Pathogenic aspects of dermatomyositis, polymyositis and overlap myositis

Romain K. Gherardi

CHU Henri-Mondor, AP-HP, centre de référence des maladies neuromusculaires « Garches-Necker_Mondor-Hendaye », service d’histologie, 94010 Créteil, France

Correspondence: Romain K. Gherardi, CHU Henri-Mondor, service d’histologie, avenue du Marechal-de-Latte-de-Tassigny, 94010 Créteil, France. romain.gherardi@hmn.aphp.fr

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Summary

Inflammatory myopathies (IMs) often have distinct histopathologic features suggesting humorally mediated involvement of the microcirculation in dermatomyositis (DM), including early capillary deposition of the complement C5b-9 membranolytic attack complex (MAC) and secondary ischaemic changes; and CD8 T-cell-mediated and MHC1-restricted autoimmune attack of myofibers in polymyositis (PM) and inclusion body myositis. Novel insights in these specific diseases include emerging evidence that capillary loss involves whole microvascular units in DM, and that regulatory T-cells strongly protect myofibers from experimental autotoxic attack in PM. However, all IMs do not exhibit pathophysiology-relevant histopathologic features of DM or PM. Autoimmune necrotizing myopathies (AINM) occur in the absence of endomysial inflammatory cells and may be specifically associated with anti-SRP autoantibodies. Moreover, IM histopathological features may be scarce, unspecific and overlapping. Therefore, increasing attention is paid to features shared by IMs regardless of their type, relevant to the innate immune response and to non-immune mechanisms. Innate immune responses to myodamage (and/or as yet unknown stimuli), involves release of chemokines, activation of specific Toll-like receptors (TLRs) and complex Th-1, Th-17 and other cytokine interplays; it triggers DC recruitment and maturation, and is associated with type 1 IFN signature (especially in DM where type 1 IFN-producing cells called plasmacytoid DCs are mainly detected). Non-immune mechanisms mainly include endoplasmic reticulum stress induced in myofibers by up-regulation of MHC-class I antigens (as typically observed in PM with a diffuse pattern and in DM with perifascicular predominance). ER stress may favour autoimmune reactions but may also be associated with myofiber damage and dysfunction in the absence of lymphocytes. Overlap myositis (OM) may be associated with other connective tissue diseases and a variety of autoantibodies, such as those directed against IRNA synthetase. Myositis specific autoantibodies are mainly expressed by regenerating myofibers, that may also express MHC-1 and endogenous ligand-binding TLRs, thus drawing a picture in which the regenerating myofiber plays a central pathophysiological role.
There is still no formal international consensus about the diagnostic and classification criteria for patients with inflammatory myopathies (IMs) [1]. There is almost general consensus, however, to consider inclusion body myositis (IBM) separately from the other IMs since its clinical presentation, chronic evolution, unresponsiveness to immunomodulatory treatments, and accumulating data from basic research strongly suggest a degenerative disorder associated with an autoimmune reaction rather than a bona fide autoimmune muscle disease [2]. Besides IBM, three main types of IMs can be identified on the basis of characteristic muscle biopsy findings: dermatomyositis (DM), polymyositis (PM), and autoimmune necrotizing myopathy (AINM). All three types may be associated with connective tissue diseases or myositis specific autoantibodies (overlap myositis), which may confer subtle additional pathological features [3,4]. In this review, we shall first focus on distinct, pathophysiology-relevant, myopathologic features of DM and PM [5], and then on immunopathologic mechanisms shared by DM, PM and overlap myositis. Although somewhat artificial, this was deliberately done in an attempt to increase clarity.

**Dermatomyositis**

DM typically includes skin rash and muscle weakness. Even the so-called “amyopathic DM” is commonly associated with some typical myopathological alterations. Histopathologic alterations are heterogeneous distributed, markedly necrotic and inflammatory muscle fascicles often neighbouring less affected or even nearly unaffected ones.

