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Dermatomyositis

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Abstract

Dermatomyositis (DM) is a chronic inflammatory disorder of the skin and muscles. Although thought to be autoimmune in origin, many questions remain as to the etiopathogenesis of this disease. Dermatomyositis has classically been considered a humorally-mediated disease. Current evidence, however, seems to increasingly support alternative (though not mutually exclusive) mechanisms of pathogenesis, including cell-mediated and innate immune system dysfunction. Pathologic findings of DM in muscle include infarcts, perifascicular atrophy, endothelial cell swelling and necrosis, vessel wall membrane attack complex (MAC) deposition, and myocyte-specific MHC-I upregulation. As for the skin, histopathologic findings include hyperkeratosis, epidermal basal cell vacuolar degeneration and apoptosis, increased dermal mucin deposition, and a cell-poor interface dermatitis. Autoantibodies, particularly those that bind nuclear or cytoplasmic ribonucleoprotein antigens, are also commonly found in DM, although their importance in pathogenesis remains unclear. Defective cellular clearance, genetic predilection, and environmental exposures, such as viral infection, may also play an important role in the pathogenesis of DM. The seminal work regarding the pathogenesis of dermatomyositis is reviewed and an update on the recent basic and molecular advances in the field is provided.

Introduction

Dermatomyositis is a chronic inflammatory disorder of the skin and muscles. Although thought to be autoimmune in origin, many questions remain as to the etiopathogenesis of this disease. Adult onset DM can start at any age and generally affects females three times as frequently as males [1]. Symptoms usually manifest themselves in both the skin and muscle during the initial acute attack. Muscle symptoms, which include weakness, myalgias, or tenderness, more frequently involve the proximal muscles [1]. The skin usually presents with at least one of a number of characteristic features, including Gottron's papules over the metacarpophalangeal, proximal and distal interphalangeal, elbow, and knee joints, a heliotrope rash around the eyes, periungual telangiectasias, and dystrophic cuticles [2]. DM is associated with an increased risk of internal malignancy, including neoplasms of the gastrointestinal tract, ovary, and breast [3, 4]. An amyopathic subset of DM in which subjects do not experience muscle weakness or myalgias is well described [5]. A recent review of amyopathic DM shows that this group may also be at increased risk of malignancy

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and interstitial lung disease (ILD) as those with clinical features of muscle disease [6]. In this chapter we present a review of the seminal work regarding the pathogenesis of dermatomyositis and provide an update on the recent basic and molecular advances in the field.

Pathogenesis

Muscle

Dermatomyositis (DM) is currently viewed as a humorally-mediated autoimmune disease in which antigen-specific antibodies are deposited in the microvasculature, either secondary to immune complex deposition or specific anti-endothelial cell binding [2, 7]. C1 or C3 activation then follows, leading to C5b-9 membrane attack complex (MAC) deposition in the walls of the blood vessels. The present model implicates MAC deposition in capillary necrosis, perivascular inflammation, and infiltration of muscle by B-cells, which theoretically results in endofascicular hypoperfusion, muscle ischemia, and perifascicular atrophy [7, 8]. Complement activation also results in cytokine and chemokine release, which recruits CD4⁺ T-cells and macrophages to the affected muscle tissue. While this is an attractive model, it remains unproven.

Muscle disease is a common and bothersome element of dermatomyositis. Although clinically amyopathic forms of dermatomyositis are well described [5, 6], the extent of muscle dysfunction on the microscopic or molecular level in this subgroup is not well described. Evidence suggests that muscle pathology may still be present despite the absence of key findings on biopsy, including inflammation, tubuloreticular inclusions and membrane attack complex deposition highlighted by immunohistochemistry [9]. In evaluating the genetic expression profile of the idiopathic inflammatory myopathies, Greenberg found that the myocyte genetic expression profile in at least one dermatomyositis patient with a normal muscle biopsy was shown to be similar to that seen in those with classic dermatomyositis [9].

The typical histopathology findings of dermatomyositis in muscle include infarcts, perifascicular atrophy, endothelial cell swelling, vessel wall membrane attack complex (MAC) deposition, capillary necrosis, MHC-I upregulation, and the presence of an inflammatory infiltrate consisting of T and B lymphocytes, macrophages, and plasma cells [10]. Dermatomyositis has classically been considered a humorally-mediated disease in part because of these findings, specifically the predominant perimysial and perivascular B/CD4⁺ T cell infiltrate and intravascular MAC deposition. Current evidence, however, seems to increasingly support alternative (though not mutually exclusive) mechanisms of pathogenesis, including cell-mediated and innate immune system dysfunction.

