CHAPTER 18

# Idiopathic Inflammatory Myopathies
## B. Pathology and Pathogenesis

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- Major pathology consists of focal inhomogeneous inflammation with injury, death, and repair of muscle cells.
- Each subgroup of myositis has characteristic changes on microscopy and immunochemistry.
- Etiology is still unclear but selected environmental exposures in genetically predisposed hosts have been found.

## PATHOLOGY AND IMMUNOPATHOLOGY

The characteristic skeletal muscle pathology in the idiopathic inflammatory myopathies (IIM) consists of chronic inflammation with infiltration by mononuclear cells, including lymphocytes, plasma cells, macrophages and dendritic cells, in the endomysium (between myocytes), perimysium (within fascicles), or perivascular (vessels in interstitium surrounding muscle fibers) areas (Figure 18B-1). The muscle fibers (myocytes), which may be necrotic or non-necrotic, show evidence of degeneration and regeneration, fiber hypertrophy or atrophy, and replacement by fibrosis or fat, and are often accompanied by increased connective tissue or fibrosis in the interstitial areas around the muscle cells (1).

These features collectively are characteristic of myositis, but each feature may be seen as part of the pathology of other muscle disorders, particularly muscular dystrophies. Macrophages may infiltrate to scavenge necrotic muscle as a secondary inflammatory process in dystrophies and other myopathies. Some features of other neuromuscular disorders, such as small angulated fibers, may also be present in myositis. A muscle biopsy is not always diagnostic of myositis. First, the inflammation is often focal and inhomogeneous. Inflammation is also diminished after the initiation of immunosuppressive therapy. A muscle biopsy should also not be performed at the site of an electromyogram (EMG), due to artifactual changes from the EMG. In inclusion body myositis (IBM), the inclusions are not always apparent, either because of their patchy nature or because they may appear later in the course of illness. Paraffin processing also dissolves the vacuoles, so that a Gomori trichrome stain is needed for detection.

A muscle biopsy should be performed, processed, and evaluated by persons experienced in these procedures because careful attention to selection of the biopsy site, to collection of the tissue, and to rapid freezing and appropriate histochemistry is needed to obtain the most informative biopsies. Standard procedure should include hematoxylin and eosin and Gomori trichrome stains to highlight the cellular infiltrates as well as muscle architecture. Alkaline phosphatase positive connective tissue, even in the absence of cellular infiltrates, can also aid in the diagnosis of myositis. A portion of the frozen tissue block should be saved for enzymatic and metabolic stains, as well as immunohistochemistry or detection of muscle sarcolemmal proteins if needed for diagnosis (1).

Each subgroup of myositis has somewhat characteristic changes on routine microscopy and immunohistochemistry. In dermatomyositis (DM), the mononuclear cells are focused more along the vessel walls of perimysial arterioles and venules, with such changes more prominent in the juvenile form of DM (2,3). Vessel thrombosis may also occur. Infarcts from the perifascicular region to the center of the fascicle are

