

Review

Sporadic inclusion body myositis: a continuing puzzle

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Abstract

There is now compelling evidence that sporadic inclusion body myositis (sIBM) is a muscle-specific autoimmune disease in which both T and B-cells play a part and in which both cytotoxic muscle fibre necrosis and degeneration occur. However the factors responsible for breakdown of immune tolerance and the nature of the target antigens expressed by muscle fibres remain unknown. Genetic factors are known to contribute to susceptibility, in particular MHC haplotypes which may influence antigenic presentation, and could also operate through genetic variations in muscle fibre constituents or immune effector mechanisms. Viral infection may act as a trigger mechanism, as in cases of HIV-associated sIBM. Our understanding of the mechanisms leading to the degenerative changes in muscle fibres is still incomplete. Protein misfolding and proteasomal dysfunction rather than defective transcriptional control is likely to underlie the abnormal accumulation of multiple proteins in the muscle fibre inclusions. However, aberrant transcription is thought to be the basis for the accumulation of potentially toxic mutant protein forms (e.g. UBB⁺¹). The origin of the multiple clonally expanded somatic mtDNA mutations in COX-negative segments of muscle fibres remains uncertain but may be linked to the effects of oxidative stress. It is proposed that the disproportionate involvement of certain muscles in sIBM may be due to the existence of muscle group-specific transcriptomes which are differentially affected by the disease process and that the male predominance of the disease may indicate the influence of genes preferentially expressed in males. There is a need to develop better animal models of sIBM in which the relationship between the inflammatory and degenerative components of the disease as well as the gender difference in susceptibility and differential vulnerability of different muscle groups can be more critically investigated.

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1. Introduction

Since the first description of a form of chronic polymyositis with intranuclear and cytoplasmic filamentous inclusions by Chou in 1967 [1] and the subsequent designation of 'inclusion body myositis' for such cases by Yunis and Samaha in 1971 [2], the condition has come to be recognised as the most frequent inflammatory myopathy over the age of 50 years, and the most important muscle disease associated with aging. Its aetiopathogenesis is still poorly understood but is thought to involve a complex interaction between genetic and environmental factors and aging.

Pathologically sIBM is characterised by a unique combination of changes comprising a T-cell predominant inflammatory infiltrate with invasion of MHC-I expressing muscle fibres, cytotoxic necrosis and the presence of congophilic inclusions and rimmed vacuoles containing β -amyloid, phosphorylated tau and a variety of other proteins. In addition, an increased number of fibres show segmental loss of cytochrome oxidase *c* (COX) activity, which is associated with the presence of multiple clonally expanded somatic mitochondrial DNA mutations. A number of pathogenetic theories have been proposed over the past 40 years, but it is still debated whether sIBM is primarily a T-cell mediated inflammatory myopathy or a myodegenerative disorder with abnormal protein aggregation, inclusion body formation and a secondary inflammatory response in muscle.

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In this review we discuss the latest concepts in the pathogenesis of sIBM and attempt to bring together the various lines of evidence derived from recent immunological, genetic and molecular studies and from previous studies. The relevance of genetic susceptibility factors and of aging-related changes in the intracellular milieu, and factors that might underlie the differential susceptibility of different muscle groups and the male predominance of the disease are also discussed.

2. Immunopathogenesis

The evidence supporting a primary role for the immune response in sIBM is substantial (Fig. 1). Firstly, quantitative histological observations show that non-necrotic muscle fibres invaded by T-cells are several times more frequent than fibres containing rimmed vacuoles or inclusions [3]. Whilst some investigators [4] found that the inflammatory changes are a consistent finding throughout the course of the disease, others have reported that inflammation is more abundant in the early stages, and only minor or even absent in the later stages of the disease [5,6], contrasting with the numbers of vacuolated fibres which increase in the middle or later stages of disease [4–6]. These observations suggest that the cellular immune response plays an active role at least in the early stages of the disease, and that the rimmed vacuoles and other degenerative changes in muscle fibres are probably later manifestations.

In addition, the endomysial inflammatory cells have been shown to be predominantly activated CD8+ T-cells [7,8] which are clonally expanded and have a restricted expression of the V β chain in the complementary determining region 3 (CDR3) of the T-cell receptor (TCR) [9,10]. These T-cell clones have been shown to be identical in different muscles in the same individual [11] and to persist over a period of years [12]. They have recently also been found to be present in peripheral blood [13] and *in vitro* studies have shown that they respond to IL-2, implying that the T-cells had been primed *in vivo*. These observations

support the notion of a sustained antigen-driven immune response to a limited repertoire of antigens presented by MHC-I-expressing myocytes. In addition to clonally expanded activated CD8+ T-cells, a recent study of sIBM muscle [14] showed that there is also an abundance of dendritic cells, which are known to play an important role in antigen presentation and local T-cell activation.

