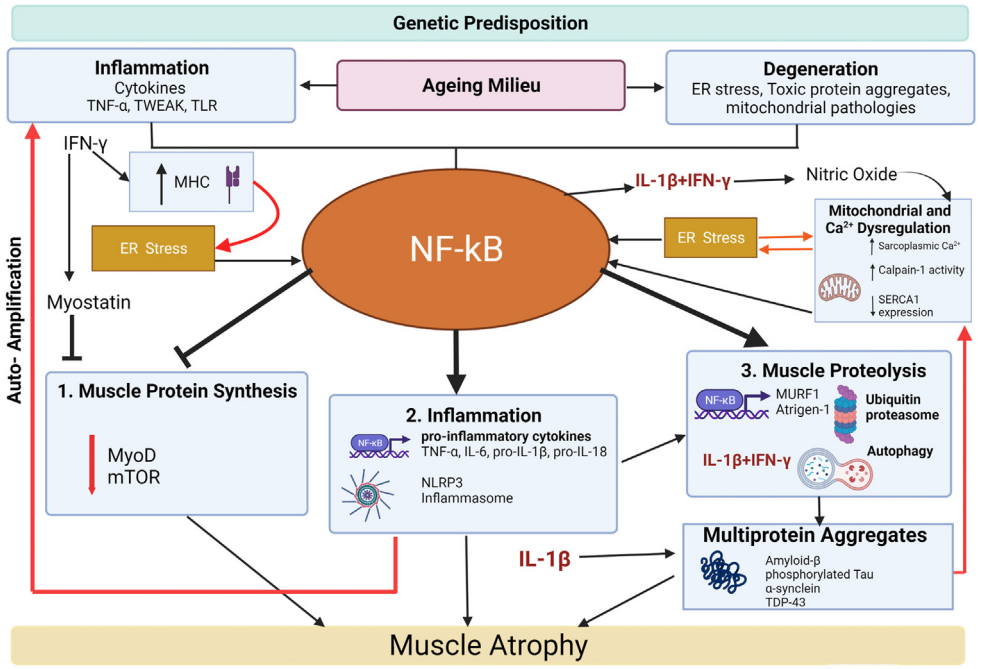

Fig. 4. Schematic representation of the interactions between inflammation and degeneration in IBM. Genetic predisposition and an ageing milieu contribute toward inflammatory and degenerative changes. Both inflammation and degeneration activate NF-κB pathway. NF-κB facilitates muscle atrophy by one of three main pathways: **1.** inhibition of protein synthesis predominantly through degrading MyoD mRNA [98]. Protein synthesis can also be inhibited by myostatin blocking mTOR which is activated through IFN-γ and JAK/STAT signalling [99]**. 2.** Activation of pro-inflammatory cytokines and the inflammasome [92]. **3.** Activation of the ubiquitin proteasome pathway through MURF1/Atrigen1 [97]. Furthermore, NF-κB, stimulated by both pro-inflammatory cytokines and cell stress, can establish two self-sustaining cycles which ultimately lead to ongoing inflammation (via MHC-I and ER stress), as well as cell stress and protein accumulation (mitochondrial dysfunction, inflammasome and overloading the proteasomal and autophagic pathways), resulting ultimately in muscle atrophy and impaired regeneration.

IBM studies reported high concentrations of proinflammatory cytokines including interferon-gamma (IFN-γ), tumour necrosis factor-alpha (TNF-α) and interleukin 12 in serum [52]. Over the past two decades, numerous cytokines have been reported to be elevated in IBM (Supplementary Table 1). Sustained elevated levels of cytokines and myokines facilitate skeletal muscle atrophy by multiple ways, including accelerating muscle degeneration and impairing regeneration, perhaps with NF-κB playing a central role (Fig. 4).

NF-κB is a pleiotropic nuclear transcription factor responsible for the regulation of a plethora of genes, essential for a variety of biological processes. NF-κB remains in the cytoplasm in an inactivated state; following cell stimulation (e.g., by cytokines), it translocates to the nucleus and binds regulatory sequences of multiple genes associated with the inflammatory response [82]. The activation of NF-κB and its role in muscle atrophy has been well documented across various muscle diseases, including muscular dystrophies, cachexia and inflammatory myopathies [83,84]. NF-κB activity also increases during ageing in muscle and may contribute to sarcopenia [85].

Perhaps, the most well-described orchestrator of NF-κB activation is TNF-α; however, other cytokines/molecular proteins, including tumour necrosis factor-like weak inducer of apoptosis (TWEAK) as well as DAMPS/PAMPS, are also known to initiate this pathway [86–89]. Similarly, other cytokines may indirectly activate NF-κB pathways. For instance, IFN-γ is largely responsible for facilitating the transcription of many immunoregulatory genes, including MHC [90]. However, sustained overexpression of MHC, as seen in IBM muscle biopsies, can inadvertently activate ER stress pathways (i.e., ER overload

response and UPR) [91]. ER stress can drive further NF-κB signalling inducing NF-κB target genes, including the up-regulation of MHC and other proinflammatory cytokines, thus creating an auto-amplificatory loop with sustained inflammation and ER stress.