**Dermatomyositis myopathology**

DM myopathology consistently suggests primary involvement of microcirculation mediated by humoral processes with secondary ischaemic changes of muscle fibers [3–5]. Myofiber alterations include:

- progressive atrophy of marginal layers of myofibers (perifascicular atrophy); major histocompatibility complex (MHC) class I antigens (HLA-ABC) are also typically expressed in perifascicular areas (often at both the sarcolemma and sarcoplasmic level) with or without concurrent diffuse myofiber expression throughout muscle; MHC class II antigens (at least HLA-DR) are typically not expressed by myofibers in DM; selective perifascicular involvement may only appear as rims of perifascicular myofibers expressing the CD56/NCAM regeneration marker;
- myofibers with ischaemic punch-out vacuoles with a clear honeycomb-like content, that are usually located in perifascicular areas; focal myosin loss with or without occasional cytoplasmic body or rod-like formation may be associated with punch-out vacuole formation and are best detected on trichrome stains; non-specific, but sometimes severe, selective type 2 fiber atrophy is commonly observed in DM;
- microinfarcts consisting of small foci of contiguous necrotic or regenerating fibers usually located in perifascicular areas; necrotic myofibers in DM typically have a necrotic center surrounded by a rim of regenerative CD56+ myoblasts stuck to the basement membrane; extensive skin and muscle infarcts in adulthood is likely to predict paraneoplastic DM.

Microvascular changes include:

- early capillary deposition of the complement C5b-9 membranolytic attack complex (MAC); MAC deposition may be also observed along sarcolemma of a limited number of non-necrotic myofibers and, as a non specific feature, in sarcoplasm of necrotic fibers; MAC deposition is typically associated with microvascular C3 and IgM or IgG deposition; detection of MAC in arterioles is physiologic and has, therefore, no diagnostic value;
- endothelial hyperplasia with constant presence of typical tubuloreticular inclusions at electron microscopy; microthrombi are rarely observed in DM muscle;
- destruction of endothelial cells assessed by the presence of free basement membranes at electron microscopy; it results in focal loss of capillaries predominating in perifascicular areas, best assessed by CD31/PECAM immunostaining. An indirect sign of muscle ischaemia consist in the replacement of normal muscle capillaries by microvessels with widely opened lumens and thickened walls secondary to smooth muscle cell appositions in place of pericytes. This likely reflects arteriolization of capillaries in response to ischaemia.
Inflammatory infiltrates include:
- septal perivascular mononuclear infiltrates; mural fibrinoid necrosis is never observed; endomyial mononuclear infiltrates, when present, typically predominate in perifascicular areas;
- a mixture of mononuclear cells including CD3+ T-cells, with CD4+ cells > CD8+ cells, CD20+ B-cells, and CD68+ macrophages; some of the CD4+ cells in the perivascular infiltrates are not T-cells but BDCAs 2+ plasmacytoid dendritic cells (PDCs, section 1.2). Occasionally, macrophages harbour by place a ribbon like basophilic cytoplasms in the perimysium, often close to necrotic areas; extensive form of this pattern has been described as inflammatory myopathy with abundant macrophages (IMAM) a condition that must be distinguished from post-vaccinal aluminium inclusion macrophagic myofasciitis [6];
- no CD8+ lymphocytic invasion of non-necrotic myofoibers (in fact this may occur, possibly as a secondary phenomenon, in association with particularly strong MHC-1 expression by perifascicular myofoibers).

**Skeletal muscle microcirculation in dermatomyositis**

The pathophysiologic impact of microcirculatory disturbances in IMs is explored by an increasing number of investigators [7]. Although data supporting a proinflammatory role of hypoxia are still scant, there are obvious, but rarely pointed out, anatomic and pathologic characteristics of muscle microcirculation that deserve attention.

**Concept of microvascular unit**

Knowledge of skeletal muscle microvascularization comes exclusively from small animals (such as rats, hamsters or cats) subjected to in vivo observations by transillumination, selective injection of opaque media, whole body perfusion and vascular casting. China ink injection studies of the rat spinotrapezius muscle described feeder arterioles in the epimysium (the connective tissue wrapping the whole muscle) continuing into a network of interconnected arcade arterioles in the perimysium (the connective tissue wrapping each muscle fascicle) [8,9]. These interconnections allow for compensation if blood flow is compromised by occlusion of one arcade arteriole [10]. Arcades give off, at regular intervals, transverse arterioles which penetrate into the endomysium (the connective tissue interposed between muscle fibers), and divide asymmetrically to yield terminal arterioles, which, in turn, resolve into capillaries. Transverse arterioles do not intercommunicate, and their occlusion could not be compensated for. Once formed, capillaries reorient themselves and run in parallel to the muscle fibers to collect in venules situated at another level further down the length of the fiber.