Plasmacytoid dendritic cells (pDCs) provide immune surveillance and serve as a link between the adaptive and innate arms of the immune system [11]. Recent studies provide evidence that pDCs are dysregulated in muscle samples of dermatomyositis patients [8, 12]. More than 30–90 % of the CD4⁺ cells found in DM muscle are pDCs [8]. Page reports the presence of immature, CD1a⁺ pDCs localized in perivascular infiltrates within the endomysium [12]. In this study, immature pDCs were thought to be recruited by CCL20 upregulation. Mature pDCs were also found in high numbers, though they are thought to result from in-situ maturation of immature pDCs instead of mature pDC extravasation. Dysregulated pDCs are thought to release type I IFNs locally, likely resulting in widespread effects. In examining the gene expression profile of DM muscle, most of the highly upregulated genes include IFN α/β inducible gene promoter sequences [8]. The protein products of these IFN α/β responsive genes have been shown to mediate myofiber and endothelial cell injury [8]. Elevated levels of the IFN α responsive gene MxA have been

found in DM muscle samples and may play a role in muscle damage and inflammation [8]. For example, Greenberg has suggested that MxA may be the primary component of the tubuloreticular inclusion (TI), a characteristic pathologic feature of DM which may be involved in endothelial dysfunction [7, 8]. If true, MxA overexpression could provide the link between the damaging effects of TI's and the dysregulated arm of innate immunity [8]. All of these findings suggest that DM may be caused by a dysregulation of innate immunity to an unknown trigger.

Contrary to current dogma, T-cell mediated cytotoxicity may play a role in the muscle inflammation and damage in DM. Bank et al. has shown that *in-vitro* cell-mediated myocytotoxic damage induced by autologous peripheral blood CD3+ cell clones isolated from dermatomyositis patients can be blocked with OKT3, an anti CD-3 molecule [13]. Furthermore, perivascular perforin+ CD8 cells have been identified in muscle samples taken from a group of dermatomyositis subjects, which also supports the role for T-cell mediated cytotoxicity [14]. As CD4+ pDCs may also stimulate the adaptive arm of the immune system, it is likely that multiple arms of the immune system contribute to the pathogenesis of DM [11].

Other cytokines of importance have also been demonstrated. IL-4 is increased at perimysial sites, potentially secondary to the increased number of perimysial CD-4+ T lymphocytes [15]. Upregulation of IL-17 and IFN γ has been reported in DM muscle as well [8].

Certain cell trafficking molecules have also been examined in DM. Increased expression of monocyte chemoattractant protein 1 (MCP-1), a regulator of lymphocyte trafficking, has been shown in endomysial and perifascicular arterioles and capillaries [16]. Upregulated by TNF α , MCP-1 was also found expressed in some control samples too, suggesting its possible role in normal immune surveillance. A recent linkage analysis, however, did not identify a strong genetic association of MCP-1 gene polymorphisms and DM [17]. The cell trafficking regulators CXCR2 and IP-10 (a CXCR3 ligand) have been found in perimysial blood vessels and infiltrates of DM, suggesting a T_H1 mediated disease process [18]. Furthermore, increased levels of the cell adhesion molecules VCAM-1 and ICAM-1 have been shown within the muscle fibers, perimysial arteries, and perimysial venules of DM muscle biopsies [15, 19].

Role of MHC I in muscle—The expression of MHC-I, which is generally not expressed in adult myocytes, is upregulated in dermatomyositis [20, 21], specifically in type II muscle fibers [22]. Karpati et. al. specifically noted upregulation of MHC-I in perifascicular myocytes in conjunction with other associated morphological changes within the muscle fibers (atrophy, z-disc streaming, punched out myofibrillar areas, and mitochondrial maldistribution) [20]. Described as an early event preceding the inflammatory infiltrate, MHC-I upregulation may result from mononuclear cell-cytokine independent mechanisms [23]. Others have postulated that muscle damage secondary to capillary drop out, ischemia and the subsequent reparative process, viral infection, interferons, prostaglandins, or cellular stress may lead to MHC-I upregulation [20]. Pavlath has shown in a muscle freeze injury mouse model that γ -IFN can induce MHC-I expression in regenerating myocytes [21]. This explains why MHC-I may be upregulated after the cycle of damage and regeneration has been initiated, but does not account for the early upregulation. Nevertheless, Pavlath suggests that the MHC-I upregulation in regenerating myofibers in the setting of perifascicular inflammation implicates T-cells in the pathogenesis of DM [21]. It does seem, however, that understanding the timing of MHC-I upregulation will be important in ultimately describing the pathogenesis of DM. For example, the overexpression of MHC-I in skeletal muscles of adult mice initiates what seems to be a self-sustaining autoimmune myositis more similar to polymyositis than dermatomyositis, where the perivascular

inflammation or perifascicular atrophy seen in DM was not found to be present [23]. MHC-1 upregulation may directly contribute to the muscle damage in DM via activation of a cytotoxic T-cell host response.

