Dermatomyositis (DM) and polymyositis (PM) are autoimmune myopathies characterized clinically by proximal muscle weakness, muscle inflammation, extramuscular manifestations, and frequently, the presence of autoantibodies. Although there is some overlap, DM and PM are separate diseases with different pathophysiological mechanisms. Furthermore, unique clinical phenotypes are associated with each of the myositis-specific autoantibodies (MSAs) associated with these disorders. This review will focus on the clinical features, pathology, and immunogenetics of PM and DM with an emphasis on the importance of autoantibodies in defining unique phenotypes and, perhaps, as clues to help elucidate the mechanisms of disease.

Keywords: myositis; dermatomyositis; polymyositis; autoantibodies; myopathy; autoimmunity

Introduction

The inflammatory myopathies are a group of acquired skeletal muscle diseases that includes polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM). Although these disorders share several common features including muscle weakness and inflammatory infiltrates on muscle biopsy, they are a heterogeneous group both in terms of presentation and pathophysiology. For example, PM and DM are characterized by the subacute onset of symmetric proximal muscle weakness, common involvement of other organ systems such as lung and skin, a strong association with autoantibodies, and responsiveness to immunosuppression. Both are widely accepted as having an autoimmune basis. In contrast, patients with IBM typically have slowly progressive weakness in both proximal and distal muscles, rarely have other extramuscular involvement or autoantibodies, and most often do not respond to immunosuppressive therapies. Considerable evidence suggests this disease is a myodegenerative disorder and the pathologic relevance of the inflammatory response is highly controversial.

This review will focus on the diverse presentations of adult-onset DM and PM, emphasizing the association of distinct clinical phenotypes with unique myositis-specific autoantibodies (MSAs). The possible relevance of autoantibodies to the pathophysiology of the disease, including an association between cancer and myositis, will be discussed.

Historical perspective

In 1863, Wagner documented the first case of myositis in a patient who also had significant cutaneous findings. Twenty-four years later, Hepp reported that inflammatory myopathies can also occur in the absence of skin involvement. In the same year, Hans Unverricht described a 27-year-old stonemason who developed myalgias and proximal muscle weakness followed by diffuse edema, low-grade fevers, and a blue-tinted rash over his eyelids. Over the ensuing weeks, this patient’s condition worsened with the development of dysarthria, dysphagia, dyspnea, and ultimately, pulmonary arrest. A postmortem analysis revealed the presence of a cellular infiltrate within the affected muscles. After describing a second case in 1891, Unverricht coined the term “dermatomyositis” to describe patients with an inflammatory myopathy associated with dermatologic findings. Although
Eaton, Walton and Adams, Rowland, and Pearson and Rose all contributed to our modern understanding of DM and PM, Bohan and Peter published diagnostic criteria for these diseases in 1975 that, although imperfect, are still widely used today.

Pathology of myositis

Patients with both PM and DM typically experience the onset of symmetric proximal muscle weakness over weeks to months that is usually, but not always, accompanied by high serum creatinine kinase levels. In both diseases, electromyography often reveals fibrillations, positive sharp waves, and small polyphasic motor units with early recruitment patterns that characterize an irritable myopathy. Skeletal muscle MRI in DM and PM shows areas of T2 hyperintensity in edematous areas as well as fatty replacement of muscle tissue in those patients with chronic disease (Fig. 1). However, despite these clinical similarities, muscle biopsies from DM and PM patients each have distinguishing features. Although there is frequently overlap in pathology, I will emphasize here those disease-specific findings suggesting that different mechanisms underlie DM and PM.

Muscle biopsy findings in dermatomyositis

The hallmark histopathologic feature of DM is the strongly perifascicular distribution of atrophic, degenerating, and regenerating myofibers (Fig. 2A). This striking perifascicular pathology has been proposed to result from the destruction of capillaries populating this region. It is thought that a critical depletion of capillaries here could result in localized hypoxia and subsequent myofiber injury. Indeed, abnormal capillary morphology and capillary loss is an early feature of DM that may occur in the absence of inflammatory infiltrates. Even prior to capillary dropout, studies of DM muscle tissue reveal the deposition of the C5b-9 membrane attack complex (MAC) on endothelial cells and the presence of abnormal tuboreticular structures within the smooth endoplasmic reticulum of endothelial
cells. Presumably as a consequence of capillary destruction, there is also evidence of neovascularization in DM muscle biopsies, particularly in the juvenile form of the disease. Recent work suggests that neovascularization in myositis muscle may be induced by increased muscle expression and serum concentrations of vascular endothelial growth factor (VEGF), an angiogenic growth factor known to be induced by hypoxia.

Although these findings have led numerous investigators to propose that the immune response in DM is primarily directed against capillaries, no antiendothelial autoantibodies have been identified. Moreover, a recent study demonstrated that capillary number is reduced in both DM and PM muscle biopsies lacking inflammatory infiltrates, indicating that early capillary loss is not disease specific. Finally, animal models of muscle ischemia have demonstrated that the central domains of muscle fascicles are more vulnerable to ischemia than perifascicular regions. Taken together, these findings call into question the hypothesis that capillary reduction and subsequent hypoxia underlie the perifascicular atrophy found exclusively in DM.