All capillaries issued from the one terminal arteriole and collected by one venule define the muscle microvascular unit (MVU) [11]. One MVU irrigates and drains a cylinder of muscle tissue of 750–1000 μm in length in all animals studied [11,12]. On cross sections one MVU comprises a set of six to eight capillary sections located in-between three or four adjacent myofoibers. Our own estimates indicate a similar size of the MVU in normal human deltoid muscle.

**Dermatomyositis: a paradigm of muscle capillary loss of unknown mechanism**

Mechanisms of capillary damage in DM remain elusive. Classically DM is regarded as a complement-mediated microangiopathy affecting skin and muscles. The disease is commonly believed to begin when putative antibodies directed against endothelial cells activate complement C3. Activated C3 leads to formation of C3b and C4b fragments and MAC. MAC, C3b, and C4b are detected early in serum and are deposited on capillaries at both the adluminal and abluminal aspect of microvascular cells, with consequent capillary necrosis and loss, microinfaracts, inflammation, endofascicular hypoperfusion and eventually perifascicular atrophy [13].

In fact, neither putative antigens nor factors activating complement, such as immune complexes, have been reliably identified. A comprehensive review by Greenberg has summarized these and other uncertainties in the pathogenesis of DM [14].

As shown in *table I*, ischemia is the single pathogenic mechanism which evidence is scaled as strong.

Our experience is that both MAC microvascular deposits at an early stage of DM, and capillary loss at any stage, occur in clusters corresponding the size of one to several MVUs (Christov, in preparation). For example, in amyopathic DM were pure capillary loss can be observed [15], distinct 6-by-6 capillary loss is seen, and MAC deposits in acute DM often takes the form of one or several clusters of 5–9 decorated capillaries. Significance of these observations is at present unknown. Arteriolization of capillaries which is observed in DM is likely induced by hypoperfusion [16]. In addition, reperfusion of an ischemic region is known to lead to supplementary damage called ischemia/reperfusion (I/R) injury, which results from oxidative stress and causes microvascular alterations at the origin of the “no reflow” phenomenon [17]. It seems likely that I/R can occur in DM, possibly as a result functional changes originating in arcade, transverse and terminal arterioles where inflammatory changes predominate:
- microvascular lesions are similar in DM and experimentally induced I/R, including endothelial abnormalities, thrombi, vessel hypepermeability, and edema [17];
- endothelial tubulo-recticular inclusions typical of DM, reflect endoplasmic reticulum stress which is inducible by both hypoxia or viral infections [18];
- autoimmune/inflammatory prone backgrounds enhance severity of I/R lesions, as demonstrated in the lupus mouse model [19].

In addition, there is ample evidence that I/R injury also activates complement. It could do so either by the classical...
way, through fixation of natural low avidity IgMs on newly formed antigens such as non-muscular myosin in microvascular cells [20,21], or by the alternative pathway [22], or by the lectin pathway [23].

**Polymyositis**

PM occurs separately or, more often, in association with other connective tissue diseases or with retroviral infections (e.g. HIV) [5].

**Polymyositis myopathology**

PM is a CD8+ T-cell-mediated and MHC-I-restricted autoimmune myopathy. In contrast with DM, PM is not conspicuously associated with capillary loss, perifascicular atrophy or other ischemic changes.

Inflammatory infiltrates are mainly composed of CD8+ T-cells and CD68+ macrophages (MPs). They are found in the endomysium where they initially surround individual healthy myofibers, then attack and invade them focally, together with MPs, tunnel the center of the fiber and, finally, destroy it.

Myofiber involvement, besides this auto-invasive inflammation, consists in scattered necrosis and regeneration, best assessed by CD56 expression. Widespread and strong MHC-I (HLA-ABC) expression by myofibers constitute a major immunopathologic feature of PM. MHC-I expression may be detected even in the absence of endomysial inflammatory cells, as observed in patients with inactive PM following therapy.

**T-cell: myofiber interactions in polymyositis**

Electron microscopy studies in PM strongly suggest cytotoxicity of CD8+ T-cells toward myofibers [25]. These T-cells express perforin [26]. Clonal expansions of T-cells have been found in muscle and blood of patients with PM and IBM [27–32], but not DM [33]. Autoinvasive T-cells exhibit selective gene rearrangement of their TCR (T-cell receptor) and restricted amino acid sequences in the CDR3 region (complementary-determining region 3), suggesting that the cytotoxic CD8+ T-cells that use their TCR to recognize peptide antigens presented by MHC-I observed in small number, rimmed vacuoles found in combination with multifocal auto-invasive inflammation are diagnostic of IBM.