Although other immune-mediated mechanisms of muscle damage (MHC-1 cross presentation by dendritic cells to CD4 or direct autoantibody binding) are also plausible, Nagaraju et al. has proposed a unique mechanism for the myocyte damage seen in DM. Nagaraju et al. postulated that MHC-I upregulation itself, independent of cytotoxic mediator cells, may directly induce cell death via the endocytosplasmic reticulum (ER) stress response [24]. According to this proposal, the ER overload response and unfolded protein response, which together comprise the ER stress response, are initiated after MHC Class I overexpression - a response to some unknown stimulation (transgene induction, infection, denervation, etc.). The downstream events of the ER stress response were shown in this study to upregulate NF- κ B and its targets (ICAM-1, VCAM, β_2 -microglobulin), the ER chaperone protein GRP 78, and caspase-12, a critical mediator of cell death [24].

Skin

Although much effort has focused on muscle pathology in dermatomyositis, studies have recently shed light on the pathogenesis of skin disease. The study of skin pathogenesis will be important, as specific cutaneous findings may be the common denominator for this disease. The classic findings of Gottron's papules, heliotrope rash, mechanics hands, macular violaceous erythema (shawl sign, v-neck rash, holster sign), and nailfold telangiectasia are frequently seen with dermatomyositis, even in those lacking in muscle symptoms [5]. The importance of skin disease in the ultimate pathogenesis of DM seems especially important given that the risk profile for malignancy and ILD seen between the amyopathic and classic subtypes may be similar [6].

The typical cutaneous histopathologic changes in dermatomyositis include hyperkeratosis, epidermal basal cell vacuolar degeneration, pathologic apoptosis of epidermal basal and suprabasal cells, dyskeratosis, a focally thinned epidermis, and increased dermal mucin deposition [25–27]. A cell-poor interface dermatitis comprised of lymphocytes at the dermal-epidermal junction (DEJ) is also characteristic [28]. Vascular ectasia and fibrin deposition, C5b-9 deposition in both dermal vasculature and the DEJ, and a perivascular lymphocytic infiltrate are features which are also commonly seen in DM but not cutaneous LE [28]. The superficial vascular plexus density has been reported to be lower in myopathic DM than amyopathic DM, suggesting that these two subsets are at different stages of a common pathogenic process or experience a separate but related sequence of pathologic events [28]. As in muscle, dysregulated cytokine production and cell-mediated immune mechanisms, among other pathologic findings, are thought to contribute to the cutaneous pathogenesis of DM.

Recent evidence from studies of the skin suggests a prominent role of the T-cell mediated immune response. Several studies examining the histopathology of dermatomyositis lesions have shown that the principal infiltrating cell of DM in the skin is the CD4+ T lymphocyte, distributed mainly in the perivascular upper dermis [29–31]. The majority of these cells appear to be of activated/memory phenotype [12].

A T-cell mediated host response is also implicated in the pathogenesis of DM in a recent study which suggests active involvement of the CD-40/CD-40 ligand (CD-40L) system within the skin [29]. A significantly increased number of both CD-40+ cells (including keratinocytes and mononuclear cells in the dermis), as well as infiltrating CD4+ CD-40L+ T-lymphocytes, is found in skin biopsies from patients with DM [29]. Activation of the

CD-40/CD-40L system may be responsible for upregulation of several pro-inflammatory molecules, including IL-6, IL-15, IL-8, and MCP-1 [29, 32].

Keratinocyte apoptosis appears to be dysregulated in the skin of dermatomyositis, though its full role in disease pathogenesis is not yet clear. The exact mechanism for keratinocyte apoptosis is unclear, and includes UVB light, Fas-FasL, TNF α , and CD8+ T-cell mediated activation of the apoptosis pathway [33]. Pablos et al. has reported abnormally increased amounts of apoptosis in active skin lesions of CLE and DM, most notably at the basal and suprabasal layers [27]. Consistent with this pathologic finding, the expression of the cell cycle regulator p53 is enhanced in both of these layers [27]. Furthermore, the antiapoptotic factor Bcl-2 has been shown to be downregulated in the epidermal and follicular basal cell layers [25]. Regardless of mechanism, apoptosis and inflammation at the basal cell layers may increase the likelihood of APC interaction and T-cell stimulation [27].