Another characteristic, though less specific, feature of DM muscle is the presence of perivascular inflammation (Fig. 2B). These collections of lymphocytes are composed primarily of B cells along with a smaller number of CD4+ cells long-thought to be helper T cells. However, recent investigations by Greenberg and colleagues suggest that the majority of CD4+ cells in DM muscle biopsies are actually plasmacytoid dendritic cells (PDCs). These effector cells of the innate immune system play critical roles in antiviral and antitumor immune responses and are a potent source of interferon (IFN)-α. In this regard, it is noteworthy that genes induced by IFN-α/β are highly expressed in DM muscle biopsies compared with muscle from patients with other inflammatory myopathies. This includes the human myxovirus resistance 1 protein (MxA), which helps defend against a number of RNA viruses by interfering with viral nucleocapsid transport and viral assembly. This protein is selectively upregulated in DM muscle biopsies, where it is frequently localized to perifascicular regions as well as to cytoplasmic inclusions within endothelial cells. As suggested by Greenberg and colleagues, these findings imply a potentially important role for IFN-α and IFN-α/β-inducible genes in the pathophysiology of DM. This idea has been reinforced by the finding that IFN-α/β-inducible gene expression in the periphery correlates with DM disease activity.

Muscle biopsy findings in polymyositis

The presence of autoaggressive inflammatory cells that surround, enter, and destroy morphologically normal appearing myofibers is the characteristic feature of PM (Fig. 3). These inflammatory cells are composed largely of CD8+ T cells and macrophages. In contrast to normal muscle, Major Histocompatibility Complex
I (MHC)-class I is upregulated on the sarcolemmal membrane of myofibers in PM, even on normal-appearing cells in areas devoid of inflammatory cells.\textsuperscript{26–28} Interestingly, targeted overexpression of MHC-I in the muscles of mice results in muscle inflammation and the production of myositis autoantibodies.\textsuperscript{29} Moreover, exogenous expression of MHC-I activates endoplasmic reticulum stress response pathways that could also cause muscle damage in PM.\textsuperscript{30}

The expression of MHC-I on myositis muscle fibers suggests that these cells may be killed in an human leukocyte antigen (HLA) class I restricted manner by cytolytic T cells. Supporting this concept is the observation that many of the CD8\textsuperscript{+} T cells include granules containing perforin, a pore-forming protein that mediates the entry of cytotoxic proteases and calcium into target cells. Confocal laser microscopy studies have demonstrated that these perforin-containing granules are selectively oriented toward muscle fibers, consistent with a cytotoxic mechanism of cell death in PM.\textsuperscript{31} To date, however, the autoantigens hypothesized to trigger an autoimmune response via this pathway have not been definitively identified.

Although T cells can also kill by inducing apoptosis through a ligand-mediated mechanism (via Fas and the Fas-ligand), apoptotic muscle fibers have not been identified in muscle biopsy specimens from patients with myositis.\textsuperscript{32,33} Indeed, muscle seems to be especially resistant to apoptotic cell death, perhaps through the expression of antiapoptotic factors such as Bcl-2\textsuperscript{32,34} and FLIP.\textsuperscript{35}

### Common pathologic features of DM and PM

In the preceding paragraphs, the unique pathologic features of PM and DM have been emphasized. However, there is considerable overlap between these two forms of inflammatory myopathy, and they share many important features.\textsuperscript{36} Listed below are several examples:

(i) There is an emphasis on blood vessels as a target of the immune response in DM. However, capillary depletion is characteristic of both DM and PM muscle biopsies, and in both diseases there is evidence supporting a role for VEGF in neovascularization.\textsuperscript{17} Furthermore, endothelial cells in muscle biopsy specimens from patients with both DM and PM express high levels of interleukin (IL)-1\textsuperscript{α}, IL-1\textsuperscript{β}, and transforming growth factor (TGF)\textsuperscript{β}1–3.\textsuperscript{37}

(ii) Although MHC-I expression is proposed to mediate cytolytic killing in PM, DM patients also express sarcolemmal MHC-I, albeit preferentially on perifascicular fibers.\textsuperscript{28}

(iii) Recent work has shown that perivascular infiltrates in DM muscle and endomysial infiltrates in PM muscle both include significant numbers of dendritic cells (DCs), a population of extremely effective antigen presenting cells.\textsuperscript{38}

(iv) Numerous studies have revealed very similar cytokine and chemokine profiles in muscle tissue from patients with DM and PM.\textsuperscript{37,39–41} This includes IL-17 and IFN-\gamma, suggesting that activated CD4\textsuperscript{+} T cells may be involved in both disease processes.\textsuperscript{38}

(v) IFN-\alpha/\beta transcripts are selectively upregulated in DM muscle tissue.\textsuperscript{42} However, in the periphery, these transcripts are increased in both DM and PM. Furthermore, their peripheral levels are correlated with disease activity in both diseases.\textsuperscript{23}

### Skin findings in DM

Cutaneous involvement is the primary clinical feature distinguishing those with DM from those with PM.\textsuperscript{43–45} A purplish discoloration around the eyes, especially the upper eyelid, is known as a heliotrope rash and is pathognomonic for DM (Fig. 4). In some patients with DM, this is found in
conjunction with periorbital edema. Gottron’s sign refers to an erythematous rash over the extensor surfaces of the metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints. This rash can evolve into a scaly eruption known as Gottron’s papules (Fig. 5). Gottron’s sign or papules may also occur on the extensor surfaces of the elbows and knees, where they are occasionally misdiagnosed as psoriasis. Like the heliotrope rash, Gottron’s papules are specific for DM. It should be noted that the coloration of the heliotrope rash and Gottron’s sign may vary depending upon the skin tone of the patient. For example, in African-American patients, these rashes may appear hyperpigmented rather than violaceous or erythematous.