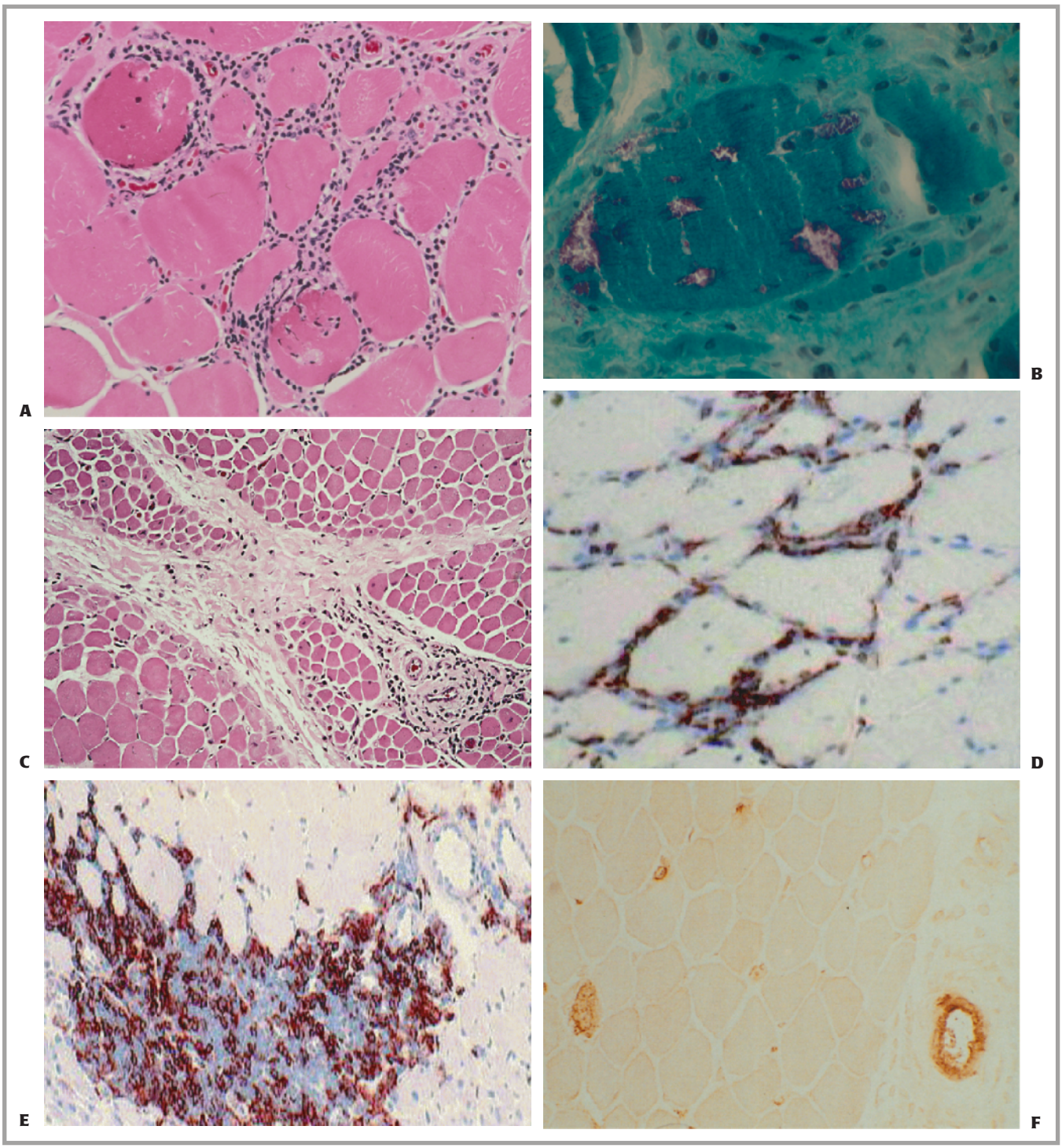




**FIGURE 18B-1**

Muscle pathology and immunopathology by light microscopy. Cross-sectional views of muscle biopsies showing characteristic changes in IIM. (A) Endomysial mononuclear cell infiltrates surrounding and invading myocytes in a patient with polymyositis (hematoxylin and eosin stain). (B) Similar findings are present in inclusion body myositis, with the exception of typical multiple reddish-rimed vacuoles in myocytes on trichrome staining that define the inclusion bodies (trichrome stain). (C) Dermatomyositis and juvenile dermatomyositis show more prominent vascular changes, including perivascular mononuclear cell infiltration and vessel thrombosis, as well as perifascicular atrophy. (From Rider LG, Targoff IN. In: Lahita RG, Chiorazzi N, Reaves WH, eds. Textbook of autoimmune diseases. Philadelphia: Lippincott Raven; 2000.) (D) Immunohistochemistry demonstrating staining for CD8+ cells that are surrounding myocytes in polymyositis. (From Figarella-Branger D et al., Muscle Nerve 2003;28:659.) (E) Positive immunostaining for B cells in dermatomyositis. (From Figarella-Branger D et al., Muscle Nerve 2003;28:659.) (F) Staining for the C5–C9 membrane attack complex on capillaries and myocytes in dermatomyositis. (Courtesy of Dr. J.T. Kissel.)

particularly present in juvenile DM and less frequently in adult DM (3). Perifascicular atrophy with small fibers at the external rim of a fascicle is also characteristic of DM. In contrast, in polymyositis (PM) and IBM, the inflammatory cells invade non-necrotic muscle fibers in a primarily endomysial distribution (4,5).