Photosensitivity is an important clinical feature of DM. Exposure to sunlight and specifically UVA and UVB radiation may serve a central role in disease onset and persistence. Increased levels of apoptosis after exposure to UV radiation has been described in dermatomyositis and cutaneous lupus erythematosus [34, 35]. Kuhn evaluated apoptosis in skin biopsies of 85 CLE patients and noted that defective clearance of apoptotic cells may lead to secondary necrosis, inflammation, and enhanced self-antigen presentation [35]. Neo-antigen presentation, which has been described in a lupus model following exposure to UV light [36–39], may be involved in dermatomyositis as well. Although lupus and dermatomyositis are distinct clinical entities, they share many common pathogenic findings [7, 28, 40, 41]. Exposure to UVB radiation has also been shown to upregulate TNF- α [42], an important pro-inflammatory cytokine which is increasingly supported by the literature to be involved in DM. An association between TNF α promoter polymorphisms has been reported in DM [43] and the related diseases subacute cutaneous lupus erythematosus [44] and juvenile dermatomyositis [45]. Important differentiating features of DM and CLE, however, have been noted previously. For example, Werth et al. showed no increase in the HLA-DR3 linkage in DM patients with the -308A TNF promoter polymorphism, though one was found in SCLE [43]. The association between UVB exposure and TNF- α release is consistent with a model in which UV light triggers cytokine-mediated inflammation and keratinocyte apoptosis [42].

Type I IFNs (α & β) are thought to play an important role in the pathogenesis of DM as well [30]. One case report of DM following treatment with IFN α 2b as an adjuvant in the treatment of metastatic melanoma suggests a primary role of type I IFN in DM [46]. Similar to the pDC dysregulation described in muscle above, Wenzel et al. has reported increased numbers of infiltrating plasmacytoid dendritic cells in DM skin lesions, which are thought to enhance lymphocyte recruitment via Type I IFN-mediated upregulation of the CXCR3 ligand IP-10/CXCL10 and subsequent interaction with the lymphocyte CXCR3 receptor [30]. Besides recruiting and activating resting T-cells, NK cells, and monocytes, CXCR3 receptor stimulation is also thought to be promote T_H1 mediated immunity and inhibit angiogenesis [47]. Although IFN- α itself has not been detected in the skin, IFN- α -dependent proteins (such as MxA) are elevated, which suggests the presence of active IFN- α [30]. Besides its effects on lymphocytes, IFN- α may also be instrumental in causing endothelial cell damage, as is postulated for muscle disease.

Secondary mucinosis, although not as frequently described in DM as in lupus erythematosus, has been reported in a number of subjects with dermatomyositis [48–50]. Excess mucin deposition in DM has been postulated to occur secondary to increased hyaluronic acid production by dermal fibroblasts following immunological stimulation as opposed to decreased hyaluronidase-mediated resorption [26]. Although IL-1, IL-6, TNF α ,

TNF β , platelet-derived growth factor have all been implicated in increased mucin deposition [51–53], dermatomyositis-specific studies indicating this are lacking.

Other Mechanisms of Pathogenesis

Autoantibodies

Although autoantigens and autoantibodies are classically thought to be responsible for downstream events of DM, little evidence exists for direct pathogenesis. First, in a study of patients with DM, 44% did have sera containing IgM and /or IgG antibodies against endothelial cells, while none of the patients with other myopathies had a positive titer [54]. However, none of the serum from patients with endothelial antibodies had a cytotoxic effect on endothelial cells and cross-reactivity to other tissues was not measured [54]. Second, in a study measuring IgG, IgM, and C3 deposits in blood vessels from skeletal muscle of three patients with DM, 100% had immunoglobulin deposits and 33% had C3 deposits in the walls of perimysial veins [55]. However, similar deposits were seen in other inflammatory disorders such as RA and SLE. Third, it is unclear if complement is activated via the classic pathway as proposed or via an alternative pathway, or if immune complexes including MAC are formed within the vasculature and subsequently deposited in the endothelium [7]. Fourth, in a recent review of amyopathic DM, Gerami and Sontheimer have shown that myocyte-specific antibodies are less common in amyopathic DM [6], suggesting that the muscle inflammation and symptoms are a secondary event or a difference in the immunogenic background exists between the groups.

Antibodies to nuclear or cytoplasmic ribonucleoprotein antigens (anti-synthetase, anti-signal-recognition particle, anti-Mi-2, anti-polymyositis-Scl, and anti-KL6 autoantibodies) are found in approximately 20% of patients with DM [2, 56, 57], but their importance in the etiology and pathogenesis of DM remains unclear. Myositis-specific antibodies (MSA), found in patients with DM, PM, or inclusion-body myositis, include antibodies to components of the translation machinery such as aminoacyl tRNA-synthetases and RNAs [58]. The most common autoantibody found in myositis patients, anti-Jo-1, targets histidyl-tRNA synthetase (HisRS) and is found in several subsets of patients. Antibodies directed against alanyl-, asparaginyl-, glycyl-, isoleucyl-, and threonyl-tRNA synthetases have also been reported in a smaller percentage of patients with DM [59]. Anti-p155 is a newly described autoantibody for dermatomyositis. Although its target antigen has not yet been identified, anti-p155 was found to be present in 29% of DM patients, whereas it was only seen in 4.2% of PM patients, 2% of SLE, and no patients with systemic sclerosis, other myopathies, or healthy controls, suggesting it is also may be a myositis specific autoantibody [60].