DM patients may also have a combination of atrophy, dyspigmentation, and telangectasias known as poikiloderma. The poikilodermatous rash is commonly found on the upper chest as a V-shaped rash or on the upper back where it is known as a “shawl sign.” Facial erythema and scalp involvement are sometimes associated with DM. Nailbed abnormalities are a common feature of DM and may include both periungal telangectasias and cuticular hypertrophy. Although less frequently recognized, the oral mucosa may also have cutaneous manifestations in DM. These include erythema, hemorrhage, vesicles, ulcers, leukokeratosis, and gingival telangiectasias. Unlike the heliotrope rash and Gottron’s sign, these cutaneous features are not necessarily specific for DM. For example, facial erythema may be found in patients with rosacea, and periungal telangectasias are seen in patients with scleroderma.

While not all DM patients report that their rashes are photosensitive, several studies suggest that they are aggravated by exposure to UV light. In a typical DM patient, the cutaneous manifestations may precede, coincide with, or occur after muscle involvement. Occasionally, however, the characteristic skin lesions of DM occur in patients without overt signs of muscle disease. Although these patients with amyopathic DM (or dermatomyositis-sine myositis) do not have weakness or elevated CK levels, they may have subtly abnormal magnetic resonance imaging, electromyography, or muscle biopsy findings. Interestingly, a recent analysis of 16 patients initially diagnosed with amyopathic DM and followed longitudinally showed that close to 20% developed overt muscle disease within 5 years.

Diagnostic skin biopsies are often obtained during the evaluation of patients with DM and typically reveal a cell-poor vacuolar interface dermatitis, characterized by a sparse infiltrate of inflammatory cells at the dermoeidermal junction. Pathologic studies have also demonstrated dermal perivascular
Figure 6. Dermatomyositis skin biopsy. The arrow indicates a collection of perivascular inflammatory cells in the dermis (paraffin H&E).

infiltrates consisting of activated T lymphocytes (Fig. 6) and the deposition of membrane attack complex along vessel walls of the dermis. These vascular findings, along with the muscle pathology findings discussed below, suggest that blood vessels may be a primary target of the immune response in DM. Furthermore, a recent study showed an increased number of Ki-67 positive keratinocytes and reduced numbers of Bcl-2 positive cells in the basal cell layer of the epidermis, indicating increased proliferation and disrupted apoptotic pathways in DM skin. It should be noted, however, that routine pathologic studies cannot distinguish between the rashes of DM and those of lupus erythematosus. Consequently, a definitive pathological diagnosis of DM can only be made by muscle biopsy (discussed below).

Myositis-specific autoantibodies and their associated clinical features

As in other systemic autoimmune diseases, a strong association of autoantibodies with distinct clinical phenotypes is found in patients with myositis. These antibodies have classically been divided into myositis-associated autoantibodies (MAAs), which can also be found in patients with other connective tissue diseases, and MSAs. MSAs are found primarily (if not exclusively) in patients with myositis; they are not found in other connective tissue diseases and are virtually absent in patients with muscular dystrophies, including those, such as facioscapulohumeral dystrophy, which have inflammatory cell infiltrates on muscle biopsy.

This review will focus on the MSAs. Although it remains unclear why they arise and whether they play a pathologic role in the disease process, clues about the pathophysiologic relevance of these antibodies are emerging. I will highlight these along with the important clinical features typically associated with some of these antibodies.

Anti-Jo-1 and other anti-tRNA synthetase autoantibodies

The aminoacyl-tRNA synthetases are ubiquitously expressed cytoplasmic enzymes that catalyze the esterification of a specific amino acid to its cognate tRNA to form an aminoacyl-tRNA. There is a unique tRNA for each of the 20 amino acids. For example, the histidyl-tRNA synthetase attaches histidine to the appropriate tRNA. The aminoacyl-tRNA complex subsequently transfers the appropriate amino acid to an elongating polypeptide chain as the ribosome “reads” the coding sequence of an mRNA.

Autoantibodies against the histidyl-tRNA-synthetase (anti-Jo-1) are the most common MSAs and were first described in 1980. They were subsequently recognized to identify a group of patients with a unique clinical syndrome including myositis, interstitial lung disease (ILD), nonerosive arthritis, fever, and characteristic hyperkeratotic lesions along the radial and palmar aspects of the fingers known as “mechanic’s hands.” This constellation of symptoms has come to be known as the antisynthetase syndrome. Since then, antibodies targeting a number of additional aminoacyl-tRNA synthetases (ARS) have been identified, including those recognizing threonyl-tRNA synthetase (anti-PL-7), alanyl-tRNA synthetase (anti-PL-12), glycyl-tRNA synthetase (anti-EJ), isoleucyl-tRNA synthetase (anti-OJ), asparaginyl-tRNA synthetase (anti-KS), anti-tyrosyl-tRNA synthetase, and, most recently, anti-phenylalanyl synthetase (anti-Zo).