Immunohistochemistry also implicates different pathogeneses in the various forms of myositis. In DM, more frequent in the juvenile than adult form, the earliest changes include activation of the complement cascade through C3, deposition of the complement C5b-9 membrane attack complex on the endomysial vasculature, with resultant capillary destruction, muscle ischemia, and dilatation of the remaining capillaries (high endothelial venule formation) (6–8). This leads to resulting inflammation, with the infiltrating cells consisting mainly of B lymphocytes and CD4+ helper T cells in perimysial areas around the muscle fascicles and small blood vessels. MHC class I antigen and intracellular adhesion molecule (ICAM) are upregulated on the cell surfaces of damaged fibers or in perivascular areas, respectively (9). In PM and IBM, the weight of evidence suggests a predominant cytotoxic T lymphocyte–mediated process with CD8+ T cells, accompanied by smaller numbers of macrophages, surrounding and invading otherwise normal-appearing myocytes in endomysial areas (10). MHC class I antigen is upregulated on the surface of the majority of muscle fibers, even those not affected by inflammation, although this is not specific to myositis (1). Necrotic muscle fibers may be scattered in the biopsy, particularly in PM.

In IBM, in addition to these inflammatory findings, there are vacuolated myofibers occurring in the center or periphery of muscle fibers, with wide variation in myofiber size, including scattered atrophic fibers, and prominence of central muscle nuclei. The vacuoles are rimmed by granular eosinophilic material, which on Gomori trichrome stains purple-red and on Congo red staining reveals amyloidlike deposits, including phosphorylated tau, ubiquitin, beta-amyloid, and presinilin 1 (9). Diffuse inflammatory infiltrates and ragged red fibers are sometimes seen. In IBM-characteristic tubulofilaments, 15 to 18 nm in diameter and seen most often in the cytoplasm and less often in the nuclei, are often visible by electron microscopy (1).

In terms of the pathologic features of other organs, the skin in DM demonstrates interface dermatitis, often with basement membrane thickening and mucin deposition. Many of the changes in muscle, including the types of infiltrating cells and the predominance of perivascular inflammation, are also evident in the skin. In the gastrointestinal tract, ischemic ulceration is a potentially life-threatening manifestation and may include a noninflammatory acute endarteropathy with arterial and venous intimal hyperplasia and occlusion of intestinal vessels by fibrin thrombi in the submucosa, muscularis, and serosal layers (3). A chronic endarteropathy characterized by narrowing or complete occlusion of multiple small and medium-sized arteries, subintimal foam cells, fibromyxoid neointimal expansion, and significant luminal compromise and infiltration of macrophages through the muscle layers into the intima may also be seen. The pathology of the interstitial lung disease most commonly is that of nonspecific interstitial pneumonitis (NSIP), but occasionally diffuse alveolar damage, usual interstitial pneumonitis (UIP), and bronchiolitis obliterans organizing pneumonia (BOOP) may be present. The myocardium may demonstrate myocarditis with subsequent fibrosis.

# PATHOGENESIS

While the etiology and pathogenesis of the IIM remain unclear, a number of lines of investigation have suggested possible ways in which selected environmental exposures in genetically susceptible individuals may lead to chronic immune activation and the ultimate immunologic attack on muscle and other involved tissues (Figure 18B-2). A number of these mechanisms, which include upregulation of MHC class I on muscle fibers, immune activation, and activation of the endoplasmic reticulum stress response, are processes common to other myopathies besides myositis. While some of the mechanisms are found in all forms of myositis, others are likely unique to selected groups.

## Genetic Factors

The finding of families in which two or more blood relatives have myositis and associations of myositis with particular genes support the hypothesis that myositis is at least in part inherited. Polymorphic alleles in the major histocompatibility locus (MHC) are the major immunogenetic risk and protective factors identified for the IIM. The A1-B8-Cw07-DRB1*0301-DQA1*0501 ancestral haplotype is the major immunogenetic risk factor for PM, as well as adult and juvenile DM in Caucasians, with the risk factor likely in the class II HLA region at or near human leucocyte antigen (HLA) DRB1*0301. For IBM, DRB1*0301 and its linked allele DQA1*0501 are risk factors along with the class I Cw*14 allele. HLA DQA1*0201 is protective for all forms of myositis, and other DRB1 or DQA1 alleles are protective for specific clinical groups (11). In the class III MHC region, the tumor necrosis factor alpha (TNF-alpha)-308A allele is a risk factor for adult and juvenile DM and PM in Caucasians, and may also be a severity factor, perhaps related to photosensitive rashes and the development of calcinosis. DMA*0103 and DMB*0102 are possible risk factors for juvenile DM. Outside the HLA region, the IL1 receptor antagonist VNTR A1