Anti-Jo-1 antibodies are found associated with interstitial lung disease, inflammatory arthritis, and Raynaud's phenomenon in patients with the anti-tRNA synthetase syndrome [58, 61–64]. For example, in a study of 15 patients with DM or PM and anti-Jo1 antibodies, 73% presented with ILD, 82% with joint involvement, and 55% with Raynaud's phenomenon [65]. However, 60% of patients with ILD and DM had no anti-Jo-1 antibodies, and all patients with ILD had similar therapeutic outcomes. In a study of patients with anti-Jo-1 antibodies, 91% had HLA-DR3 and 80% had HLA-DQ2 loci, indicating a possible common genetic susceptibility [58]. A second group of patients with anti-Jo-1 antibodies have muscle biopsy findings similar to patients with DM, but no capillary loss on muscle biopsy and no cutaneous findings, suggesting that the anti-Jo-1 antibody plays a role in generating some of the phenotypic signs of DM [66]. Immunization of mice with anti-Jo-1 (anti-HisRS), however, was shown to not initiate a generalized myositis [67]. Greenberg has shown that the gene expression profile of muscle in anti-Jo-1 patients is essentially the same as that seen in classic DM [9]. These observations support the theory that the immune

response to known autoantigens in DM may be unrelated to the primary pathogenic mechanisms causing muscle and/or lung disease and may represent epiphenomena [64].

Autoantibody production in DM is currently thought to result from cross-reaction with an infectious agent through molecular mimicry or a breakdown in tolerance to self-antigens [68]. However, neither theory accounts for the limited number of autoantigens described to date in inflammatory myopathies. In order to account for this paucity, Plotz argues that, in myositis, potential autoantigens must possess certain intrinsic structural, biological, and immunological properties. The presence of a coiled-coil domain, differential protease cleavage susceptibility, and target tissue up-regulation of autoantigens, among a variety of other reasons, may determine the autoantibody repertoire [68]. For example, the NH₂-terminal domain of histadyl-tRNA synthetase (HisRS, anti-Jo-1), a component of translation against which antibodies are formed in approximately 25% of patients with either polymyositis or dermatomyositis, was shown to be chemotactic for T-cells, monocytes, and immature dendritic cells *in vitro* [69, 70]. Granzyme B, a serine protease released by activated lymphocytes during the induction of apoptosis, was found to cleave most autoantigens, including HisRS at the NH₂-terminal domain, producing unique fragments [59, 71]. Interestingly, non-autoantigens were either resistant to Granzyme B cleavage or did not produce novel fragments which were susceptible to cleavage by other proteases [72]. The authors hypothesize that HisRS, among a host of other myositis specific autoantigens including asparaginyl-tRNA synthetase, is released from dying cells in sites of tissue damage and inflammation, cleaved by Granzyme B, taken up by chemokine receptors on antigen-presenting cells, subsequently enters the processing and presentation pathway, and ultimately elicits an immune response [68, 69]. Thus, autoantigens may act as danger signals to alert the immune response to tissue damage, with dendritic and T-cell activation [68]. Supporting this hypothesis, when myositis was induced in a mouse model by overexpression of MHC Class I molecules, anti-Jo-1 antibodies developed secondarily [57].

To further assess the role of autoantibodies in myositis, Casciola-Rosen and colleagues examined autoantigen expression in muscle from patients with DM [73]. In lysates from muscle biopsies of patients with DM and controls with histologically normal biopsies, Mi-2, a regulator of nuclear transcription, was expressed at levels 10-fold higher in patients with DM versus control patients. In addition, similar to MHC class I expression, regenerating cells in the perifascicular region in DM muscle expressed high levels of HisRS and cultured myoblasts expressed high levels of Mi-2 and HisRs. Since muscle injury and subsequent myocyte regeneration can be seen in a heterogenous distribution within muscle, the authors suggest this may explain the sometimes patchy histologic changes in myostis [73]. Mi-2 antibodies have been reported with similar prevalence in different subtypes of myositis, supporting the theory that these are reactive from inflammation instead of pathogenic in origin [74, 75]. The clinical relevance of Mi-2 antibodies is unknown. An increased rate of malignancy has been associated with antibodies against the N-terminal fragment of Mi-2 β [74]. Others, however have cited the usefulness of Mi-2 antibody presence in exclusion of paraneoplastic disease [75]. Overall, the data support the view that regenerating muscle cells are the source for a currently unknown autoantigen which may stimulate the immune response in myositis and perpetuate the inflammatory cycle.