Expression of MHC-I, which is a necessary pre-requisite for CD8+ T-cell mediated cytotoxicity, is up-regulated in invaded myocytes as well as many morphologically normal fibres in sIBM [4,15–17]. Myocytes also express the co-stimulatory molecules inducible co-stimulatory-ligand (ICOS-L) [8,18] and BB-1 [19], which are essential for T-cell stimulation. These observations strongly suggest that the muscle fibres are acting as antigen-presenting cells, interacting with CD8+ cells with resulting cytotoxicity and segmental myonecrosis. The mechanism of cell death does not appear to involve Fas–Fas-ligand-dependent apoptosis, as despite up-regulation of Fas immunoreactivity [20], the myocytes also express Bcl-2 as well as the cell death suppressor molecule ‘human IAP-Like-Protein’ (hILP) [21] and do not show the usual histological markers of apoptosis such as DNA fragmentation [22,23]. On the basis of the known properties of the HLA class-I restricted pathway [24], the antigens being presented to the immune cells can be predicted to be short peptides (8–10 amino acids), which could be derived either from endogenously synthesized self-proteins, or possibly from viral proteins (see below). Characterizing the nature of the antigen(s) remains an important priority for future investigation and could lead to the development of more specific immunotherapeutic approaches for the treatment of the disease.

Although sIBM has traditionally been thought of as a CD8+ T-cell-mediated disorder, there is also increasing evidence for a humoral immune component as shown by the presence of abundant plasma cells in the inflammatory infiltrate [25]. In addition, microarray studies have consistently demonstrated that immunoglobulin transcripts are among the most abundant of all transcripts in sIBM muscle

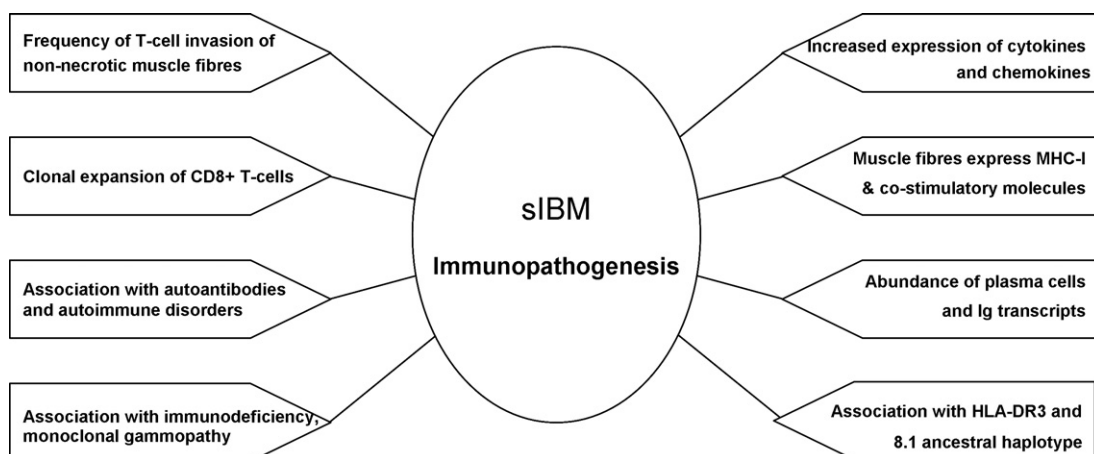


Fig. 1. Summary of the major lines of evidence supporting the immunopathogenesis of sIBM.

[26,27]. Moreover, Dalakas et al. [28] reported a higher incidence of monoclonal gammopathy among sIBM patients than in an age-matched control population, again implying that chronic B-cell activation and immunoglobulin production may play a role in the pathogenesis. However, it remains unclear whether this antibody response is antigen-specific, or if it is part of the effector mechanism of muscle fibre injury. It is of interest however, that serum IgG from patients with sIBM has been shown to bind to myonuclear antigens [28].