Lymphocytic vasculitis is usually not observed in idiopathic PM. When present, it may suggest an association with a connective tissue disease.

AINM have long been considered as PM variants with prominent necrosis and very little T-cell infiltrates. Although overlapping conditions may exist, AINM should be individualized from PM and other IMs since they may occasionally form entities with specific autoantibodies (anti-SRP) [24]; and their myopathology is usually stereotypical, including: little and heterogeneous MHC-1 expression by myofibers contrasting with extensive regeneration (assessed by CD56 immunostaining); virtually no endomysial inflammatory infiltrate; and conspicuous sarcolemmal MAC deposits, with or without concurrent microvascular deposits. Their pathophysiology is obscure but it may include humoral factors targeting myofibers.

**Table I**

<table>
<thead>
<tr>
<th>Currently proposed sequential chain of events</th>
<th>Current strength of direct evidencea</th>
<th>Uncertainties and alternative considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody binding to endothelial cell self antigen</td>
<td>Weak</td>
<td>Antibody binding does not occur</td>
</tr>
<tr>
<td>Activation of complement system by the classic (antibody-dependent) pathway</td>
<td>None</td>
<td>Activation of complement system by alternative pathway</td>
</tr>
<tr>
<td>Endothelial cell MAC deposition</td>
<td>Established for most but not all patients</td>
<td>Unclear if MAC is in the form of immune complexes or bound to endothelial surface</td>
</tr>
<tr>
<td>Endothelial cell injury, resulting in swelling, necrosis, perivascular inflammation</td>
<td>Established</td>
<td>Endothelial cell injury may not be caused by MAC but other factors (cytokines, other); in particular IFN α/β</td>
</tr>
<tr>
<td>Muscle fiber ischemia</td>
<td>Strong</td>
<td>Muscle may not be ischemic; mechanism of myofiber injury speculative</td>
</tr>
</tbody>
</table>

MAC: Membrane-attack complex.

a Evidence graded from least to most as none, weak, moderate, strong, established.

Table I Pathogenesis of dermatomyositis from Greenberg [14].
molecules have been subjected to antigen-driven. These T-cell clones are specific of as yet unknown muscle auto-antigens. Of note, a recent study has identified CD28null T-cells as the dominating effector T-cell subsets in muscle tissue of patients with PM/DM [34]. These cells are resistant to apoptosis and proinflammatory, and may therefore account for recurrence of disease after treatment. Intriguingly, they are known to emerge as the result of chronic viral (e.g. CMV) and possibly other antigen stimulation.

T-cell activation is the result of two synergistic events. The first one is MHC- and antigen-dependent and consists in the interaction between the TCR and an appropriate peptide processed from the antigen and loaded on MHC molecules at the membrane of the APC; the second one is a co-stimulatory antigen-independent signal. Skeletal muscle is one of the few body compartments lacking MHC expression under physiological conditions. It is, therefore, very unlikely that myofibers may serve as APCs at steady state. However, myoblasts constitutively express MHC-I, and strongly upregulate MHC-I expression, upon exposure to interferon (IFN)γ, lipopolysaccharide and other cytokines [35]. IFNγ can also induce de novo expression of MHC-II expression by myoblasts [35], and favours antigen processing by immunoproteasome [36]. It remains to be elucidated whether in vivo myofiber expression of MHC molecule is induced by proinflammatory cytokines or by infectious agents or by a nonspecific response to tissue injury and regeneration or by a combination of these factors [37].

The second event required for T-cell activation is related to co-stimulatory molecules of the B7 family. The conventional B7.1 (CD80) and B7.2 (CD86) costimulatory molecules are neither expressed by muscle cells incubated with proinflammatory cytokines nor in IIM muscle [38,39]. However, ICOS-L (B7-H2), another co-stimulator of the B7 family [40,41], CD40 [42] are markedly expressed by muscle cells upon stimulation with proinflammatory cytokines and appear as potent activators of T-cells upon ligation to ICOS receptor and CD40L, respectively. ICAM-1 is also strongly induced by proinflammatory cytokines [35] thus allowing adhesion of muscle cells to LFA-1-expressing leucocytes, a finding reminiscent of what has long been observed in inflammatory myopathies [43]. Functional relevance of BB-1 as a co-stimulator [44] is debated [45].

