Molecular Immunology and Genetics of Inflammatory Muscle Diseases

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Polymyositis, dermatomyositis, and inclusion body myositis, although immunopathologically distinct, share 3 dominant histological features: inflammation, fibrosis, and loss of muscle fibers. Progress in molecular immunology and immunogenetics has enhanced our understanding of these cellular processes. Based on the T-cell receptor gene rearrangement, the autoinvasive CD8+ T cells in polymyositis and inclusion body myositis, but not dermatomyositis, are specifically selected and clonally expanded in situ by heretofore unknown muscle-specific autoantigens. The messenger RNA of cytokines is variably expressed, except for a persistent up-regulation of interleukin 1β in inclusion body myositis and transforming growth factor β in dermatomyositis. In inclusion body myositis, the interleukin 1, secreted by the chronically activated endomysial inflammatory cells, may participate in the formation of amyloid because it up-regulates β-amyloid precursor protein (β-APP) gene expression and β-APP promoter and colocalizes with β-APP within the vacuolated muscle fibers. In dermatomyositis, transforming growth factor β is overexpressed in the perimysial connective tissue but is down-regulated after successful immunotherapy and reduction of inflammation and fibrosis. The degenerating muscle fibers express several antiapoptotic molecules, such as Bcl-2, and resist apoptosis-mediated cell death. In myositis, several of the identified molecules and adhesion receptors play a role in the process of inflammation, fibrosis, and muscle fiber loss, and could be targets for the design of semi-specific therapeutic interventions.

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Distinct clinical, histological, and immunopathologic characteristics separate the acquired inflammatory myopathies into dermatomyositis (DM), polymyositis (PM), and sporadic inclusion body myositis (s-IBM).1,2 In DM, early activation of complement leads to the deposition of membranolytic attack complex on the endomysial capillaries, resulting in perivascular inflammation, capillary depletion, muscle ischemia, necrosis, and muscle fiber atrophy.1,2 In PM and IBM, sensitized CD8+ cytotoxic T cells invade and destroy muscle fibers that aberrantly express class I major histocompatibility complex antigen. Abnormal mitochondria and vacuoles containing 15- to 18-nm tubulofilaments that immunoreact for β-amyloid and amyloid-related proteins are important factors in the pathogenesis of s-IBM.1,2

Despite their clinicohistological and immunopathologic differences, the end result of the affected muscles in PM, DM, and s-IBM associated with clinical symptoms is the triad of chronic inflammation, fibrosis, and the loss of muscle fibers. This review focuses on the recent advances in molecular medicine that relate to the antigenic specificity of the infiltrating T cells and their T-cell receptors (TCRs) and the participating role of certain adhesion or regulatory molecules in fibrosis and the death of myofibers.

TCR GENE rearrangement of endomysial inflammatory cells

The T cells recognize an antigen by the TCR, a heterodimer of 2 α and β chains, encoded by multiple gene families in the V (variable), D (diversity), J (joining), and C (constant) regions of the TCR. The part of the TCR that
recognizes an antigen is the CD3 region, which is encoded by genes in the V-J and V-D-J segments of the TCR gene. If the endomyosial T cells are selectively recruited by a muscle-specific autoantigen, the use of the V and J genes of the TCR should be restricted, and the amino acid sequence in their CD3 region should be conserved. Three independent laboratories (Department of Neurology, Stanford University School of Medicine, Stanford, Calif, along with the Istituto Nazionale Neurologico “Carlo Besta,” Milan, Italy; National Institutes of Health [NIH], Bethesda, Md; and Neuroimmunology Laboratory, Max Planck Institute, Martinsried, Munich, Germany) have examined the TCR gene families of the infiltrating or the autoinvasive CD8+ T cells with polymerase chain reaction and immunocytochemistry and showed that in patients with PM, but not in those with DM, only certain T cells of specific TCRα and TCRβ families are recruited to the muscle from the circulation.5,6 Cloning and sequencing of the amplified endomyosial or autoinvasive TCR gene families demonstrated a restricted use of the Jβ gene with conserved amino acid sequence in the CD3 region. These findings indicate that in PM, the CD8+ cells are specifically selected and clonally expanded in situ by muscle-specific autoantigens, the nature of which remains unknown. Such antigens, presented to the autoinvasive CD8+ T cells by the class I major histocompatibility complex antigen on the sarcolemma, are expected to be either endogenous muscle peptides or viruses. The failure, however, by several laboratories to amplify known viral RNA from muscles affected by PM points to endogenous muscle proteins, rather than vi-
proteins, resulting in fibrosis and chronic inflammation.\textsuperscript{14} Mice double knockout for the Tgfβ gene (Tgfβ \textsuperscript{−−}) lack TGF-β and develop prominent endomyal inflammation similar to that seen in human PM (M.C.D., S. Wahl, PhD, unpublished observations, 1997). Because the adhesion of T cells is mediated by the up-regulated integrins on their lymphocytic surface and cellular fibronectin is a ligand for β\textsubscript{1} integrin, treatment of the Tgfβ \textsuperscript{−−} mice with fibronectin peptides has suppressed the endomyal inflammation (M.C.D., S. Wahl, PhD, unpublished observations, 1997). These findings suggest that fibronectin or other small peptides that interfere with the binding of integrins to their respective ligands on the endothelial cell wall may provide new, promising therapeutic approaches for the treatment of patients with PM and DM.