3. MHC-I up-regulation, cytokines and ER stress

The mechanism of the MHC-I up-regulation in muscle fibres remains uncertain. It has been hypothesised that it may be due to the release of cytokines [29], on the basis that in human myoblast cultures MHC is up-regulated by interferon- γ (IFN- γ) [30–32]. Immunohistochemical, reverse transcription-PCR, mRNA and gene profiling studies [26,27,33–36] investigating cytokine and chemokine expression have found varying patterns, but with IL-1 β , IFN- γ , TGF- β and TNF- α being the most consistently expressed. These are produced not only by the invading inflammatory cells, but also by endothelial cells and the muscle fibres themselves. IL-1 β , which is derived from activated macrophages and T-cells, is known to enhance transcription of amyloid precursor protein (β APP) acting through the protein kinase C pathway [37], and co-localizes with the amyloid deposits in vacuolated muscle fibres [38]. This could therefore be one of the links between the inflammatory and degenerative processes as first proposed by Dalakas [38]. For a more detailed discussion of the molecular interactions between the inflammatory/immune and degenerative processes in sIBM the reader is referred to the review by Dalakas in 2006 [39].

An alternative explanation is that the up-regulated MHC-I expression is a result of the endoplasmic reticulum (ER) overload response [40] acting via NF κ B activation, and resulting in a self-sustaining loop involving further MHC-I up-regulation, cytokine release and APP production [39–42]. The ER has important roles in the processing, folding and exporting of newly synthesised proteins, and in response to a variety of cell stressors including viral infections or the accumulation of misfolded proteins [40,43], initiates the ER stress response which involves both the unfolded protein response (UPR) and the ER overload response. The UPR is associated with up-regulation of ER chaperone proteins such as Grp78, while the ER overload response causes an up-regulation of NF κ B and a resultant increase in transcription of cytokines, MHC-I [44] and APP [45]. Both these signalling pathways are known to be active in sIBM muscle, as shown by the demonstration of increased expression of ER chaperone proteins including Grp78 [41], and of NF κ B in immunohistochemical studies [46].

Further evidence for the important role of MHC-I expression comes from the experimental observation that

transgenic mice with targeted over-expression of MHC-I in muscle develop a self-sustaining form of myositis [47]. Furthermore, there is evidence that MHC-I expression may directly attenuate muscle differentiation and interfere with muscle repair [32]. Thus MHC-I up-regulation, whether due to cytokines, ER stress or both, seems to play a central role in the ongoing disease process not only by facilitating antigen presentation to CD8+ T-cells, but also by causing or perpetuating ER stress, resulting in further protein accumulation and cytokine release, and possibly also by retarding muscle regeneration.

4. Viral involvement

Although the cytoplasmic and nuclear tubulofilamentous inclusions in muscle fibres were first thought to be viral in origin, and subsequent immunohistochemical studies suggested the possibility of an aberrant mumps virus [48], this hypothesis was not supported by PCR studies of muscle tissue [49,50]. The failure of repeated attempts to identify viral antigens or genomes in sIBM [51–54] might therefore favour an autoimmune response to muscle auto-antigens. However it does not preclude the possibility of a transient viral infection initiating an autoimmune response by inducing transient muscle injury, MHC expression and presentation of auto-antigens by myofibres, or on the basis of molecular mimicry [55].

Evidence that viral infections may trigger sIBM comes from the reported association with retroviral infections including HTLV [56] and HIV [57,58]. In these cases, retroviral proteins were found only in endomysial macrophages and not within myocytes. Further investigation by Ozden et al. [59] in a HTLV-infected patient found mononuclear cells producing the immunodominant viral Tax protein and anti-Tax perforin-producing CD8 T-cells in muscle tissue which persisted over time, indicating that a chronic viral infection with immune recognition is sufficient to trigger an inflammatory myopathy. This was recently confirmed by Dalakas et al. [60] who demonstrated the presence of virus-specific clonally expanded CD8+ T-cells surrounding and invading muscle fibres in HIV-infected patients with sIBM.

