Advances in the Immunopathophysiology of the Idiopathic Inflammatory Myopathies: Not as Simple as Suspected

Gerald J.D. Hengstman, MD, PhD

Corresponding author
Gerald J.D. Hengstman, MD, PhD
Department of Neurology, Máxima Medical Centre, P.O. Box 90052, 5600 PD Eindhoven, The Netherlands; and Department of Neurology, Catharina Hospital, PO Box 1350, 5602 ZA Eindhoven, The Netherlands.
E-mail: g.hengstman@mmc.nl

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In the past three decades, not much has changed in the pathophysiologic concepts of dermatomyositis and polymyositis. However, in the past couple of years, many changes have occurred reflecting the extremely complex nature of the immune response in general. New pathophysiologic models are needed, but at present, none of them encompasses all the recent findings. The changing concepts of dermatomyositis and polymyositis offer new opportunities for unraveling these diseases and developing better strategies for prevention and treatment. This article discusses the most important developments and their methodologic short-comings.

Introduction

Idiopathic inflammatory myopathy (IIM) is a group of systemic diseases characterized by acquired muscle weakness and the presence of inflammatory infiltrates in skeletal muscle tissue. The three main diseases within this group are dermatomyositis (DM), polymyositis (PM), and sporadic inclusion body myositis (s-IBM). DM and PM are regarded to be autoimmune diseases, whereas the immune response in s-IBM is thought to be secondary to degenerative changes. This review focuses on the immunopathophysiology of DM and PM and only mentions s-IBM sporadically.

Simplicity of the Past

Until recently, IIM was not very difficult to understand. The landmark review articles by Bohan and Peter [1,2] clearly show the existence of two different forms of IIM: DM and PM. The major difference between the two is that the former is characterized by a typical rash, and the latter is not. Not much had changed by the time the next major review article was written by Dalakas [3]. The major difference was that a subgroup of patients with PM turned out to have a different myopathy: s-IBM. Over time, it became clear that s-IBM differs from PM and DM, clinically, histologically, and pathophysiologically. The most recent major clinical review article on the subject does not add many changes to this view of IIM [4].

Also pathologically, the field of IIM was rather simple. DM was though to be a humorally mediated autoimmune disease in which the immune process is mainly directed against the intramuscular microvasculature [3]. On the other hand, PM and s-IBM were regarded as diseases characterized by an antigen-directed cytotoxic immune response mediated by cytotoxic T cells [3].

All in all, this view was rather simple. There are three diseases: DM, PM, and s-IBM. DM is a humorally mediated angiopathy, PM is the result of a cytotoxic immune response directed against the myofibers, and s-IBM has some features of PM but is mainly characterized by Alzheimer-like degenerative changes.

A bulk of convincing evidence supports these pathophysiologic models. The earliest histologic change in DM is the deposition of C3b, C4b, and the membrane attack complex on the intramuscular capillaries [5]. This complement activation is thought to be induced by antibodies directed against the endothelial cells. This activation subsequently leads to swelling and vacuolization of the endothelial cells, capillary necrosis, and perivascular inflammation. These perivascular inflammatory infiltrates mainly consist of B cells and CD4+ T cells, thus reflecting the humoral nature of the immune response. As a result of the capillary damage, reflected histologically by a clear reduction of the number of capillaries, ischemia and eventually destruction of muscle fibers occur. As a result of this process, the typical histologic feature of perifascicular atrophy develops, caused by the hypoperfusion of the perifascicular regions.

Widespread expression of major histocompatibility complex (MHC) class I molecules on the sarcolemma is one of the earliest features of PM. Subsequently, autoinvasive

CD8+ T cells invade non-necrotic muscle fibers. A subset of these autoinvasive CD8+ cells are clonally expanded, indicating that the immune response is driven by certain antigens, presumed to be present in the muscle tissue.