On the other hand, inflammatory stimuli also induce expression of negative immunoregulatory molecules at the muscle cell surface, including B7-H1 (PD-L1) [46], and the non classical MHC-1 antigen HLA-G [47], likely aiming at protecting muscle fibers from immune aggression [45].

More generally, strong tolerance mechanisms protects skeletal muscle from immune attacks targeting muscle antigens. These mechanisms are far from clear. Using transgenic SM-OVA mice (selectively expressing OVA in skeletal muscle), bred with OVA-specific TCR Tg mice (OT-I or OT-II, restricted by MHC class I or class II, respectively) Olivier Boyer and his group elegantly showed that tolerance to muscle Ag (OVA neoAg) may not involve clonal deletion, anergy or an increased regulatory T-cell compartment as in other organs. Instead, they identified a tolerance mechanism in which CD4+ T-cells are tolerant by ignorance, whereas CD8+ T-cells become refractory to induction of a cytotoxic response [48].

Nevertheless, FOXP3+ regulatory T-cells (Treg), which main subset is also CD4+ CD25+, were recently to play a role in IIMs. The number of FOXP3+ Tregs in muscle biopsies correlated with the total number of infiltrating T-cells irrespective of the clinico-pathologic IM subset, suggesting that Tregs were attracted as part of the overall inflammatory reaction [49]. In vitro tests showed their “myo-protective” function against allogeninc cytotoxic CD8+ T-cells. Prior to this report, seminal evidence that Treg may be involved in IIM pathophysiology arose from a model of experimental autoimmune myositis associated anti-synthetase autoantibodies, based on depletion of Tregs [50]. It is known that autoimmunity develops when self-reactive T-cells that have survived thymic negative selection (central tolerance) escape peripheral tolerance mechanisms, which are primarily mediated by Tregs. Consistently, Treg depletion facilitated the development of experimental autoimmune myositis (EAM) induced by myosin emulsified in complete Freund’s adjuvant and aggravated disease activity, whereas administration of ex vivo expanded Treg ameliorated disease activity and induced regression of muscle inflammation [50].

Taken together these data show little evidence for direct activation of naive CD4+ T-cells by muscle cells, this function being more likely exerted by professional APCs, e.g. dendritic cells (DCs) in lymphoid organs (section 3). However, they strongly support that in an appropriately inflammatory milieu, regenerating muscle cells express MHC and other surface molecules at levels allowing their recognition by auto-toxic T-cells and conferring to muscle cells accessory APC functions that could amplify specific T-cell subsets.

**Pathophysiologic mechanisms shared by dermatomyositis, polymyositis and overlap myositis**

Although there are clinical and histopathological differences between the subsets of myositis, histopathological features may be scarce, unspecific and overlapping. Therefore, increasing attention is paid to features shared by IIMs regardless of their type, relevant to the innate immune response and to non-immune mechanisms.

**Innate immune response**

Myofiber necrosis/regeneration is typically observed in inflammatory myopathies, and, thus, understanding of cell interplays...
at work in innate immune post-myoinjury reactions could prove most relevant to pathophysiology of IM. For example, a link between the inflammatory reaction induced by myofiber damage and development of autoimmune reactions has been suggested in Duchenne muscular dystrophy [51]. Myofiber injury induces a coordinate immune cell reaction:
- within seconds/minutes resident mast cells degranulate and release preformed TNF-alpha and other inflammatory mediators;
- within minutes/hours, neutrophils accumulate and also release TNF-alpha;
- from 8 h post-injury, monocytes appear along with further infiltration by mast cells and neutrophils;
- between 24 and 48 h post-injury, MPs become the major leukocyte subset and remain so for days, until progressive fading [52].