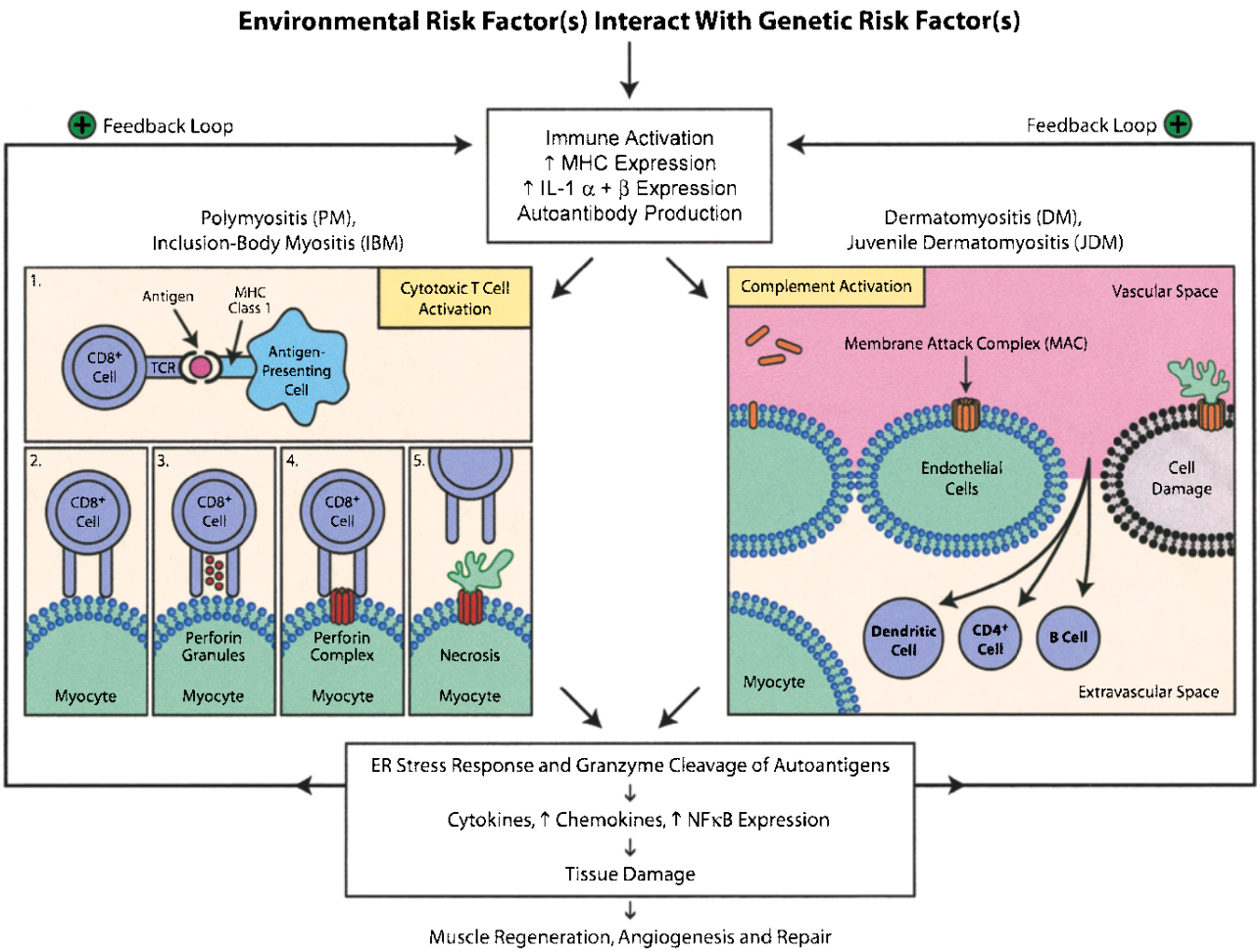


**FIGURE 18B-2**

Possible pathogenic mechanisms in IIM. All forms of myositis appear likely to involve immune activation following specific exposure to environmental risk factors in genetically susceptible individuals. Common immune activation processes in muscle and other tissues include upregulation of MHC expression and IL-1 alpha and beta, leading to autoantibody production prior to clinical disease onset. Following this, myocyte-directed cytotoxic T-cell mechanisms predominate in PM and IBM, while complement-mediated endothelial damage, leading to CD4, B-cell, and dendritic-cell infiltrations, predominate in DM and JDM. Other general mechanisms may involve hypoxia, activation of the endoplasmic reticulum stress response, and cleavage of autoantigens, resulting in cytokine and chemokine release and positive feedback loops that lead to further immune activation. Later processes include muscle regeneration, angiogenesis, and repair, and in some cases fibrotic changes and other damage in affected tissues.



allele is a risk factor for juvenile DM in Caucasians. The Gm allotypes, serologic markers on the heavy chains of IgG, rather than HLA alleles, are genetic risk or protective factors for myositis in Koreans and Mesoamericans, suggesting that genetics likely varies among ethnic groups (12).

Human leukocyte antigen risk factors are more strongly associated with specific autoantibodies (13). The ancestral haplotype A1-B8-Cw07-DRB1*0301-DQA1*0501 is a strong risk factor for patients with antisynthetase autoantibodies, including Jo1, in Caucasian patients. MHC class II alleles DRB1*0701 and DQA1*0201 are risk factors for Mi 2 autoantibodies. DQA1*0301 is a risk factor for p155, a myositis-associated autoantibody common in adult and juvenile DM.

## Environmental Factors

The temporal association of exposure to a number of infectious and noninfectious agents prior to the onset of the IIM in certain individuals, as well as reports documenting temporal, seasonal, or geographic clustering of

IIM cases suggest a role for environmental factors in initiation of disease (12).