The deleterious effect of TGF-β in chronic inflammation and fibrosis is best evident in the muscles of patients with DM, where fibrosis is prominent and TGF-β and TGF-β messenger RNA are up-regulated.\textsuperscript{12} In the repeated muscle biopsy specimens of patients with DM who improved after successful immunotherapy, we have observed not only the suppression of class I major histocompatibility complex antigen, vascular cell adhesion molecule, intracellular adhesion molecule-1, endomyal inflammation, and fibrosis, but also substantial down-regulation of TGF-β and the TGF-β messenger RNA. More direct anti-TGF-β strategies, therefore, may be reasonable future therapeutic strategies in suppressing the deleterious inflammatory fibrosis in patients with DM.

**IL-1β AND s-IBM**

In s-IBM, the excess of IL-1β is derived by activated endomyal macrophages and T cells and probably by endomyal β-amyloid precursor protein (APP), which is a known enhancer of IL-1β production.\textsuperscript{14} There appears to be a closed loop between IL-1β and β-APP because IL-1β up-regulates the β-APP gene expression and β-APP promoter through protein kinase C.\textsuperscript{14} Consistent with these data is the observation that IL-1β co-localizes with β-APP not only in the amyloid plaques of patients with Alzheimer disease\textsuperscript{15} but also within the vacuolated muscle fibers of patients with s-IBM (Figure 2).\textsuperscript{10} It can be proposed that the microglia in the brain and the macrophages in the muscle, both cells of the same lineage, promote the production of IL-1 the evolution and continuous formation of amyloid in both the brain of patients with Alzheimer disease and muscle of patients with IBM, as depicted in Figure 3.

The endomyal excess of IL-1β in patients with s-IBM may also be connected with the development of abnormal mitochondria and the ragged-red fibers that are commonly seen in this disease. In human myotubes, treatment with IL-1 causes cellular destruction and abnormal mitochondria that immunoreact with anti–IL-1 (C. Mora, MD, M.C.D., unpublished observations, 1996-1998). Furthermore, antisera to IL-1 immunostains the subsarcolemmal mitochondrial accumulations of the ragged-red fibers in these patients’ muscle biopsy specimens, as shown in Figure 2. Because ragged-red fibers are seen only in s-IBM where inflammation is prominent, but not in the hereditary form of IBM where inflammation is absent, a connection of pathogenic significance may be proposed between chronic inflammation, IL-1β production, and mitochondrial toxicity.

**APOPTOTIC OR ANTIAPOPTOTIC MOLECULES IN PM AND IBM**

Cytotoxic T cells induce cell death either through the perforin pathway or the Fas-Fas-L–dependent process. In PM and IBM, the autoinvasive activated T cells contain perforin granules that are reoriented toward the surface of the muscle fibers and, when released, induce pores on the plasma membrane, causing osmotic cell lysis.\textsuperscript{18} Whether the Fas-dependent pathway is also involved in myocytic cell death is unclear. Many of the regenerating and degenerating muscle fibers in patients with PM or IBM express the Fas antigen,\textsuperscript{19} and the autoinvasive CD8+ **}[7668]/ on 06/06/2017](http://archneur.jamanetwork.com/pdfaccess.ashx?url=/data/journals/neur/7668/ on 06/06/2017)
cells express the Fas-L. Despite these Fas-Fas-L interactions, however, no signs of apoptosis have been detected in the muscle fibers of patients with inflammatory myopathies. This is the case even in the muscles of patients with myositis associated with human immunodeficiency virus infection where apoptosis of CD8+ cells takes place in the circulation. In the muscle, the expression of Fas does not seem to imply susceptibility to apoptosis, probably because the Fas-positive muscle fibers coexpress neural cell adhesion molecule or Bcl-2, a 26-kd antiapoptotic protooncogene protein, both molecules associated with regeneration or the prevention of apoptosis. Bcl-2 is also expressed on satellite cells, which renders the multinucleated muscle fibers even more resistant to apoptotic death. The balance of the interacting proapoptotic or antiapoptotic molecules and the signals responsible for the transduction of myocytic cell death in the inflammatory myopathies need further study.

GENETICS IN HEREDITARY IBM

Among the autosomal recessive or dominantly inherited adult-onset, nondystrophic myopathies, there exists a heterogeneous group of vacuolar myopathies, collectively called hereditary IBM, owing to the presence of endomyosial vacuoles and tubulofilamentous inclusions identical to those seen in s-IBM. Patients with hereditary IBM have various clinical phenotypes, some of which are prevalent in certain ethnic groups. One subset of hereditary IBM, initially described in Iranian Jews as a quadriiceps-sparing, noninflammatory vacuolar myopathy, has now been seen in other ethnic groups in several countries—United States, Mexico, India, and Morocco—and has been linked to chromosome 9p. A clinicohistologically similar type of hereditary IBM described in Japan has also been linked to chromosome 9. When this area is narrowed down within a sequencing size, the gene responsible for hereditary vacuolar myopathies may be identified.

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