Anti-Jo-1 is found in approximately 25–30% of myositis patients, and the other anti-ARS autoantibodies occur in about 1–5% of myositis patients. Interestingly, the various antisynthetase antibodies seem to be mutually exclusive in that individual
patients do not produce more than one.\textsuperscript{71} Although all of the anti-ARS autoantibodies are associated with the antisynthetase syndrome first described for anti-Jo-1, certain differences between patients with the different antisynthetases have been noted. For example, a recent study carefully analyzed the clinical characteristics of 31 patients with anti-PL-12.\textsuperscript{72} Ninety percent of these had ILD and 65\% presented initially to a pulmonologist. By comparison, only 50–75\% of patients with anti-Jo-1 have ILD. Although 90\% of the anti-PL-12 patients had some underlying connective tissue disease, only 32\% had PM and 19\% had DM (the remainder had diagnoses of systemic sclerosis, undifferentiated connective tissue disease, systemic lupus erythematosus, and rheumatoid arthritis). In contrast, 90\% of Jo-1 patients have evidence of muscle disease. Compared with Jo-1 patients, PL-12 patients also had much lower rates of arthritis (58\% vs. 94\%), mechanic’s hands (16\% vs. 71\%), and fever (45\% vs. 87\%). It should also be noted that ILD occurs in about 30\% of myositis patients in the absence of known antisynthetase autoantibodies\textsuperscript{73–75}; an intriguing possibility is that these patients may have as yet unidentified autoantibodies.

It is notable that patients with anti-PL-12 and certain other antisynthetases are more likely to have lung disease without clinically detectable muscle disease.\textsuperscript{67,72,76,77} In a large study of Japanese patients with antisynthetase antibodies, seven of 88 patients had ILD but did not develop clinically apparent myositis even after more than 6 years.\textsuperscript{77} These patients had anti-KS, anti-PL-7, anti-PL-12, anti-EJ, and anti-OJ autoantibodies, but not anti-Jo-1. Interestingly, patients with amyopathic DM may also develop ILD.\textsuperscript{55} Whether patients with amyopathic ILD have a separate disease entity or a “forme fruste” of DM or the antisynthetase syndrome remains unclear.

The antisynthetase autoantibodies may be found in patients with either PM or DM, and certain antisynthetases may be more strongly associated with one or the other of these diseases. However, different studies of the same antisynthetase have yielded very different results.\textsuperscript{78} For example, in a recent study by Fathi and colleagues, 6/14 (43\%) PM and 0/9 (0\%) DM patients had anti-Jo-1.\textsuperscript{79} Similarly, another study found that only 2/96 (2\%) DM patients had anti-Jo-1.\textsuperscript{80} On the other end of the spectrum, a third study found anti-Jo-1 in 5/27 (18\%) PM patients and 9/59 (15\%) DM patients.\textsuperscript{81} Different demographic and referral patterns may account for these differences.

The prognostic significance of ILD has been the subject of several studies. In 1988, Arsur and Greenberg published a report evaluating 67 cases of myositis and ILD described in the literature between 1956 and 1980. This study revealed a mortality rate of 40\% after an average follow-up of 31 months for those with lung disease compared with a mortality rate of 24\% in 745 PM/DM patients selected without regard for the presence of lung disease.\textsuperscript{73} In contrast, a more recent study found that only one of 12 patients (8\%) with anti-Jo-1-autoantibodies and the antisynthetase syndrome died after an average follow-up time of 66 months.\textsuperscript{82} These conflicting results could be due to different inclusion criteria such as the fact that biopsy-proven lung fibrosis was required for inclusion only in the earlier study. Another contributing factor may be the improved mortality for myositis patients\textsuperscript{83}; the 5-year survival rate in the 1960s was 65\%\textsuperscript{84} and in the last decade has risen to 75–95\%.\textsuperscript{85–89}

Although the relationship between antisynthetase antibodies and myositis has been studied for almost 30 years, many questions remain about their pathologic significance. Several observations suggest they may play a role in the initiation and/or propagation of disease. For example, the antibody response to the Jo-1 protein (i.e., the histidyl-tRNA synthetase) undergoes class switching, affinity maturation, and spectrototype broadening.\textsuperscript{90–93} These features of the immune response suggest that this is a T cell-dependent, antigen-driven process directed against the Jo-1 protein.

Additionally, a number of studies have demonstrated that anti-Jo-1 autoantibody titers are correlated with disease activity.\textsuperscript{62,92,94,95} The most recent and extensive of these studies, conducted by Stone and colleagues,\textsuperscript{95} included a cross-sectional study of 81 anti-Jo-1 positive patients. This showed that autoantibody titers correlated modestly with CK levels and other measures of both muscle and lung involvement. In 11 patients with serial samples available for study, there were even more dramatic associations of Jo-1 autoantibody titers with indicators of muscle, joint, and lung disease. This included three patients who became anti-Jo-1 negative during periods of disease inactivity. Thus, serial anti-Jo-1 titers followed in an individual patient may be a...
useful marker of disease activity, particularly in the lung, where this is often difficult to assess. Furthermore, the association of anti-Jo-1 levels with both muscular and extramuscular manifestations of disease activity suggests that there may be a link between the Jo-1 antigen and inflammation in various tissues.

In this regard, Levine and his colleagues have provided some evidence that the immune response against Jo-1 could actually be initiated in the lung. These investigators had previously found that many autoantigens, including Jo-1, are cleaved by granzyme B, a proteolytic enzyme found in the granules of cytolytic T cells. Such cleavage has been proposed to generate “cryptic” epitopes, novel conformational epitopes of self-proteins not usually encountered by lymphocytes during their development. Theoretically, lymphocytes that recognize cryptic epitopes within Jo-1 would not be deleted during maturation, should remain in the circulation, and could be activated to drive an autoimmune response.