Epidemiologic investigations have also suggested a number of environmental factors which may be important in the development of IIM. Most are not proven environmental risk factors, but for some exposures, case-controlled epidemiologic studies, cases of de-challenge and re-challenge, and biomarker assays strengthen the association with illness onset. Of the infectious agents, Group A streptococcus and influenza have the strongest evidence of association with onset of juvenile IIM and toxoplasmosis with adult DM from case-controlled epidemiologic studies. With Group A streptococcus, peripheral blood T lymphocytes from juvenile DM patients react with streptococcal M5 protein and a myosin peptide with homology to M5. The evidence is mixed for coxsackie B virus, with reports of isolation of the virus from some affected muscles but a case-controlled study not supporting an association with onset of juvenile DM. Echoviruses, however, have been clearly associated with a DM-like illness in patients with agammaglobulinemia. Other infections temporally associated with onset of IIM which are not yet defined as definite risk factors for IIM include retroviruses, hepatitis viruses, *Borrelia burgdorferi,* and *Trypanosoma cruzi.* Parvovirus B19 is not associated with onset of juvenile DM in a case-controlled study. A search for viral genomes by sensitive molecular methodology in DM and PM biopsies has failed to identify consistently any viral nucleic acid, suggesting that known viruses are not contributing to the persistent inflammation (12).

Noninfectious agents, including ultraviolet light, physical exertion, psychological stress, medications, and vaccines have been suggested as possible triggers for some forms of IIM. Growing evidence suggests a role for ultraviolet radiation (UV) in the onset of DM. DM patients have a number of photosensitive rashes and, anecdotally, illness may exacerbate following sun exposure. Adult DM patients also have increased sensitivity to UVB as demonstrated by an abnormally low minimal erythema UVB dose. An increase in the proportion of DM relative to PM and an increase in the proportion of patients with the DM-associated Mi 2 autoantibody in areas of the world with higher surface UV radiation suggest that UV light exposure may modulate the clinical and immunologic expression of myositis. Keratinocytes damaged by UV radiation also undergo apoptosis, with increased autoantigen expression on the surface of such cells.