But nature, and thus disease processes, are extremely complex. The conceptual difference between inflammatory processes and noninflammatory processes are arbitrary. Where does the inflammation end, and where does degeneration, necrosis, or apoptosis begin? Humoral and cellular immune mechanisms work in close harmony with each other and are usually intertwined. Proteins including cytokines and chemokines never have just one activity. Their activity depends on the complex cellular environment, and degradation or modification of proteins renders completely different functions. Especially in the past few years, the story of IIM has been shown to be more complex than it had once appeared.

Common Problems in Pathophysiology Studies of IIM

One of the main problems haunting research in IIM is the lack of clear internationally accepted and tested diagnostic criteria, especially for PM. Some authors have stated that PM does not exist, whereas others still use the Bohan and Peter criteria [1,2], resulting in many patients being diagnosed with PM.

DM and especially PM are very inhomogeneous groups of diseases. Sometimes they are associated with other inflammatory connective tissue diseases or with cancer. Very specific autoantibodies can be found in some patients, and they have been shown to define very distinct clinical syndromes including typical pathologic abnormalities. It is not unlikely that the pathophysiology in all of these cases differs from each other to some extent. Yet, most studies do not take these differences into account, and they lump all cases together under the heading PM or DM.

Another methodologic problem is that most studies do not use appropriate control groups. Most studies have two or three diagnostic groups (DM, PM, and s-IBM) and compare these to each other and to a control group of normal subjects. Only rarely is a non-IIM myopathy control group used. The most ideal control group would consist of patients with a non-IIM myopathy with known inflammation in muscle tissue (eg, facioscapulohumeral muscular dystrophy and dysferlinopathies). Most of the studies discussed in this review article used normal controls. Thus, the reported findings could possibly be common in many myopathies, and may at least in theory, have nothing to do with the immunopathophysiology typical for DM or PM.

Changes in Pathophysiologic Concepts

Perifascicular atrophy is not caused by hypoperfusion

The perifascicular atrophy in DM is thought to be due to ischemia, as stated earlier. Recently, though, this concept has been challenged [6]. Perifascicular atrophy is not seen in models of ischemic myopathy [7]. Instead of the perifascicular regions, the central portion of the fascicles appears to be most vulnerable, whereas the perifascicular regions are spared [7]. In the recent study by Greenberg et al. [8•], it is shown that MxA, an interferon (IFN)-α–inducible protein, is strongly expressed in regions of perifascicular atrophy and also in normal-appearing perifascicular fiber. MxA was also expressed in the capillaries. MxA has not been reported to be upregulated in ischemic tissue. The expression of MxA on both capillaries and perifascicular muscle fibers suggests that a common mechanism produces these abnormalities in both locations, rather than the capillary abnormalities causing the perifascicular atrophy.

Interferon-induced ELR-negative CXC chemokines may cause the vasculopathy in DM

Inflammation is characterized by marked changes in blood vessel volume. Many chemokines and cytokines exert direct angiostatic and angiogenic effects on endothelial cells, and modulate the expression of angiogenic growth factors such as angiopoietin 1 and vascular endothelial growth factor. Examples of these cytokines include tumor necrosis factor–α, interleukin-1, IFN-γ, and IFN-α. Several CXC chemokine family members are important regulators of angiogenesis [9]. CXC chemokines containing the ELR motif (three–amino acid sequence Glu-Leu-Arg) are angiogenic, whereas CXC chemokines lacking this motif are angiostatic. Fall et al. [10•] studied the relationship between vasculopathy and the balance between ELR-positive and ELR-negative CXC chemokines in muscle biopsies from seven patients with juvenile DM and from seven healthy controls. They found that the angiostatic ELR-negative CXC chemokines were expressed at high levels, whereas the angiogenic ELR-positive CXC chemokines were barely detectable. The expression of ELR-negative CXC chemokines in the juvenile DM muscle biopsies correlated strongly with the intensity of the mononuclear cell infiltration and with the degree of capillary loss. Thus, it appears that IFN-induced ELR-negative CXC chemokines contribute to a local atrophying effect in the muscle's vasculature through a receptor-mediated process.