In a recent paper, Levine and colleagues first identified the granzyme B cleavage site within the Jo-1 protein. Next, they found that Jo-1 exists in two forms, only one of which is susceptible to cleavage by granzyme B. Finally, they demonstrated that this cleavable form of Jo-1 was robustly expressed in the lung relative to other tissues; in muscle, it did not appear to be expressed at all. Taken together, these studies implicate the lung as a likely microenvironment for the generation of cryptic Jo-1 fragments by granzyme B and the subsequent initiation of an anti-Jo-1 immune response. How a lung-initiated anti-Jo-1 response might be redirected to muscle is an open question. It also remains to be determined whether other aminacyl-tRNA synthetases are particularly susceptible to granzyme B cleavage in the lung or elsewhere.

Further evidence that an immune response against the Jo-1 protein may be important event in the initiation of myositis was published recently by Katsumata. In this study, mice were immunized with either human or murine forms of Jo-1 protein emulsified in complete Freund’s adjuvant. The anti-Jo-1 immune response was subsequently analyzed at various time points. Although the two proteins are 95% homologous, the immune response was relatively species specific, with antibodies preferentially recognizing the murine form when immunized with the murine form and vice versa. Interestingly, whereas the response to human Jo-1 immunization was uniphasic, mice immunized with the murine protein had evidence of an evolving immune response as evidenced by class switching and epitope spreading. Anti-Jo-1-specific T cells were also found in mice immunized with the murine form of this protein. Moreover, histological studies revealed that some mice immunized with Jo-1 developed inflammation within muscle and lung tissues. Foci of inflammatory cells within muscle tissue were found in a perivascular and endomysial distribution; invasion of myofibers by inflammatory cells was also reported. Within the lung, lymphocytic infiltrates were perivascular and peribronchiolar and also involved the alveoli. It should be noted that a small number of animals immunized with adjuvant alone developed muscle and lung inflammation. Although the relevance of this mouse model to human disease remains to be established, this work, along with the aforementioned studies, suggests that the immune response against Jo-1 may play an important role in the pathogenesis of the antisynthetase syndrome.

Finally, there is evidence that the Jo-1 antigen may have proinflammatory properties in addition to its role in protein synthesis. Specifically, Howard and colleagues have shown that Jo-1 protein can attract lymphocytes, monocytes, and immature dendritic cells through its interaction with chemokine receptor 5. These authors propose that damaged muscle cells could release Jo-1, leading to the recruitment of inflammatory cells which could, in turn, perpetuate autoimmune-mediated muscle destruction.

Anti-Mi-2 autoantibodies

Anti-Mi-2 autoantibodies were first described in a 60-year-old woman with DM (patient Mi), by Reichlin and Mattioli in 1976. The autoantigen recognized by her serum was initially identified only as a nuclear protein, named Mi-2. Characterizations of additional patients with autoimmune myositis showed that 20–30% of DM patients have Mi-2 antibodies. Most studies using immunoprecipitation or immunodiffusion techniques have shown that few, if any, PM patients or normal controls produce Mi-2 autoantibodies. However, studies using an ELISA detection assay have found a significant number of Mi-2 positive patients among those with PM, IBM, and even muscular dystrophy. The ELISA method of detection may simply have a
high false positive rate for anti-Mi-2 autoantibodies. Alternatively, the differences in detection between methods may reflect clinically relevant differences in epitope specificities. These issues will require additional studies to resolve.

Almost 20 years elapsed between the description of Mi-2 autoantibodies and the cloning and sequencing of the cognate antigen(s). In 1995, Nilasena and colleagues showed that Mi-2 autoantibodies immunoprecipitate a nuclear complex composed of up to eight subunits. A 240 kDa protein was found to be the subunit recognized by Mi-2 autoantibodies. Subsequently, two highly homologous proteins recognized by Mi-2 autoantibodies, Mi-2 and Mi-2β, were cloned and sequenced. Both can be found in the larger complex, but Mi-2β is thought to be the predominant form in vivo.

It is now known that Mi-2 is a major component of the nucleosome-remodeling deacetylase, or NuRD, complex. This nuclear complex consists of as many as eight distinct subunits and regulates transcription at the chromosomal level by histone deacetylation and ATP-dependent nucleosome remodeling. Specifically, Mi-2 modifies chromatin structure through its activity as a DNA-dependent, nucleosome-stimulated ATPase. Originally, Mi-2 was thought to function exclusively as a transcriptional suppressor through its association with other members of the NuRD complex including the histone deacetylases HDAC1 and HDAC2, the histone binding proteins RbAp46 and RbAp48, the metastasis-associated proteins MTA1 and MTA2, and the methyl binding domain protein Mbd3. The carboxyl terminus of Mi-2 can mediate this suppression by binding transcriptional repressors such as hunchback, Trk69, and KAP-1 corepressor. However, more recent work indicates that Mi-2 also interacts with transactivating proteins through its amino-terminal domain.

Emerging evidence suggests that Mi-2 and other members of the NuRD complex have specific functions in development. In Drosophila, the Mi-2 homolog, dMi-2, functions to repress Hox gene expression and is required for germ cell development. Likewise, in C. elegans the Mi-2 homolog, chd-4, functions to inhibit ectopic vulval development through Ras-induced pathways. Very recently, the creation of tissue-specific knockout mice has shown that Mi-2 expression is crucial for proper development of the epidermal basal cell layer. DM patients with anti-Mi-2 autoantibodies tend to have more fulminant cutaneous manifestations, including heliotrope rashes, shawl rashes over the upper back and neck, and cuticular overgrowth. Nonetheless, patients with Mi-2 antibodies have a more favorable prognosis, with better response to steroid therapy, and a diminished incidence of malignancy compared to others with DM. These observations suggest that, among individuals with DM, those with anti-Mi-2 antibodies may represent a distinct group.