We recently described how resident muscle MPs govern the innate immune response to myoinjury and how this response is linked to adaptive immunity [53]. Using BM transplantation experiments and selective resident MP depletion in mice, we observed that resident muscle MPs reside in the epimysium, concentrate locally after myoinjury, selectively release KC and MCP-1 chemokines, and, in so-doing, crucially contribute to massive recruitment of circulating neutrophils and monocytes triggered by either myoinjury or TNF-alpha injection. We had previously shown that, upon activation, muscle satellite cells (i.e. myogenic stem cells) also strongly chemoattract and interplay with monocytes and MPs [54]. Very recently, it was reported that in PM/DM, regenerating myofibers expressing MHC-I antigens also express Toll-like receptor (TLR) 3 and TLR7. These TLRs bind nucleic acids and endogenous ligands. Consistently, necrotic muscle debris activated in vitro cytokine production by muscle cells, in part through TLR3 signaling [55]. Therefore, immature fiber-driven amplification of the immune response is likely to occur in PM/DM.

Interestingly, inflammatory monocytes recruited from blood to muscle after injury give rise to classically activated Ly6C\textsuperscript{hi} phagocytic MPs, which secondarily switch their immunophenotype into alternatively activated Ly6C\textsuperscript{lo} cells with both myorepair-supporting properties [56] and immature APC function [53]. These APCs correspond to the so-called “inflammatory DCs” with intermediate rather than high level of CD11c expression [57] and can migrate to, and mature in, draining lymph nodes [53]. Thus myoinjury is sufficient per se to induce recruitment of immature myeloid DCs into muscle. However, as suggested by AINM where extensive necrosis is associated with very little inflammation, other factors are likely at play to sustain inflammation. In PM/DM, DCs almost always harbour a mature phenotype assessed by DC-LAMP expression [58–60]. This could be linked to specificities of the myositis inflammatory milieu since complex interplays exist between DCs and pro/anti-inflammatory cytokines [61]. Most studies have reported overexpression of IFN\textgamma suggesting a Th-1 response in PM/DM [62], to which one may add detection of IL17-producing cells, so-called Th-17 cells, that promote autoimmune inflammation that seems to be highly responsive to IVIG treatment [59,60].

DCs encompass different subsets with specific functions in lymphoid and non-lymphoid tissues [63]. Homeostatic tissues may contain conventional DCs and pDCs (section 3.2), two genetically distinct entities. As opposed to lymphoid tissues that contain both “resident” DCs (generated from blood-borne DC progenitors) and pDCs, homeostatic peripheral tissues (e.g. dermis) may be patrolled by non-resident “migratory” DCs serving as sentinels. However, homeostatic muscle hosts very little, if any, CD11c\textsuperscript{hi} migratory DCs probably because it is not routinely exposed to bacterial challenge. “Inflammatory DCs” that are generated by myoinjury [53] can be viewed as emergency nonconventional DCs, taking over the APC functions attributed to preexisting migratory DCs in other tissue [63]. The primary activation of naive T-cells after local antigen challenge takes place within the draining lymph nodes (LNs). The differential contributions of the different DC subsets in shaping adaptive immune responses or in inducing self-tolerance remain incompletely delineated. It has been shown that LN-resident DCs capture soluble or shed antigens drained from peripheral tissues through lymphatic vessels and are required to trap and initiate activation of cognate naive CD4+ T-cells within the LN, whereas migratory DCs are required to induce CD4+ T-proliferation [64]. Another important function of both conventional migratory DCs [65] and nonconventional “inflammatory” DCs (Gherardi, in preparation) in dLNs is efficient immunogenic material transfer to a large network of APCs. Long-lived memory T-cells constitute a sizable proportion of the overall T-cell pool of the body, controlling Ag rechallenge in peripheral tissues. Interestingly, expansion of memory CD8\textsuperscript{+} T-cells on secondary antigen encounter is induced by monocyte-derived DCs of the “inflammatory type” in peripheral tissue [66]. Thus DCs may well take part to clonal CD8\textsuperscript{+} T-cell expansions observed in muscle tissue of patients with inflammatory myopathies (section 3).

pDCs are primarily type I IFN-secreting cells centrally involved in antimicrobial immune defense. As they are DCs, pDCs can prime CD4+ T-cell responses in LNs (not in spleen) in certain situations, but, as opposed to other DCs, this is not associated with concomitant CD8\textsuperscript{+} T-cell priming [67].