The presence of a truly specific antibody which shows transferable pathogenesis would suggest a primary role of the antibody in the pathogenesis of DM. We are unaware of any studies which indicate that serum containing myocyte-specific antibodies is able to induce dermatomyositis-specific changes and keratinocyte apoptosis. Mi-2 is generally considered DM specific, though a number of studies have reported their presence in inclusion body myositis (IBM), polymyositis (PM), and other connective tissue diseases (CTD) [74, 75]. This difference, however, may be contributed to the type of test used to identify the

antibodies. In a recent analysis, Ghirardello et al. reported positive Mi-2 antibodies only in the six subjects with DM but not those with PM or an overlap syndrome when analyzing the tissue specimens with western blot analysis instead of the previous attempts which used immunodiffusion, immunoprecipitation, or ELISA-based techniques [75]. Sato et al. recently reported an amyopathic dermatomyositis antibody Anti-CADM-140 [76]. Further studies are required to determine whether this indicates a meaningful difference in the disease cascade among subsets of dermatomyositis or not.

Endothelial dysfunction

The vasculopathy present in DM is one of the only ways to differentiate the histologic appearance of skin in DM and CLE [25, 28, 77]. The classic features of endothelial dysfunction in DM include tubuloreticular inclusions, swelling, microvacuolization, and necrosis [7, 78]. A decreased capillary index is found in DM, even in those with no clinically present muscle disease [78]. Interestingly, a recent study of muscle samples in adult DM indicates that neovascularization and angiogenesis-specific gene expression may be increased in response to capillary loss [79]. Endothelial cell swelling is one of the earliest pathologic changes seen in the muscle of DM, often present before the inflammatory infiltrate can be visualized [10]. The endothelial histologic findings of amyopathic and classic DM are equivalent [28], suggesting that the same underlying mechanisms of disease may be active in both. Interestingly, gene expression profiles do not show differential regulation of known intramuscular endothelial cell proteins or growth factors [21, 80].

The muscle atrophy seen histologically in DM is sometimes credited to perimysial ischemia following complement-mediated thrombosis and capillary drop-out [1]. Considering muscle anatomy and its vascular supply, vessel damage may induce damage in a watershed distribution, leading to preferential myocyte destruction in the perifascicular region and ultimately localized atrophy, although it has been noted that no real evidence exists to support such a claim [7]. However, increased succinate dehydrogenase (SDH) and reduced cytochrome c oxidase (COX) enzyme staining, which indicates mitochondrial dysfunction, was identified in 11/12 patients with DM, suggesting ischemia as the culprit in perifascicular atrophy [80]. Complement activation and subsequent membrane attack complex (MAC) deposition into the larger vessels may cause muscle ischemia and subsequent myocyte damage [1]. Nagaraju et. al propose an alternative theory for how vasculopathy may indirectly initiate myocyte damage. Ischemia, perhaps secondary to MAC deposition, or any one of a group of potential triggers (infection, denervation, etc.), may induce myocyte MHC-I upregulation and initiate muscle damage via the ER Stress Response, as mentioned previously [24]. Besides these theories, it has been suggested that endothelial damage may also allow for enhanced perifollicular T-cell migration, which in the setting of MHC-I upregulation, may promote a cytotoxic T-cell response [20, 21].

The evidence supporting the role of ischemia in muscle atrophy of DM is not uncontested, however. Complement activation and deposition, if thought to be the cause of vessel loss and myofiber ischemia, should lead to subsequent complement deposition in the vessel walls. Linking the vasculopathy, ischemia, complement dysfunction, and atrophic changes is difficult, however, since complement deposits in perifascicular and endomysial endothelium have been found to be inversely correlated to perifascicular atrophy [78]. Furthermore, there has been no consistent correlation between zones of capillary depletion and perifascicular atrophy [78]. Although ischemia may cause muscle atrophy, whether this is a direct consequence of the complement cascade has been questioned [7]. Alternatively, some have suggested dysregulated type I IFN release may be responsible for perifascicular atrophy [8]. Overall, the relationship between the perimysial vasculopathy and the myocytotoxicity in DM is not well understood.

Endothelial dysfunction in dermatomyositis is also implicated by data showing the presence of both IL-1 α and ICAM-1 both in muscle samples with [80] and without [21] inflammatory infiltrates. Although endothelial dysfunction seems to play an important role in the pathogenesis of DM, neither the onset nor the downstream events are well understood. Besides the potential relationship between muscle damage and endothelial dysfunction, anti-endothelial antibodies have also been implicated in the pathogenesis of DM-related interstitial lung disease (ILD). In one study by Cervera et al. examining 18 patients with dermatomyositis, all 6/6 with ILD had endothelial antibodies in comparison to 2/12 without ILD [54].