5. Rimmed vacuoles and the nuclear hypothesis

The most widely accepted hypothesis is that the rimmed vacuoles are autophagic and are composed of lysosomes, as shown by the presence of cathepsin B & D [61,62] and lysosome-associated membrane proteins (LAMPs) [63]. Other major lysosome-related proteins such as mannose-6-phosphate receptor (M6PR) and clathrin are also present in the rimmed vacuoles as well as the cytoplasm of vacuolated and non-vacuolated muscle fibres [64]. In addition, in a recent study microtubule-associated protein 1 light chain 3 (LC3), which is a human homologue of the yeast autophagy-related gene 8 (Atg8), and a marker of autophagic activity, was found to be increased in sIBM muscle fibres,

and co-localized with β APP and β -amyloid [65]. This indicates that the lysosomal system is activated in sIBM, and that activation or possibly dysfunction of this system may play a central role in the formation of rimmed vacuoles. However, not all of the vacuoles are positive for lysosomal components and many are not fully encircled by membrane [66,67] suggesting that other processes may also play a role in rimmed vacuole formation.

Nuclear abnormalities such as chromatin clumping, filamentous inclusions and focal rupture of nuclear membranes are well-recognised in sIBM [66,68]. This has led some investigators to hypothesise that rimmed vacuoles may also arise as a consequence of myonuclear breakdown and discharge of nuclear contents into the cytoplasm [69,70], possibly due to dysfunction of the nuclear envelope. Further evidence for nuclear dysfunction and for a nuclear origin for rimmed vacuoles was the finding of an uncharacterised protein which binds single-stranded DNA that was localized predominantly to structurally abnormal myonuclei but was also present in rimmed vacuoles [69]. In addition, recent immunohistochemical studies have shown that rimmed vacuoles are frequently lined by remnants of the nuclear membrane (labelled by antibodies to lamin A/C and emerin), and also contain nuclear histones and the nuclear transcription factor pELK-1 [67,71].

Nuclear abnormalities also occur in other rimmed vacuole myopathies, including ‘distal myopathy with rimmed vacuoles’ (DMRV) and oculopharyngeal muscular dystrophy (OPMD), with nuclear localization of the mutated GNE protein in DMRV [72] and of the mutant polyadenylate-binding protein (PABP2) in OPMD [73]. Moreover, similar nuclear abnormalities have been reported in Emery-Dreifuss muscular dystrophy [74], in which there is a deficiency of the nuclear envelope proteins lamin A/C and emerin, and in which rimmed vacuoles may also occur [75]. These observations therefore indicate that the origin of rimmed vacuoles is heterogeneous, and that more than one mechanism may be responsible for their formation in sIBM.

6. Protein accumulation and proteasomal function

The factors responsible for the abnormal accumulation of multiple proteins in muscle fibres in sIBM are poorly understood. Microarray studies [26,27] have shown that there is increased expression of multiple immune and non-immune genes in sIBM muscle, but that some genes considered relevant to the pathogenesis of sIBM, including β -amyloid and tau, are also over-expressed in other inflammatory myopathies such as polymyositis and dermatomyositis, some to a greater degree than in sIBM. The results of these studies, and of proteomic studies [76,77], indicate that whilst there is up-regulation of some genes, the wide range of the proteins accumulated in sIBM is unlikely to be due to large-scale uncontrolled gene activation and aberrant transcription, but is more likely to be due to post-transla-

tional mechanisms such as protein misfolding and impaired proteasomal breakdown.

Protein misfolding can result from a variety of factors including genetic mutations, faulty mRNA processing, translational errors, oxidative stress, interference from viral gene products or other factors [78,79]. While correctly folded proteins are soluble and remain localized to the appropriate intracellular compartment or are associated with cell membranes, misfolded proteins are ejected from the ER into the proteasome for degradation. When the degradative capacity of the proteasome is exceeded, protein accumulation occurs. Functional studies of proteasomal degradation in sIBM muscle have produced varying results, with one study finding a reduced activity, which was not confirmed in another study [80,81]. However, both of these studies found an increased expression of 26S proteasome subunits which may represent a compensatory mechanism to deal with an increased protein load in muscle fibres [81]. Impaired proteasomal function is known to occur with aging (see below), and could also result from the processing of mutant or misfolded proteins, as the function of the ubiquitin-proteasomal system (UPS) is known to be profoundly impaired by such proteins [82,83]. The other possibility, that inefficient proteasomal function might be due to mutations or genetic polymorphisms in certain key components of the UPS, as in familial forms of Parkinson’s disease associated with mutations in parkin and ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) genes [84], should also be considered and warrants investigation.