At least two studies have identified a correlation between latitude and the relative proportion of DM among patients with myositis. For example, in Guatemala City 83% of myositis patients have DM and in Glasgow only 27% of patients have DM. A report published by Okada and colleagues demonstrated that increased exposure to ultraviolet (UV) radiation, rather than global gradients in genetic risk factors, is primarily responsible for this gradient. Interestingly, they also observed that the production of Mi-2 autoantibodies occurs more frequently at lower latitudes; in Guatemala City 60% of DM patients are Mi-2 positive and in Glasgow a mere 6.7% of DM patients produce anti-Mi-2 antibodies. Increased surface UV radiation intensity was the single variable identified that increased the odds of developing an immune response against Mi-2.

Given the association of surface UV radiation intensity and the development of an anti-Mi-2 immune response in DM patients, Burd and associates examined the expression of Mi-2 in human keratinocyte cell lines exposed to UV radiation. They found that UV exposure increases Mi-2 protein expression (especially Mi-2α), but not levels of other NuRD complex proteins, in these cells. This up-regulation of Mi-2 protein levels occurred rapidly, within 30 min of light exposure, and was regulated through translational and posttranslational mechanisms rather than transcriptionally. Based on their findings, these investigators proposed that the increased expression of Mi-2 protein in UV-induced dermatitis drives the anti-Mi-2 response and explains why this autoantibody is more prevalent at lower latitudes where surface UV radiation intensity is greatest.

In a related prior study by Casciola-Rosen and coworkers, Mi-2 protein levels were found to be relatively low in both normal muscle and in PM muscle biopsy specimens. In contrast, muscle biopsy
specimens from many patients with DM had significantly increased expression of Mi-2. These results also support the notion that increased expression of Mi-2 in the DM target tissues serves to drive the anti-Mi-2 immune response.

**Anti–signal recognition particle autoantibodies**

As discussed above, biopsies from patients with DM and PM are characterized by the conspicuous presence of inflammatory cells. However, about 10% of patients with apparently autoimmune muscle disease have biopsies revealing degenerating, necrotic, and regenerating myofibers with few, if any, infiltrating lymphocytes (Fig. 7). Some of these patients with a “necrotizing myopathy” have autoantibodies targeting components of the signal recognition particle (SRP).

The SRP is a complex of six polypeptides (72, 68, 54, 19, 14, and 9 kDa) and a single 7SL RNA molecule. This cytosolic ribonucleoprotein binds to the endoplasmic reticulum (ER) signal sequences of elongating polypeptide chains during their synthesis and translocates them to the ER membrane. In 1986, Reeves first described the presence of anti-SRP autoantibodies in a “typical polymyositis” patient. Subsequent work has demonstrated that autoantibodies may be directed to one or more of the six polypeptides as well as to the 7SL RNA. In the first comprehensive analysis of an anti-SRP patient cohort, Targoff identified these autoantibodies in 13/265 (4%) “PM/DM” patients. In this study, it was noted that SRP-positive individuals did not have overlap syndromes or DM rashes. Although they only infrequently had ILD or Reynaud’s phenomenon, these patients were noted to have unusually severe muscle disease.

In their 2002 paper, Miller and colleagues reported on the clinical and pathologic features of seven anti-SRP-positive patients. They confirmed that these often have severe and rapidly progressive weakness associated with very high CK levels and respond initially to steroids. Furthermore, they demonstrated that muscle biopsies from these patients reveal abundant necrotic and regenerating fibers, but much less frequent lymphocytic inflammation than seen in patients with DM or PM. As in DM, anti-SRP-positive patients had reduced numbers of capillaries, enlarged capillaries, and capillaries that stained positive for deposition of the membrane attack complex (MAC). However, these patients had neither characteristic rashes nor evidence of perifascicular atrophy as seen in DM.

Subsequently, Kao published a study examining a larger cohort of 19 anti-SRP-positive patients. This confirmed the severity of the initial disease and reported that multiple immunosuppressive medications were frequently required for its control. Despite this, there was no significant difference in 5-year mortality rates between SPR-positive and SRP-negative patients. Like others, these investigators found that muscle biopsies from most of these patients have relatively sparse inflammation, with abundant myofiber degeneration and regeneration; capillary deposition of MAC was observed in 67%. Interestingly, they identified three anti-SRP-positive patients who did not have active muscle disease. Of these, two had systemic sclerosis and one had features of the antisynthetase syndrome, suggesting that these antibodies may not be specific for PM.

Another study of 23 anti-SRP-positive patients confirmed that this antibody is associated with a unique syndrome characterized by a necrotizing muscle biopsy, severe weakness, dysphagia, and high CK levels. Three of these patients had DM. However, myofibers from SRP-positive patients did not
stain positive for MHC-I. In contrast to the prior reports, these investigators found MAC deposition only in necrotic muscle fibers, but not on capillaries.

Although patients with anti-SRP autoantibodies have a unique phenotype distinguished by a relative absence of inflammation and abundant myofiber degeneration, the pathologic relevance of these antibodies remains unclear. Future studies will be required to determine what causes their production, whether titers correlate with disease activity, and whether the antibodies play a direct role in mediating muscle damage. It should also be noted that some patients with autoimmune necrotizing myopathies do not have anti-SRP antibodies. Whether these individuals have heretofore unidentified autoantibodies remains to be determined.