Case-controlled studies support a role for psychological stress, muscular exertion, and collagen implants in the onset of adult DM or PM (14). Exposure to D-penicillamine may induce myositis in 1% to 2% of patients and this has been associated with HLA B18, B35, and DR4 in Caucasians but with DQw1 in patients from India, which are genes distinct from those associated with IIM. Similarly, although there is no epidemiologic evidence from population studies confirming an association between silicone exposure and myositis, Caucasian women who develop myositis following silicone implants do not have the characteristic genetic features seen in IIM, but rather have an increased frequency of HLA DQA1*0102. Temporal associations of onset of the IIM with certain other drugs (including lipid-lowering agents, zidovudine, leuprolide, and local anesthetics), biologic therapies (such as interferon alpha and interleukin 2), and vaccines have been reported, but additional evidence is needed to confirm their potential associations (12). Certain alum-containing vaccines have also been associated with the distinct entity of macrophagic myositis, in which macrophages are the predominant infiltrating cell.

## Cytotoxic Mechanisms in Polymyositis and Inclusion Body Myositis

Many lines of evidence suggest that cytotoxic mechanisms play a more important role in PM and IBM than adult or juvenile DM (15). First, as is the case for the quantitation of subsets of lymphocytes in the affected muscle, studies of peripheral mononuclear cells demonstrate that PM and IBM are virtually indistinguishable in showing higher numbers of circulating activated T cells. Second, peripheral blood cells from PM patients have an increased proliferative response to, and demonstrate cytotoxicity to, autologous muscle tissue in vitro. Third, T cells in PM and IBM contain perforin and granzyme granules that are directed towards the surface of the myofibers and that, on release, induce pores in the myocyte membranes (10). Fourth, based on restricted T-cell receptor usage, there is clonal expansion of muscle-infiltrating T cells selected for certain gene families in PM and IBM, implying an antigen-driven process, in contrast to a more polyclonal pattern of T-cell receptor usage in DM. Additionally, the CD8+ cells found in PM and IBM appear to preferentially target MHC class I–expressing myocytes, which would be required for their antigen-specific recognition of cellular targets. These findings, taken together, suggest that in PM and IBM, subpopulations of T cells are selected and expanded in response to as yet uncharacterized antigens and may explain some of the T-cell–mediated pathology seen in these diseases.

## Humoral and Endothelial Mechanisms in Adult and Juvenile Dermatomyositis

Humoral and endothelial mechanisms appear to be more important for adult and juvenile DM compared to

PM and IBM (15). First, higher numbers of circulating B and CD4+ T lymphocytes are present in the periphery as well as in the affected muscle. Second, immunoglobulin and the terminal portion of complement are deposited on blood vessels in the earliest phases of illness (6), resulting in a decrease in the number of capillaries and muscle injury, including ischemia. From microarray experiments, in some cases confirmed by immunohistochemistry or real-time polymerase chain reaction (PCR), a number of promoters and inhibitors of angiogenesis are overexpressed in the affected muscle tissue (16,17). There is also increased expression of genes promoting endothelial differentiation and activation, as well as classical and alternative complement pathway regulators that facilitate angiogenesis in the muscle tissue of adult DM patients (16). In juvenile DM, a number of angiostatic ELR-chemokines are increased in expression and correlate with the degree of capillary loss (17). Upregulation of leucocyte adhesion molecules, particularly ICAM-1 on the muscle arterioles and venules in juvenile DM and somewhat in adult DM, results in the infiltration of B and CD4+ T lymphocytes, dendritic cells, and macrophages (9). Proinflammatory cytokines result in damage and further infiltration of cells.

Immune dysregulation is also a key part of the pathogenesis, with upregulation of interferon alpha/beta inducible genes and genes upregulated in a type I interferon response, as well as genes involved in antigen presentation, suggesting either viral initiation of disease or activation of plasmacytoid dendritic cells (18,19). Some of these factors are also angiostatic.