The protein inclusions in sIBM also contain ubiquitin [85] and parkin [86], which both play important roles in the ATP-dependent proteasomal breakdown of proteins [87,88]. Moreover, mutated ubiquitin (UBB^{+1}) which lacks the essential C-terminus glycine rendering it incapable of ubiquitinating other proteins, has been shown to be present in both vacuolated and non-vacuolated muscle fibres [89]. This is of interest as UBB^{+1} is known to inhibit proteasomal function in neuronal cells [90]. The accumulation of mutant proteins such as UBB^{+1} also occurs in other age-related diseases such as Alzheimer’s disease, and is thought to be the result of molecular misreading at the mRNA level [91]. Therefore, parallels can be drawn with other neurodegenerative diseases in which proteasome inhibition is thought to play a role, such as Huntington’s disease, whereby the accumulation of one mutant protein (e.g. huntingtin), can lead to inhibition of the UPS [82] and to the secondary accumulation of many other proteins. In the same way, as proposed by Askanas and Engel [42], it is possible that in sIBM the accumulation of one abnormal protein, such as β -amyloid or even UBB^{+1} , could be responsible for the secondary accumulation of other proteins.

7. Role of β -amyloid

It has been proposed that the abnormal accumulation of β APP epitopes and mRNA are key upstream pathogenic events which precede the appearance of amyloid deposits

and other changes in muscle fibres [42]. Abnormal processing of β APP can lead to the preferential accumulation of the β -amyloid42 epitope [42], which is more prone to aggregate and more cytotoxic than the β -amyloid40 epitope [92], and has been shown to be the predominant form present in sIBM muscle fibres [93]. In addition, over-expression of β APP in muscle cultures [94], and in transgenic mice [95–97] induces sIBM-like changes including β -amyloid accumulation, congophilic inclusions and vacuolation, as well as intranuclear inclusions and mitochondrial abnormalities in muscle cultures [98]. Moreover, MCK-APP/PS1 double transgenic mice which preferentially over-express the β -amyloid42 epitope have more severe sIBM-like changes, including accumulation of phosphorylated tau and CD8+ T-cells and an earlier onset of motor impairment [99].

Thus, these findings are in keeping with β APP and β -amyloid having a pivotal role in the development of the cellular changes in sIBM [42]. However, the factors responsible for the increased expression of β APP have remained elusive. The finding that, unlike hIBM cells sIBM myogenic cells do not overproduce β APP in short-term culture [100], suggests that the increased β APP expression *in vivo* is unlikely to represent a primary defect but is more likely to be secondary to factors affecting levels of transcription, such as IL-1 β [37]. The demonstration in sIBM muscle of increased expression of the β -secretase enzymes (BACE1 and BACE2) which cleave β APP [101], also supports the notion that there is enhanced amyloidogenic processing of β APP, and raises the possibility of reducing amyloidogenesis by the therapeutic administration of secretase inhibitors.

Another factor that has been postulated to influence β APP processing is the abnormal trafficking of cholesterol in muscle fibres [102]. Cholesterol is known to increase β -amyloid production in non-muscle cells [103], and in human muscle cultures over-expressing β APP [104], and has been shown to be accumulated in sIBM muscle fibres in a non-esterified form [105], together with the cholesterol transporter caveolin-1 [106]. These observations also have potential therapeutic implications as treatment with the 3,4-hydroxy-methyl-glutaryl-CoA inhibitor lovastatin, which reduces cholesterol biosynthesis, has been shown to lower β -amyloid production in cultured cells [107].

8. Oxidative stress and mitochondrial abnormalities

Markers of oxidative stress have been shown to be increased in sIBM muscle [108–110], even in morphologically normal muscle fibres [111]. In addition, other markers of cell stress including the small heat shock protein α B-crystallin have also been reported to be increased even in structurally normal myofibres [112]. Oxidative stress could therefore be an important upstream event triggering over-expression of β APP via NF κ B [46] and Ref-1 [113]. This could initiate a self-perpetuating cascade, as β -amyloid itself is also known to induce oxidative stress (reviewed in

[114]). Multiple factors could contribute to increased generation of reactive oxygen species (ROS) and oxidative stress. These could include genetic variations in components of the respiratory enzyme chain, as have been reported in Parkinson's disease [115].

The pattern of segmental COX deficiency which occurs in a subset of muscle fibres, and is associated with clonal expansion of multiple large-scale mtDNA deletions or point mutations (reviewed in Oldfors et al. [116]), is similar to that which occurs in normal aging [117]. Multiple mtDNA deletions have been demonstrated in different muscle fibres in sIBM [118], and can differ even between different segments of the same fibre [119–121]. In addition, segmental duplications and depletion of mtDNA also occur [120,121]. It has been proposed that the mutations are likely to occur during the repair of mtDNA damage induced by oxidative stress (Krishnan KJ and Turnbull D, personal communication). The mitochondrial changes could also be related to abnormal β APP processing, as mitochondrial abnormalities have been demonstrated in muscle cultures over-expressing β APP [98], or to the effects of pro-inflammatory cytokines, as muscle cultures treated with IL-1 β also demonstrate mitochondrial abnormalities [35].