Unfortunately, the authors did not study muscle biopsies from patients with PM and non–immune-mediated myopathies. Therefore, the exact role of ELR-negative CXC chemokines in myositis is not known, but the study does indicate that the balance between certain chemokines may play a fundamental role.

Immature dendritic cells are recruited and mature focally in DM and PM

Dendritic cells (DCs) play a key role in the development of the innate and adaptive immune responses. Two main classes of DCs are recognized: myeloid DCs and plasmacytoid DCs [11]. Myeloid DCs are potent antigen-presenting cells that stimulate the adaptive immune response. Plasmacytoid DCs are capable of producing

large amounts of IFN-α and IFN-β and are important in the innate immune system.

Most studies on IIM have focused on the adaptive immune system, humoral in DM and cellular in PM. In recent years though, it has been shown that there is a considerable innate immune response in both DM and PM. Page et al. [12•] showed that immature DCs are present in the inflammatory infiltrates in DM and PM, and that maturation of these DCs appears to occur in the inflamed muscle tissue. Immunohistochemical techniques were used on muscle biopsy specimens from six patients with DM, six patients with PM, and five normal controls. Patients were diagnosed according to the Bohan and Peter criteria [1,2]. DCs were not seen in normal muscle tissue, but they were observed in four of six DM patients and in three of six PM patients. In DM, both mature and immature DCs were mainly seen in the perivascular infiltrates, whereas in PM, they were observed in the inflammatory infiltrates surrounding muscle fibers.

The chemokine CCL20 and its receptor CCR6 are critical for the recruitment of immature DCs [13,14]. Both CCL20 and CCR6 were present in the inflammatory infiltrates in DM and PM, in close association with immature DCs [12•]. The chemokines CCL19 and CCL21 and their receptor CCR7 are involved in the attraction of mature DCs [15]. CCL19, CCL21, and CCR7 were not seen in the muscle biopsies of DM and PM patients, thus indicating that the immature DCs that are actively attracted to the inflamed muscle tissue mature locally.

Based on their findings, the authors presented a model in which, in response to local inflammation and the production of proinflammatory cytokines, immature DCs are attracted to muscle tissue in response to local CCL20 production in perivascular infiltrates. The contribution of the cytokine microenvironment leads to the differentiation to mature DCs, which can interact with T cells and thus cause a further recruitment of immature DCs.

The authors did not find any clear differences between DM and PM, indicating that their findings are not disease specific but apparently part of the general immune response seen in IIM. Unfortunately, they did not study non-IIM myopathies. DCs were not observed in all IIM muscle biopsies studied. Two DM patients did not show any evidence of mature or immature DCs, as did two PM patients. One PM patient only showed the presence of mature DCs. Apparently, attraction of immature DCs and focal maturation of these cells does not occur in every patient or in every stage of the disease.

The majority of CD4+ cells in DM are plasmacytoid dendritic cells and not T cells

As stated earlier, CD4+ cells are present in the perivascular infiltrates in muscle biopsies of patients with DM. These cells are usually thought to be T-helper cells, as would be expected in a humorally mediated immune response [16]. Greenberg et al. [8•] demonstrated that most of these CD4+ cells are not CD3+, and thus not T-helper cells. In fact, most of the CD4+ cells in DM are plasmacytoid DCs. Plasmacytoid DCs secrete IFN-α [17], and in the same study it is shown that IFN-α and IFN-β play an important role in DM. Furthermore, the authors found that these CD4+ cells are not mainly located in the perivascular regions. Most cells were in fact located in the endomysium and perimysium.