Complement, Mannose Binding Lectin (MBL), & Clearance

The current dogma regarding the pathogenesis of DM is that it is a humorally-mediated autoimmune disease in which antigen-specific antibodies bind to endothelial cells followed by activation of the complement system [2, 7]. As a result of C1 or C3 activation, the C5b-9 membrane attack complex (MAC) is deposited in blood vessel walls, causing capillary necrosis, perivascular inflammation, and infiltration of muscle by B-cells, resulting in endofascicular hypoperfusion, muscle ischemia, and perifascicular atrophy [7, 8]. Complement activation also results in cytokine and chemokine release, which recruits CD4⁺ T-cells and macrophages to the affected muscle tissue.

The role of complement in either the onset or the maintenance of DM is unclear, especially in light of a case of DM found in someone with C9 deficiency [81]. MAC deposition has been found surrounding capillaries instead of binding endothelial cell surfaces directly, which challenges the classic model of complement activation in DM [78]. It is still unclear if anti-endothelial antibodies are primarily responsible for activating complement and initiating endothelial damage. In light of discovering complement-complexes outside of vessel walls, complement may actually bind to intravascular complexes and undergo subsequent extravascular migration. Kissel et al. have noted the lack of evidence supporting the co-aggregation of IgM, C3, and MAC [82], further questioning the classic model.

Complement deficiencies, which have been reported in systemic lupus erythematosus (SLE) [83], are thought to result in decreased clearance of apoptotic bodies and necrotic debris [83], which may lead to prolonged antigen presentation, immune activation, and stimulation of cell-mediated host immunity. Interestingly, the complement receptor 2 (CR2) has been shown to play a role in B cell and T cell tolerance [83]. The appropriate stimulation for CR2 induced tolerance may be lacking in a complement deficient state [83]. Since similarities in pathogenesis of DM and lupus have been noted [7, 28, 40, 41, 84], it is reasonable to think that impaired clearance of apoptotic bodies through complement in DM may contribute to disease pathogenesis as well. Impaired clearance through deficiencies in mannose-binding-lectin have been associated with DM [84]. Despite some of the similarities that exist between DM and LE, they are separate disease entities; recent molecular studies have shown clear differences in HLA genetic frequencies in DM and LE, highlighting an important and potentially fundamental difference in the two diseases [43].

Genetics

Susceptibility to DM is thought to result from a complex interplay of various gene products. The search for HLA linkage markers has only yielded a few candidate loci for further study [85]. Reed summarizes these HLA associations in a recent review [81, see Table 1). Associations between HLA class III and non-HLA immune-modulations IL-1 α , IL-1 β , TNF- α , and mannose binding lectin have been described as well [43, 84, 85].

An association of both HLADR3 and HLADQ2 [58] and anti-Jo-1 autoantibody has been reported. Tezak et al. [40] has demonstrated a relationship between HLA DQA*0501 and the similar entity juvenile dermatomyositis.

Environment

Various environmental triggers, including medications, sunlight, infection, etc., have been examined for a relationship to DM [85]. Both atorvastatin and phenytoin have been shown to induce DM, as is true for IFN- α 2b [5, 46]. Both spatial and temporal clustering in DM has been reported [89], suggesting a viral trigger [5, 85]. Various attempts to isolate or identify viral infection, however, have been unsuccessful for a host of pathogens including coxsackie, influenza, paramyxovirus, adenovirus, HIV, HTLV-1 or HTLV-II, encephalomyocarditis virus, parvovirus, enterovirus, and hepatitis C virus [64, 85]. Testing seeking out infection with toxoplasmosis and lyme (*borrelia burgdorfi*) has also turned out negative [85]. Although a consistent infection has not been identified, it is still likely that some not yet identified infection serves as a trigger for a self-sustaining autoimmune response that continues long after elimination of the pathogen. Sunlight is also affected by geography and season, which may explain the spatial and temporal clustering patterns described in DM as well [85].