The clinical significance of the mitochondrial abnormalities in sIBM is still unclear, particularly given that *in vivo* 31 P magnetic resonance spectroscopy studies have not shown any evidence of impaired muscle oxidative metabolism [122,123]. However, the numbers of fibres showing these changes in muscle biopsies are usually in excess of what would be expected for the patient's age [119,124], and in some instances are more numerous than in cases of mitochondrial myopathy where they would be considered to be pathogenic. Moreover, in normal aging mtDNA mutations have been associated with muscle fibre atrophy and breakage, and are thought to be an important factor in the sarcopenia of aging [125]. As suggested by Oldfors et al. [116] it is therefore possible that the mtDNA mutations and associated respiratory deficiency may contribute to the atrophy of muscle fibres and muscle weakness in sIBM.

9. Effects of aging

Normal aging is associated with a number of biological and functional changes both in skeletal muscle and the immune system. Aging skeletal muscle is characterised by an accumulation of mtDNA mutations, increased generation of ROS and oxidative stress, and a decline in energy metabolism and activity of the electron transport chain [117]. In addition, gene expression studies have shown up-regulation of genes involved in inflammatory pathways [126], while cytokines known to be associated with cachexia and proteolysis such as TNF- α are also increased [127]. There is also a progressive decline in proteasomal activity with aging, as well as an up-regulation of ER stress-response chaperones, preferential oxidation of ER-resident proteins and a disturbance of calcium homeostasis, all of which could contribute to the formation and accumulation

of misfolded proteins [128]. The deteriorating cellular environment associated with aging is therefore likely to be a contributory factor in the pathogenesis of sIBM and a number of the cellular derangements in sIBM could be seen as an exaggeration or acceleration of the normal aging-related processes in muscle fibres. Moreover, aging changes in the immune system, which include a decline in the ability of T-cells to recognise ‘self’ and ‘foreign’ antigens (reviewed in [129,130]), could contribute to the breakdown of tolerance and could be one of the factors responsible for the late onset of sIBM.

10. Genetic susceptibility

The rare occurrence of inclusion body myositis in twins and in families with more than one affected individual suggested that genetic factors might also play a part in the pathogenesis of sporadic IBM. The strongest evidence for genetic susceptibility in Caucasians is the association with HLA-DR3 and the extended MHC 8.1 ancestral haplotype (marked by HLA-A1, B8, DRB1*0301, DRB3*0101, DQB1*0201). This was originally reported by Garlepp et al. [131] in Western Australia, and has since been confirmed in studies from the Netherlands, Germany and the United States [132], being found in ~75% of patients with sIBM and also in familial cases [133]. The reported prevalence of sIBM is highest in Northern European, North American and Australian Caucasian populations, which also have the highest frequencies of HLA-DR3, whereas the prevalence is low in African-American, Australian aboriginal and Turkish populations which have a low frequency of HLA-DR3 [134]. Other reported associations are with alleles of the 35.2 ancestral haplotype [135], while DR53 and DQA1 have been reported to be protective [136,137]. In contrast, in Japanese there is an association with the 52.1 ancestral haplotype (marked by B*5201, DRB1*1502) [138].

The association between sIBM and the 8.1 MHC ancestral haplotype has been considered to support a primary immune pathogenesis for the disease as this haplotype is also associated with a number of other classical autoimmune disorders including type 1 diabetes mellitus, myasthenia gravis and Sjögren’s syndrome [139]. Recent recombinant mapping studies by our group have indicated that susceptibility may be conferred by multiple genes in the central MHC region in linkage disequilibrium with DRB1*0301 [135,140]. It is of interest that a number of candidate genes in this region are known to be expressed in muscle and are not associated with the immune system. Further characterisation of these genes could provide important clues to understanding the pathogenesis of sIBM (see below).