Involvement of type 1 IFN system in pathophysiology of IIM has emerged in recent years [68]. It is supported by several lines of evidence: expression of IFN\alpha and \beta has been long reported in muscle tissue of PM/DM patients [69]; molecular profiling has identified type I IFN signature in muscle tissue [70–72] and blood [73] of patients with inflammatory myopathies; expression of type I IFN genes is greater in juvenile and adult DM compared to PM and IBM [72,74], and likely...
correlates with disease activity [73]; the MxA protein which is an indicator of type I IFN production is up-regulated in DM muscle [72]; type 1 IFN-producing PDCs are detected using the PDCA2 marker in the muscle inflammatory infiltrates, mainly in juvenile and adult DM [72,74]; anti-RNA binding autoantibodies (e.g. Anti-Jo-1 antibodies) of myositis patients have IFNα-inducing capacity through formation of immune complexes [75] and are associated with higher circulating levels of B-cell activating factor (BAFF) a molecule known to be activated by IFNα [76].

Non-immune pathogenetic pathways

Besides innate and adaptive immune responses, non-immune mechanisms including the endoplasmatic reticulum (ER) stress response, the activation of nuclear factor-κB pathway and autophagy may participate to muscle dysfunction. These mechanisms may account for patients in whom muscle function does not recover despite appropriate immunosuppressive therapy [77]. MHC-I molecules may by themselves mediate muscle fiber damage and dysfunction in the absence of lymphocytes [78]. The ER stress response has been the best studied mechanism. The folding, exporting, and processing of newly synthesised proteins, including the processing of MHC-I molecules, occur in the ER. Gene transfer of MHC class I plasmids can attenuate muscle regeneration and differentiation [79]. Chronic myofiber MHC-I overexpression obtained in a conditional MHC-I transgenic mouse model was shown to increase transcription of genes responsive to ER stress, i.e. ER chaperones, that may be also expressed in muscle tissue of myositis patients [80]. Increased expression of ER chaperones can either exert various protective effects or favor immune mechanisms and fiber damage. Except for IBM [2], knowledge about ER chaperone expression and distribution in PM/DM is at its very beginning: some chaperones (e.g. Grp94) are simply associated with myofiber regeneration independently from myositis whereas others (e.g. Grp75) seem to be upregulated by inflammatory stimuli and oxidative stress [81].

Myositis associated-autoantibodies

A variety of myositis-specific autoantibodies (MSAs) have been described in patients with IM [82]. MSAs are directed against cytoplasmic or nuclear components involved in key regulatory intracellular processes including protein synthesis, translocation and gene transcription. The best-characterized ones are directed against the aminoacyl tRNA-synthetases, the Mi-2 protein and the signal-recognition particle (SRP). The striking association between unique serological profiles and distinct clinical phenotypes suggests that target autoantigens may play a role in disease induction and propagation. For example, MSA profile seems to determine the frequency, course and severity of interstitial lung disease (ILD). Both non-Jo-1 antisyntetase antibodies (anti-PL-7 and anti-PL-12) and anti-Jo-1 (in combination with anti-SSA/Ro) antibodies are associated with pulmonary involvement. This is also the case of anti-CADM-140 auto-antibody, which combines rapidly progressive ILD and amyopathic DM [83]. DM in the elderly is often associated with cancer, which is usually detected within 1 year after IM presentation, making likely cross-reactions between the anticancer immune response and the autoimmune myopathy [84]. As MSAs target intracellular molecules that are not muscle-specific in their expression, it seems likely that the target muscle tissues itself regulates and shapes the phenotype-specific immune response in myositis [82,84]. Changes in these molecules, such as altered structure, enhanced expression, and acquisition of adjuvant properties during various forms of cellular stress, apoptosis, and transformation, appear important as they can generate neo-antigens driving autoimmune responses [84]. Moreover, myositis-specific autoantibodies are mainly expressed by regenerating myofibers [85,86]. As stated above, regenerating myofibers may also express MHC molecules and endogenous ligand-binding TLRs and can secrete inflammatory cytokines [60], thus drawing a picture in which the regenerating myofibers and immune effector pathways form a mutually reinforcing partnership allowing emergence of autoimmune reactions against neo-antigens and IM [87].

Conclusion

Until very recently, there was no reliable animal model of autoimmune myopathy. Myositis models have been now described, including conditional forced MHC-I expression by myofibers eliciting myofiber ER stress, autoimmunity and muscle inflammatory infiltrates [79], authentic EAM facilitated by Treg depletion [50] and the transgenic SM-OVA mouse allowing usage of the range of OVA-based tools for immunologic investigation of myositis [48]. Thus, it can be predicted that research on the pathophysiology of IMs will has entered its mature age.

Conflict of interest: none.
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