Relationship to Cancer: Paraneoplastic Phenomenon

Patients with DM have been shown to be at increased risk for internal malignancies, independent of the extent of muscle involvement [6, 90]. It has been suggested that the presence of cutaneous necrosis and an erythrocyte sedimentation rate greater than 40 mm per hour are significant predictive features to determine which subset of DM patients will ultimately present with a malignancy [3]. Although the process is not well understood, DM occurring in the setting of a primary malignant neoplasm is thought to occur as a paraneoplastic response to the malignancy. Cancers may present self-antigens, including myositis autoantigens, at a greater frequency than is normally seen by the immune system given the monoclonal and rapidly expanding nature of tumors [73, 90]. Non-specific muscle injury could induce myoblast development and increase the number of regenerating myocytes, which have been shown to express a similar antigen fingerprint as myositis-associated tumors [73]. In conjunction with upregulated MHC –1 [20, 21, 23], myocyte injury could result from tumor-specific CTLs that recognize antigen shared by these regenerating myocytes and tumor cells [73]. Lastly, cancers are known to produce autoantibodies causing a host of paraneoplastic phenomena including Cushing's disease and hypercalcemia [90]. Interestingly, Targoff et al. describe a newly discovered anti-p155 autoantibody which was identified in 6 of 6 subjects with cancer-associated DM but in 0 of 2 subjects with cancer-associated PM [60]. Internal malignancy may also be associated with another newly described autoantibody which precipitates both 155 and 140 kDa proteins [91]. In this study 71% of those with the anti-155/140 antibody were found to have an internal malignancy in comparison to only 11% of those who tested negative for the antibody. Although both the Targoff and Kaji autoantibodies precipitate a 155 kDa protein, they are likely distinct since the anti-155/140 antibody always co-precipitates a 140 kDa protein whereas the Targoff anti-155 autoantibody does not [91]. It is unclear, however, whether these autoantibodies represent a host response to a myositis autoantigen or a paraneoplastic phenomenon. Although the direct pathogenesis of autoantibodies in DM is unproven, myositis-associated tumors may provide a stimulus that initiates the host inflammatory.

Relationship to Interstitial Lung Disease

The association between anti-endothelial antibodies and interstitial lung disease (ILD) in DM has already been mentioned. The antibody anti-Jo-1 has also been associated with ILD [64] as part of the antisynthetase syndrome [5]. CD8+ lymphocytes were discovered upon bronchoalveolar lavage of an amyopathic DM patient with refractory ILD, suggesting role for CTL mediated lung injury in DM [92]. A recent study comparing the blood serum levels of various pro-fibrotic factors in DM or PM patients showed increased levels of TGF- β , KL-6, ET-1, TM, and PAI-1 in those with interstitial pneumonitis [93]. A study in Japanese women with idiopathic inflammatory myopathy (IIM) showed that HLA Class II haplotypes are different in those that do or do not experience interstitial pneumonitis [94]. Furthermore, Sato et. al showed a significant difference in the rapid progression of ILD in amyopathic subjects who had presence of the Anti-CADM-140 antibody [76].

Relationship to Juvenile DM

Juvenile DM (JDM) is a chronic autoimmune disorder which primarily affects the skin and muscles of children and young adults [45]. Adult DM and JDM present similarly except that the calcification in the latter is both more common and severe. Given the common features between these two diseases, lessons learned from studying the pathogenesis of JDM may be useful in understanding the adult disorder. First, like adult DM, IFNs α , β , and γ are upregulated in muscle biopsy specimens of JDM [40]. Tezak et al. propose that increased IFN expression in JDM may occur as a post-viral, innate immune response. Although good evidence linking either adult or juvenile DM to viral infection is lacking, in light of our current limited understanding of disease pathogenesis it cannot yet be dismissed either. Second, similar to how IFN responsive gene products are thought to cause muscle ischemia in adult DM, the IFN γ responsive genes IP-30 and IP-10, T-lymphocyte specific chemokines, interfere with neovascularization, leading to growth arrest of vascular endothelium, and capillary drop out [40, 95]. Thus, for both adult and juvenile DM the literature supports the role of IFN upregulation, possibly in response to viral infection, a progression to vasculopathy, functional ischemia, and myocyte death. Though separate clinical entities, adult and juvenile DM share enough in common that advances in understanding either disease may prove helpful in discerning the pathogenesis of the other.

Conclusion

In summary, the literature regarding the pathogenesis and basic science mechanisms of dermatomyositis presents a disjointed array of seemingly unrelated topics. Although some data clearly outlines specific dysfunctional mechanisms in either the skin or the muscle, oftentimes pathology is found within both tissue types as well as in a systemic distribution. Autoantibody production, endothelial damage, dysregulation of both complement and mannose binding lectin, and impaired clearance are all pathologic features of DM which are active systemically. Given the complexity of this disease, each of these systems is likely involved in a not yet well understood cascade of disease susceptibility and progression.

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Table 1

HLA allele associations with Dermatomyositis [58, 85–88]

White	DRB1*0301, DQA1*0501, DQB1*0201 EYSTS, DRB1 HRV motif DRB1*0201 and DR4 (protective)
Hispanic	None detected
Japanese	DRB1*08, DRw59