11. Differential muscle involvement

The selective pattern of muscle weakness and atrophy in sIBM remains unexplained and contrasts with the

non-selective pattern of muscle involvement in other inflammatory myopathies such as polymyositis and dermatomyositis. The factors that render some muscles more or less susceptible than others remain unknown, but one possibility is that there might be differing levels of gene/protein expression in different muscle groups, which might affect their vulnerability to a particular insult. One study investigated this hypothesis in a transgenic mouse model of dysferlinopathy [141], and found significant differences in gene expression profiles between proximal and distal limb muscles, despite similar fibre-type compositions, as well as differences in the response of these muscle groups to dysferlin deficiency. These findings imply that there are muscle group-specific transcriptomes that may react differently in the presence of a disease-associated mutation, but also that anatomically different skeletal muscles differ from one another in ways that had not previously been fully appreciated.

Fibre-type composition, workload, nutrition and age are all known to alter muscle gene transcription. Whilst workload and nutrition are unlikely to be significant factors accounting for the muscle selectivity in sIBM, an immunohistochemical study investigating fibre-type profiles [142] found a tendency towards greater numbers and sizes of type I fibres and a reduction in type II fibres in sIBM compared to controls. This predominant involvement of type II fibres has also been reported by other investigators [65,143] but is unlikely to account for the differential pattern of muscle involvement in sIBM. A greater susceptibility of type II fibres in sIBM is not surprising given that they are also more affected by the normal aging processes [127].

Sporadic IBM has features reminiscent of other muscle diseases such as the muscular dystrophies and distal myopathies that are known to be due to inherited abnormalities in muscle-specific proteins in terms of the selectivity of muscle involvement. Therefore the pathogenesis of sIBM may involve a stressor on the myocyte in the context of genetic predisposition, which interacts with a gene, gene control system (such as a promoter or microRNase), or even a particular muscle protein, such as a nuclear envelope protein, resulting in the differential pattern of muscle involvement.

12. Male predominance of sIBM

Another feature of sIBM which may hold a clue to the underlying pathogenesis is the male predominance of the disease which is in contrast to most other autoimmune diseases, in which there is a female predominance. One possible reason for this could be related to hormonal differences, in particular, the protective effect of oestrogen on skeletal muscle. It is well documented that oestrogen plays a significant role in maintaining muscle membrane stability as well as possibly having roles in attenuating inflammation and acting as an anti-oxidant [144,145]. However, if such effects are protective it would be expected that they would be lost progressively after the menopause and that any gender dif-

ferences would be less apparent in the post-menopausal period. In addition there appear to be gender differences in the levels of other important anti-oxidants such as vitamin E and glutathione [145].

An alternative hypothesis is that a currently unknown gene(s) preferentially expressed in males may play a role in the development or expression of the disease. This concept has been investigated in a rodent model of Parkinson’s disease [146], where there is also a male predominance. Here it was reported that the testis-determining *Sry* gene is specifically expressed in the substantia nigra of adult male rodents, and that targeted down-regulation of the gene leads to impaired dopaminergic function in the nigrostriatal system and motor disability resembling Parkinson’s disease. In addition, a recent study of gene expression profiles in dopaminergic neurones in the substantia nigra in Parkinson’s disease demonstrated gender differences in gene expression which may underlie the male predisposition to the disease [147]. Whether such male-specific or male-predominant genes could also have a role in determining susceptibility to sIBM warrants further investigation.

13. Conclusions and future perspectives

Recent studies summarized above have provided important new insights into the cellular and humoral immune mechanisms operating in sIBM, and the molecular derangements in muscle fibres. However, our understanding of the relationship between the inflammatory process and the degenerative changes in muscle fibres remains

incomplete and there are still outstanding questions regarding the factors responsible for increased cell stress, the mechanisms of lysosomal activation and proteasomal dysfunction, and the significance of the myonuclear and mitochondrial abnormalities. A proposed pathogenetic schema showing established or postulated interactions between these various processes is presented in Fig. 2.

Other outstanding questions relate to the factors responsible for the breakdown of immune tolerance, and the identity of the immunogenic peptides targeted by T-cells. Whether the loss of tolerance in sIBM is due primarily to an aberrant response of the immune system or to a defect in skeletal muscle, or to a combination of both, remains an open issue, as it is in most other chronic organ-specific autoimmune diseases [55]. Viral infections, which are considered to be important potential triggers in other autoimmune diseases such as multiple sclerosis and type 1 diabetes [148] could also play a part in sIBM, either by inducing antigen presentation, or by interfering with immunoregulatory mechanisms. The known occurrence of sIBM in patients with HIV and HTLV infections, which primarily affect the immune system, indicates that the latter mechanism *per se* is sufficient to cause the disease in certain individuals.