## Cytokines, Chemokines, and Related Factors

A growing number of signaling molecules have been discovered to be important in regulating the movement of immune cells from the circulation into different tissues and in altering their subsequent function (9). Immunohistochemistry and array studies have suggested an increased expression of many types of these signaling molecules in the form of cytokines, chemokines, chemokine receptors, and related proteins in muscles of myositis patients. Cytokines frequently found in inflammed muscle include: proinflammatory cytokines, such as interleukin (IL) 1 and tumor necrosis factor alpha (TNF-alpha); cytokines involved in T-cell differentitation, including interferons (IFNs), IL-2, IL-5, and IL-10; and cytokines involved in fibrotic processes, such as transforming growth factor beta (TGF-beta). Chemokines—especially macrophage inflammatory protein-1 alpha (MIP-1 alpha, CCL3), monocyte chemoattractant protein-1 (MCP-1, CCL2) and CCL5 (RANTES)—as well as CXC-chemokine ligands (CXCL 9 and 10) and chemokine receptors (CCR1-5, CCR2A, and CCR2B) are also upregulated in myositis, thus attracting monocytes, macrophages, and T lymphocytes to the inflammatory sites. The molecules that facilitate leukocyte migration from the vasculature into the tissues, including intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), CD142, and CD31 (which facilitate dendritic cell migration), have also been found to be increased in the muscle tissue of myositis patients compared to controls. ICAM-1 is upregulated on perimysial or perivascular areas in DM and on endomysial vessels in PM and IBM. Other studies demonstrate increased expression of interferon alpha/beta–inducible genes as one of the major features differentiating adult and juvenile DM from PM and IBM. Furthermore, an investigation of serial muscle biopsies from three DM and four IBM patients, before and after treatment with intravenous immunoglobulin, suggested decreases in selected chemokine and ICAM-1 genes in those DM patients who responded to therapy (20).

The cytokines present in the muscle biopsies of myositis subjects may be involved in regulating immune responses, but they may also have direct effects on muscle and other target tissues (9). For example, TNF-alpha has been shown to induce many changes in muscle from accelerated catabolism to contractile dysfunction. IL-1 alpha may play a role in direct myotoxicity via its influence on insulinlike growth factor, thereby leading to metabolic disturbances in nutrition supply, and by suppressing myoblast proliferation and fusion. Differences in methodology and patient populations under study, however, have made it difficult to determine if any of these signaling molecules are playing a primary or secondary role in pathogenesis and if there are critical differences in cytokine patterns in the different forms of IIM.

## Major Histocompatibility Complex Overexpression and Sequelae

Increased MHC class I antigen expression occurs on scattered myocytes in all forms of IIM, and MHC class I molecules are present even on myocytes far removed from inflammation, suggesting that this may be an early event in pathogenesis (1). How specific this process is to IIM remains unclear because myocytes in muscle biopsies from some muscular dystrophies also show MHC class I expression. Nonetheless, additional evidence that overexpression of MHC class I may be related to myositis comes from an animal model where directed transgenic upregulation in skeletal muscle led to muscle inflammation as well as decreased muscle strength, even before detectable histological damage in the skeletal muscles of these mice (21). The increased MHC class I not only renders muscle a possible target for the recognition by cytotoxic T cells, but it may also

negatively impact cellular metabolism. When there is an imbalance between the load of proteins in the endoplasmic reticulum (ER) and the cell's ability to process that load, signaling pathways are activated that adapt cells to ER stress. This process is called the *ER stress response* and it can be provoked by a variety of conditions, including ischemia, viral infections, mutations that impair protein folding, and excess accumulation of proteins in the ER. The assembly and folding of MHC class I molecules in the ER involves a highly regulated process to assure their proper conformation and to prevent accumulation of unfolded proteins. When excess MHC class I molecules are present, this system can be overloaded to result in many cellular changes, including activation of the NF-κB pathway, as has been demonstrated in both IIM and the transgenic upregulated MHC class I animal model (22,23). This finding suggests that excess production of MHC class I molecules may lead to the ER stress response, which may play a role in IIM pathogenesis via activtaion of NF-κB, resulting in the induction of a number of cytokines, chemokines, adhesion molecules, and further MHC upregulation, thus initiating a self-sustaining positive feedback loop.