Dendritic cells in PM and s-IBM function focally as antigen-presenting cells

DCs were studied in PM and s-IBM using immunohistochemical techniques [18•]. The BDCA-2 marker was used to identify plasmacytoid DCs and BDCA-1 for myeloid DCs. Because BDCA-1 can also be expressed by a small group of B cells, CD19 immunohistochemistry was performed to differentiate between myeloid DCs and B cells. Investigators studied muscle biopsies from 20 patients with s-IBM, 10 with PM, 15 with DM, and five normal controls.

Myeloid DCs were found in almost all patients with PM and s-IBM. They were usually seen as widely distributed cells across the section with additional focal accumulations. These accumulations were typically endomysial and either surrounded myofibers, sometimes invading non-necrotic muscle fibers, or appeared as dense collections between myofibers. The accumulations of DCs in PM and s-IBM mainly consisted of myeloid DCs rather than plasmacytoid DCs. In DM on the other hand, most DCs were plasmacytoid, as stated earlier [8•].

The clear presence of large amounts of myeloid DCs in muscle tissue from patients with PM and s-IBM suggests a crucial role of these cells in the immune response in these diseases. One of the hypotheses raised by the authors is that these myeloid DCs function as antigen-presenting cells in the inflamed muscle tissue and that they activate T cells locally.

An antigen-driven humoral immune response is present in PM and s-IBM

PM and s-IBM are characterized by a CD8+ T-cell–mediated immune response directed against MHC class I expressing non-necrotic muscle fibers, as stated earlier. Evidence that autoreactive T cells play an important role in these two diseases is very convincing: a restricted T-cell receptor repertoire is found in muscle biopsies of PM and s-IBM patients [19–21], an oligoclonal expansion of muscle-infiltrating T cells is present in both diseases [22–25], and a long-term presence of clonally expanded T cells is found in these two subtypes of IIM [26–28]. B cells are sparse in the inflammatory infiltrates in PM, and it is unknown whether they are involved in the disease process.

It has long since been recognized that some patients with PM have specific autoantibodies, indicating a role for a humoral autoimmune response to some extent [29]. More recent studies of muscle messenger RNA expression have shown an abundance of immunoglobulin tran-

scripts in PM and s-IBM [30,31] and the presence of large numbers of CD138+ plasma cells [31], providing further evidence for a humorally mediated immune response in PM and s-IBM.

In a recent study, Bradshaw et al. [32•] studied the molecular characteristics of the H chain portion of the Ag receptor. Muscle biopsies from patients with DM, PM, and s-IBM, and those from normal controls were studied. Analysis of the sequences of the variable region gene revealed clear evidence of affinity maturation based on the detection of significant somatic mutation, isotype switching, receptor revision, codon insertion/deletion, and oligoclonal expansion within the B- and plasma cell populations [32•]. These findings were present for all forms of IIM studied but were absent in the normal controls.

Analysis of tissue regions isolated by laser capture microdissection showed clonal expansion and variation, indicating that local B-cell maturation occurs in inflamed muscle tissue. Laser capture microdissection was only performed on one patient with DM, one with PM, and one with s-IBM. Clonal expansion was not observed in the muscle biopsy specimen from the patient with PM.

Nevertheless, based on these findings, it can be concluded that antigens drive a B-cell antigen-specific response in muscle in patients with DM, PM, and s-IBM. The only shortcoming of the study is that researchers used normal controls and not non-IIM myopathies as a control group. Theoretically, it is possible that a B-cell antigen-specific immune response can be found in myopathies in general. Furthermore, they did not specify the diagnostic criteria they used. All in all, this study does indicate convincingly that an antigen-driven humorally mediated immune response is present in all three subgroups of IIM.