**Anti-155/140, a DM and cancer-associated MSA**

Although the identities of the autoantigens recognized by these antibodies have not been definitively established, two recent papers, one by Kaji and colleagues and another by Targoff and colleagues, reported novel MSAs recognizing 155 and 140 kDa proteins. Each group found that the anti-155/140 autoantibody is both highly specific for DM and relatively common, being found in 13–21% of DM patients. Furthermore, each study found that anti-155/140-positive patients had a markedly higher rate of malignancy than seen in DM patients negative for this antibody (e.g., 71% vs. 11%). This was confirmed in another study showing that 8/19 (42%) anti-155/140-positive DM patients had cancer.

Targoff and his associates found a lower frequency of ILD in DM patients with the 155/140 autoantibody compared with other DM patients. Although Kaji and coworkers found that DM patients with anti-155/140 autoantibodies were more likely to have a heliotrope rash and Gottron’s papules/sign, Targoff and colleagues found no difference in such clinical features between these groups. This disparity could reflect differences between the Japanese DM population examined by Kaji and the population of subjects studied at the National Institutes of Health in Targoff’s study.

Interestingly, these and other researchers have found that anti-155/140 is also found in patients with the juvenile form of DM. This is especially remarkable because the presence of other MSAs in juvenile DM is rare. Further studies will be needed to confirm the identity of the autoantigens recognized by anti-155/140 autoantibodies and to clarify their potential pathologic role.

**Epidemiology and genetics**

Myositis, including both DM and PM, is a rare disease. Comprehensive epidemiologic data are lacking, but most studies suggest that myositis occurs in about 1 per 100,000 people annually. DM can occur at any age, but there appears to be a peak in the 30–50-year age range. As with many other autoimmune diseases, there is a strong gender bias in myositis, with roughly twice as many women affected as men.

Numerous studies suggest that some individuals may be genetically susceptible to developing inflammatory myopathy, including DM. For example, the immunoglobulin gamma heavy chain Gm 3 phenotype is associated with DM in Caucasian patients, and certain HLA alleles, especially those associated with the 8.1 ancestral haplotype (8.1 AH), may also confer increased risk or protection from DM.

Interestingly, the –308A polymorphism in the tumor necrosis factor (TNF) gene promoter is over-represented in DM patients compared with controls. The presence of the TNF-α-308A allele, also associated with systemic lupus erythematosus, leads to increased keratinocyte apoptosis following exposure to UV light and may increase susceptibility to light-induced skin damage. Furthermore, in both DM and lupus, this allele may predispose patients to the characteristic photosensitive rashes through increased production of TNF-α.

Multiple studies have demonstrated a positive relationship between certain MHC Class II alleles and the development of PM. Additionally, PM alone is weakly associated with a particular SNP within an intronic region coding for IFN-γ. In contrast, another HLA factor allele (DQAa*0201) is protective for PM; interestingly this allele is also protective for IBM which, like PM, is characterized by T cell infiltrates.

In addition to these positive and negative associations with either DM or PM, numerous studies have demonstrated that some genetic backgrounds, particularly alleles constituting the Caucasian 8.1 AH, are associated with the presence of particular
MSAs and MAAs. For example, although alleles of the 8.1 AH are risk factors for the development myositis with or without autoantibodies, they are more strongly associated with production of anti-Jo-1. One instance of this is the DRB1*0301 allele, which is a risk factor for myositis irrespective of autoantibody production, with an odds ratio of 3.6; strikingly, the odds ratio associated with this allele in anti-Jo-1 patients is 15.5. In contrast, DRB1*0701 and DQA1*0201 alleles seem to be protective for the development of anti-Jo-1 but significant risk factors for the development of anti-Mi-2. As has been pointed out by others, this is consistent with the fact that individual patients may produce either anti-Jo-1 or anti-Mi-2, but not both.

Other noteworthy examples of immunogenetic associations with MSA production include the observation that anti-PL-7 autoantibodies are positively associated with a unique HLA Class I allele (Cw*0304) distinct from the markers associated with other antisynthetase antibodies. In contrast, anti-PL-7 is negatively associated with DQA1*0501. Finally, the production of anti-SRP antibodies is positively associated with HLA-B*5001 and DQA1*0104 and, in African-Americans, the GM 6 immunoglobulin gamma heavy chain allo-type.

As has been shown in other autoimmune diseases (such as myasthenia gravis), these immunogenetic associations underscore the importance of the 8.1 AH and other immune-related alleles in the development of myositis. However, it should be noted that very few of the many individuals who harbor these alleles will ever develop an autoimmune disease. Presumably, autoimmune disease is only initiated when these predisposing alleles interact with other important genetic and environmental factors. Furthermore, it should be noted that in clinical practice the presence of autoimmune muscle disease in more than one family member is an exceptional occurrence and strongly suggests the presence of an inherited muscular dystrophy or metabolic myopathy.

Myositis and malignancy

Since the first two cases of malignancy-associated DM were reported in 1916, multiple studies have confirmed this connection. The largest population-based study, utilizing the national databases of Sweden, Denmark, and Finland, identified 618 DM and 914 PM patients. In this cohort, cancer was detected in 32% of DM and 15% of PM patients; this represented an increased risk compared with the rest of the population, with standardized incidence ratios (SIRs) of 3.0 for DM and 1.3 for PM. Although a variety of different tumors were identified, adenocarcinomas were the most common and represented about 70% of these malignancies. Most cancers were detected within 1 year of myositis diagnosis, but DM patients were still at increased risk for malignancy even 5 years later. Cancers were also found at an increased rate in DM patients up to 2 years prior to the development of myositis, suggesting that DM may be a paraneoplastic process in some patients.