Two of the pro-inflammatory cytokines induced by NF-κB are *pro-IL-1β* and *pro-IL-18* and are activated via the priming of components of the inflammasome pathway particularly of the NOD-like receptor family pyrin domain containing 3 (NLRP3) [92]. In IBM, activation and significance of the inflammasome have not been fully elucidated; however, the inflammasome has an important role in cleaving pro-IL-1β into active IL-1β, and given the expression of IL-1β is correlated to the over-expression of amyloid precursor protein (APP) [93], this suggests that this pathway plays a pathogenic role. Furthermore, IL-1β + IFN-γ induce autophagy through the ERK pathway and can induce nitric oxide (NO) production, causing cell death [94,95]. The combination of inflammation and oxidative stress (NO) can damage mitochondria, further contributing to increased muscle fatigue and weakness. Damaged mitochondria release ROS and mtDNA into the cytoplasm, which also activates both the NF-κB pathway as well as the NLRP3 inflammasome via the cGAS/STING pathway [31,96] (Fig. 4), setting up another self-sustaining loop culminating in protein deposition, cell stress and ultimately cell death.

NF-κB can also drive muscle atrophy by the regulation of genes involved in muscle proteolysis. For instance, NF-κB regulates the Muscle RING-Finger Protein-1 (MURF-1) and Atrogin-1 target protein which belong to a family of ubiquitin ligases that trigger muscle degradation via the ubiquitin-proteasome pathway [97]. The proteasome and autophagic systems are both activated in IBM, but are clearly not effective at clearing deleterious proteins [23], which suggests that these pathways may be overloaded and unable to cope, perhaps as a direct result of combined pro-inflammatory cytokines, oxidative stress and signalling cascades including NF-κB and NLRP3 pathways, possibly contributed by a combination of genetic and ageing pre-dispositions.

Not only can NF-κB influence protein breakdown, but it also affects muscle regeneration. NF-κB can directly inhibit muscle regeneration through the degradation of the myogenesis master gene regulator myoblast determination protein 1 (MyoD) mRNA, which is necessary for muscle stem cell function and differentiation [98]. Protein synthesis can also be inhibited by myokines such as myostatin suppressing the Akt-mediated mTOR signalling pathway which is activated through IFN-γ and JAK/STAT signalling [99]. In IBM, myostatin precursor protein (MstnPP) and myostatin (Mstn) dimer are increased in myofibres [100]. Therefore NF-κB, stimulated by both pro-inflammatory cytokines and cell stress, can establish two self-sustaining cycles which ultimately lead to ongoing inflammation (via MHC up-regulation and ER stress), as well as cell stress, mitochondrial dysfunction, inflammasome and protein accumulation overloading the proteasomal and autophagic pathways, resulting ultimately in impaired muscle regeneration and atrophy.

It is of note that the interaction between inflammation and degeneration was recently investigated in a xenograft model of IBM [20]. Treatment with a murine anti-CD3 monoclonal antibody (OKT3) resulted in a ~96% reduction of T cells in IBM xenografts, resulting in a significant reduction in inflammation (MHC-I and endomysial inflammation). However, IBM myofibres still displayed rimmed vacuoles and loss of TDP-43 function [20]. This could suggest that these IBM pathological features develop independently of or upstream of the inflammatory process, or that the inflammation-induced changes to myoblasts occur early in the regenerative process, leading to a cycle of irreversible degenerative changes that persist and even continue, despite the depletion of T cells.

Concluding remarks

Overall, the progressive muscle wasting and loss of function observed in IBM likely result from a combination of autoimmune mechanisms, chronic inflammation and degenerative processes. The interrelationship between inflammation and degeneration is highlighted by several cytokines and myokines capable of inducing degenerative and cellular changes. It remains unclear which of these processes begins the cascade of events, but once initiated, they both appear to promote each other. Multiple genetic risk factors have been identified, which confirm that this disease relies on multiple immunological and non-immunological susceptibility factors that set the conditions for the pathology

to emerge. Ageing appears to be an important factor with its changes on skeletal muscle, mitochondrial function, immune function and proteostasis. A comprehensive understanding of the pathogenic mechanisms and their interactions will be required to define effective therapeutic strategies.

Practice Points

- IBM is a complex multifactorial disease where ageing and genetic predisposition likely create the milieu allowing inflammatory and degenerative muscle changes.
- Degenerative changes in IBM are believed to result from dysregulated proteostasis, increased endoplasmic reticulum stress and mitochondrial abnormalities.
- NF-kB likely plays a central role in muscle atrophy by inhibiting protein synthesis, activating pro-inflammatory cytokines and the inflammasome and activating the ubiquitin-proteasome pathway.
- Both CD8 and CD4 T cells display phenotypic changes which are often attributed to refractoriness towards traditional immunosuppressants in IBM.

Research Agenda

- Further studies investigating how inflammatory and degenerative pathomechanisms interact and what drives them at the cellular and molecular levels will ultimately lead to the development of specific effective therapies.
- Re-evaluation of T cell specificity using modern techniques is required to answer the unresolved question as to what antigen triggers the $CD8^+$ and $CD4^+$ T cell autoreactivity in IBM.
- Functional studies are needed to confirm whether overactivation of NF-kB plays a key role in facilitating muscle atrophy in IBM.

Author contributions

Conceptualisation, EM, TEL and MN. Writing – original draft, EM, JDC, NS, AS AW and TEL. Writing-review and editing, EM, NS, JDC, AW, TEL and MN. Figures, EM, AW, MN and JDC. Funding acquisition, JDC, MN and TEL Supervision, JDC, TEL and MN. All authors contributed to the article and approved the submitted version.

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Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

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