Genetic factors could contribute to breakdown of tolerance in a number of ways, not only through polymorphisms in MHC genes that may influence antigen presentation, but also in genes involved in immune regulation and T-cell activation, as has been demonstrated in type 1 diabetes and other autoimmune diseases [149], and might

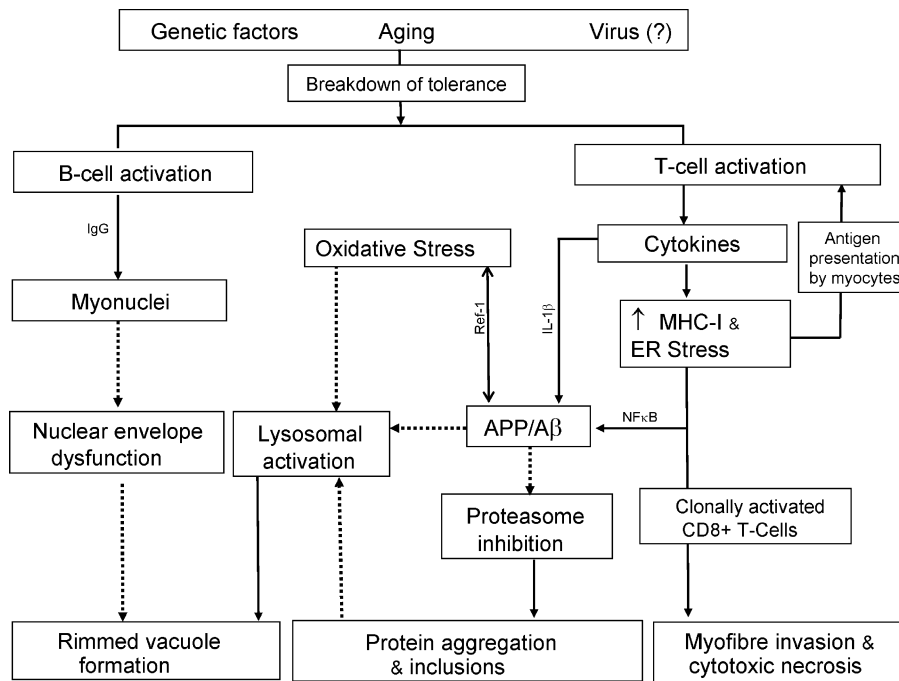


Fig. 2. Proposed schema for the pathogenesis of sIBM incorporating the known cellular and humoral immune mechanisms, putative factors leading to breakdown of immune tolerance, and downstream events linked to the immune/inflammatory process as discussed in the text of the review. The possible role of mitochondrial dysfunction is not shown but this could contribute to oxidative stress via increased generation of ROS. The interrupted lines indicate steps which are still hypothetical.

also operate at the level of the muscle. For example, genetic variations in cell stress proteins and components of the ubiquitin-proteasomal pathway could lead to the accumulation of amyloidogenic proteins and to the generation of immunogenic peptides. Establishing the identity of the disease-associated alleles in the MHC susceptibility region, and whether they are muscle-specific or more widely expressed remains a high priority for ongoing investigation. In addition, polymorphic variations in other genes such as those associated with the respiratory enzyme chain and the production and breakdown of reactive oxygen species also warrant investigation.

It has been argued that the resistance of the disease to conventional forms of immunotherapy, which is in sharp contrast to other forms of T-cell mediated inflammatory myopathy such as polymyositis, favours a primary degenerative aetiopathogenesis for sIBM. However, as in the case of multiple sclerosis and type 1 diabetes, which also respond poorly to immunotherapeutic interventions, this does not necessarily undermine the importance of the immune response in the pathogenesis of the disease but is more likely to reflect the inadequacy of current therapies, or the fact that they are usually administered late in the course of the disease. Further clarification of the immunological mechanisms, antigenic targets and downstream molecular changes in muscle fibres will lead not only to a better understanding of the pathogenesis of sIBM, but is also likely to yield novel therapeutic targets and strategies for the treatment of the disease.

There is as yet no ideal animal model of sIBM and there is a need to develop better models which reproduce both the inflammatory and degenerative components of the disease, in which the interaction between these processes, as well as the gender differences in susceptibility and differential vulnerability of muscle groups can be investigated and new therapeutic strategies can be tested.

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