A similar study from Australian databases found malignant disease in 104/537 patients with inflammatory myopathies. In about 60% of cases, the cancer was found within 1 week of the diagnosis of myositis. Patients with DM and PM had SIRs of 6.2 and 2.0, respectively, for the presence of malignancy. In another recent publication, 37 cases of malignancy were found in 309 myositis patients seen in Hungarian clinics over a 21-year period. These patients required more aggressive immunosuppression than other patients with myositis. Although successful treatment of the cancer also improved the muscle disease, patients with cancer had worse survival rates than those without cancer.

There is currently no consensus regarding what cancer screening tests should be performed—or how frequently—in patients diagnosed with myositis. However, it is noteworthy that elevated CA-125 levels at the time of myositis diagnosis have been associated with an increased risk for developing a solid malignancy over the next 5 years; this was true even in those who had unrevealing conventional malignancy screening, including pancomputed tomography scans and upper/lower gastrointestinal endoscopy. Furthermore, Chinoy and associates found that patients with most MSAs and MAAs are at a decreased risk for malignancy. For example, out of 66 patients with antisynthetase antibodies, only one had cancer. None of the seven anti-SRP patients and only 2/18 anti-Mi-2-positive patients had cancer. The notable exception, as discussed above, were those DM patients with anti-155/140; of 19
such patients had cancer. Taken together, these findings suggest that patients who are negative for anti-155/140, are positive for one of the other MSAs, and have normal CA-125 levels may not require an extensive malignancy evaluation.

Finally on the topic of cancer and myositis, it should be noted that Cao and colleagues found that of their 16 patients with amyopathic DM had associated malignancies; two of these cases were discovered at the time of diagnosis and two found more than 2 years later. This suggests that these patients, like those with muscle involvement, may require cancer screening at the time of diagnosis and, perhaps, on a routine basis for a number of years following that.

A model of autoimmune muscle disease pathogenesis

Despite concerted efforts over many years, the pathologic mechanisms leading to the initiation and propagation of autoimmune muscle disease remain obscure. For example, what is the pathologic relevance of the MSAs, which, unlike those recognizing the acetylcholine receptor in myasthenia gravis, target ubiquitously expressed intracellular proteins? Why are myositis autoantigens targeted while other muscle proteins are not? Is it significant that virtually all well-characterized myositis autoantigens bind DNA (e.g., Mi-2) or RNA (e.g., aminoacyl-tRNA synthetases and SRP)? What are environmental factors that trigger myositis in genetically susceptible individuals? Why is it that patients with autoimmune myositis are at increased risk for cancer?

While these questions remain unanswered, one recently proposed model attempts to synthesize some of the key findings already summarized in this review. Casciola-Rosen, and their respective collaborators have noted that myositis autoantigens such as Jo-1 and Mi-2 are expressed at low levels in normal muscle but at high levels in regenerating muscle fibers. Similarly, myositis autoantigens are expressed at low levels in most normal tissues, but are expressed at high levels in cancerous tissue such as breast and lung adenocarcinomas. These authors have proposed that an anticancer immune response may target myositis autoantigens expressed at high levels in these tumors where atypical processing could generate novel epitopes not recognized as self. Typically, an effective immune response would result in eradication of the tumor prior to its detection with no adverse consequences. However, in a genetically susceptible host with concurrent muscle regeneration (secondary to viral infection or myotoxins, for example), the anti-tumor response could be redirected to regenerating myofibers that also express high levels of myositis autoantigens. (Since skin cells exposed to UV light also have increased expression of myositis autoantigens, a similar mechanism could potentially underlie the targeting of skin in DM.) Cytokines, produced by infiltrating leukocytes, could upregulate MHC-I expression on muscle and thereby facilitate their killing by cytotoxic T cells. This would initiate further myofiber regeneration and increased production of myositis autoantigens, thus initiating a self-sustaining immune response against muscle. In instances where the immune response was insufficient to destroy the inciting tumor, autoimmune muscle disease and cancer would be found together. Although intriguing, future work will be required to test this model of myositis initiation and propagation.

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Conflicts of interest

The author declares no conflicts of interest.

References


Mammen: Dermatomyositis and polymyositis


Dermatomyositis and polymyositis

Central Immunogenetic Risk and Protective Factors for the Idiopathic Inflammatory Myopathies: Distinct HLA-A, -B, -Cw, -DRB1, and -DQA1 Allelic Profiles Distinguish European American Patients with Different Myositis Subtypes. European American patients with different myositis subtypes have distinct HLA-A, -B, -Cw, -DRB1, and -DQA1 allelic profiles. This suggests that these alleles contribute to the pathogenesis of different myositis subtypes.

Dermatomyositis and Polymyositis Associated with Malignancy: A Review of the Literature. Dermatomyositis and polymyositis are associated with an increased risk of malignancy. A review of the literature is presented to summarize the current understanding of this association.

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Dermatomyositis and Polymyositis: A Comprehensive Review. A comprehensive review of dermatomyositis and polymyositis is presented, covering the clinical features, diagnostic criteria, and management of these diseases.

Dermatomyositis and polymyositis: a population-based study. Dermatomyositis and polymyositis are autoimmune diseases characterized by muscle weakness and inflammation. A population-based study is presented to understand the epidemiology, clinical features, and management of these diseases.

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