## REFERENCES


1. Dalakas MC. Muscle biopsy findings in inflammatory myopathies. Rheum Dis Clin North Am 2002;28:779–798, vi.
2. Arahata K, Engel AG. Monoclonal antibody analysis of mononuclear cells in myopathies. I. Quantitation of subsets according to diagnosis and sites of accumulation and demonstration and counts of muscle fibers invaded by T cells. Ann Neurol 1984;16:193–208.
3. Crowe WE, Bove KE, Levinson JE, Hilton PK. Clinical and pathogenetic implications of histopathology in childhood polydermatomyositis. Arthritis Rheum 1982;25:126–139.
4. Engel AG, Arahata K. Monoclonal antibody analysis of mononuclear cells in myopathies. II: Phenotypes of autoinvasive cells in polymyositis and inclusion body myositis. Ann Neurol 1984;16:209–215.
5. Engel AG, Arahata K. Mononuclear cells in myopathies: quantitation of functionally distinct subsets, recognition of antigen-specific cell-mediated cytotoxicity in some diseases, and implications for the pathogenesis of the different inflammatory myopathies. Hum Pathol 1986;17:704–721.
6. Kissel JT, Mendell JR, Rammohan KW. Microvasculature deposition of complement membrane attack complex in dermatomyositis. N Engl J Med 1986;314:329–334.
7. Emslie-Smith AM, Engel AG. Microvascular changes in early and advanced dermatomyositis: a quantitative study. Ann Neurol 1990;27:343–356.
8. Estruch R, Grau JM, Fernandez-Sola J, Casademont J, Monforte R, Urbano-Marquez A. Microvascular changes in skeletal muscle in idiopathic inflammatory myopathy. Hum Pathol 1992;23:888–895.
9. Figarella-Branger D, Civatte M, Bartoli C, Pellissier JF. Cytokines, chemokines, and cell adhesion molecules in inflammatory myopathies. Muscle Nerve 2003;28:659–682.
10. Goebels N, Michaelis D, Engelhardt M, et al. Differential expression of perforin in muscle-infiltrating T cells in polymyositis and dermatomyositis. J Clin Invest 1996;97:2905–2910.
11. O'Hanlon TP, Carrick DM, Arnett FC, et al. Immunogenetic risk and protective factors for the idiopathic inflammatory myopathies: distinct HLA-A, -B, -Cw, -DRB1 and -DQA1 allelic profiles and motifs define clinicopathologic groups in Caucasians. Medicine (Baltimore) 2005;84:338–349.
12. Reed AM, Ytterberg SR. Genetic and environmental risk factors for idiopathic inflammatory myopathies. Rheum Dis Clin North Am 2002;28:891–916.
13. O'Hanlon TP, Carrick DM, Targoff IN, et al. HLA-A, -B, -DRB1 and -DQA1 allelic profiles for the idiopathic inflammatory myopathies: distinct immunogenetic risk and protective factors distinguish European American patients with different myositis autoantibodies. Medicine 2006;85:111–127.
14. Lyon MG, Bloch DA, Hollak B, Fries JF. Predisposing factors in polymyositis-dermatomyositis: results of a nationwide survey. J Rheumatol 1989;16:1218–1224.
15. Dalakas MC. Mechanisms of disease. Signaling pathways and immunobiology of inflammatory myopathies. Nat Clin Pract Rheumatol 2006;2:219–227.
16. Nagaraju K, Rider LG, Fan C, et al. Endothelial cell activation and neovascularization are prominent in dermatomyositis. J Autoimmune Dis 2006;3:2.
17. Fall N, Bove KE, Stringer K, et al. Association between lack of angiogenic response in muscle tissue and high expression of angiostatic ELR-negative CXC chemokines in patients with juvenile dermatomyositis: possible link to vasculopathy. Arthritis Rheum 2005;52:3175–3180.
18. Tezak Z, Hoffman EP, Lutz JL, et al. Gene expression profiling in DQA1*0501+ children with untreated dermatomyositis: a novel model of pathogenesis. J Immunol 2002;168:4154–4163.
19. Greenberg SA, Sanoudou D, Haslett JN, et al. Molecular profiles of inflammatory myopathies. Neurology 2002;59:1170–1182.
20. Raju R, Dalakas MC. Gene expression profile in the muscles of patients with inflammatory myopathies: effect of therapy with IVIG and biological validation of clinically relevant genes. Brain 2005;128:1887–1896.
21. Nagaraju K, Raben N, Loeffler L, et al. Conditional upregulation of MHC class I in skeletal muscle leads to self-sustaining autoimmune myositis and myositis-specific autoantibodies. Proc Natl Acad Sci U S A 2000;97:9209–9214.
22. Nagaraju K, Casciola-Rosen L, Lundberg I, et al. Activation of the endoplasmic reticulum stress response in autoimmune myositis: potential role in muscle fiber damage and dysfunction. Arthritis Rheum 2005;52:1824–1835.
23. Nogalska A, Engel WK, McFerrin J, Kokame K, Komano H, Askanas V. Homocysteine-induced endoplasmic reticulum protein (Herp) is up-regulated in sporadic inclusion-body myositis and in endoplasmic reticulum stress-induced cultured human muscle fibers. J Neurochem 2006;96:1491–1499.