Myositis antigens are expressed in immature regenerating muscle fibers and in cancer tissue

Myositis-specific autoantibodies (MSAs) are present in a subgroup of patients with IIM. These antibodies are directed against proteins involved in the process of protein synthesis and RNA translation [33]. One of the mysteries surrounding these disease-specific autoantibodies is the fact that they are directed against ubiquitously expressed proteins. An elegant study by Casciola-Rosen et al. [34••] showed that the expression of these antigens was low in normal muscle tissue but increased several-fold in myositis muscle tissue. Immunohistochemical analysis showed that the highest level of antigen expression was present in regenerating muscle cells. Furthermore, in an ex-vivo model of muscle differentiation, myositis-specific antigens were expressed at highest levels in immature myoblasts, and expression levels decreased as myotube development ensued. Based on these findings, it was concluded that damaged regenerating muscle tissue rather than normal muscle tissue provides the source of MSA development.

The link between myositis and cancer has been noted for a long time. In the same study mentioned above, it was shown that myositis-specific antigen expression does not only occur in muscle tissue in myositis but can also be found in some forms of cancer known to be associated with myositis [34••]. Based on these findings, the authors proposed a model for the development of cancer-associated myositis. Myositis-specific antigen expression in a tumor leads to a specific immune response directed against the tumor. In most cases, this immune response effectively controls or eliminates the tumor. In a subset of patients, subsequent muscle damage from a variety of potential causes (eg, infection, toxins) leads to muscle regeneration and expression of myositis-specific antigens, which can then reactivate immune responses generated initially in the antitumor response [34••].

More than inflammation alone: the endoplasmic reticulum stress response and physical demand

The inflammation observed in muscle tissue is frequently seen as the primary cause of the clinical syndrome of acquired muscle weakness in IIM; however, in the recent years, it has become very clear that this is not true. The degree of inflammation does not consistently correlate with the severity of structural changes in muscle tissue or the degree of clinical muscle weakness [35–38]. Several findings have suggested that expression of MHC class I antigens on the sarcolemma may potentially mediate muscle fiber damage and dysfunction in the absence of lymphocytes [37,39–44]. A potential link between MHC class I upregulation and the occurrence of muscle fiber damage and dysfunction in IIM may be the endoplasmic reticulum (ER) stress response. The ER stress response is caused by an imbalance between the load of proteins in the ER and the cell's ability to process that load. Due to this imbalance, several signaling pathways are activated and lead to adaptations within the cell. The ER stress response can be activated by many pathologic conditions, including viral infections, mutations, and ischemia [45,46].

Muscle biopsy specimens of five patients with PM, five patients with DM, and four healthy controls were studied. It was shown that two major components of the ER stress response were highly activated [47•]. Subsequently, it was shown that overexpression of MHC class I induces an ER stress response in a mouse model [47•]. One of the ER stress response pathways is the upregulation of nuclear factor (NF)-κB (ER overload response), which is strongly activated in myositis [47•].

Based on their findings, the authors presented a model in which the ER stress response plays an important role in the pathophysiology of IIM. MHC class I expression in muscle fibers initiates two ER stress response pathways: ER overload response and unfolded protein response. The ER overload response activates NF-κB, which will induce NF-κB target genes including MHC class I upregulation, thus initiating a self-sustained loop. NF-κB is known to suppress myoblast differentiation and to induce proinflammatory cytokine expression, thus causing muscle fiber

damage [48]. This model is attractive, because it shows that there is more to the immunopathophysiology than inflammation alone. But the model mainly consists of speculations. The authors have shown that two ER stress response pathways are activated in IIM, but this may be the case in many different nonimmune myopathies as well. Furthermore, there is no proof that the ER stress response truly results in muscle damage and dysfunction.

MHC class-I expression plays an important role in the theory above. Dorph et al. [49] studied the presence of inflammatory infiltrates, T cells, macrophages, expression of MHC class I and class II antigens, and IL-1α immunohistochemically in eight patients with PM, three patients with DM, and six healthy controls. They did this not only in weak affected muscles but also in asymptomatic muscles. No difference was observed qualitatively or quantitatively for any of the variables studied. The authors concluded that other factors are required to produce clinical symptoms, one of which may be physical demand.

Conclusions

During the past three decades not much has changed in the pathophysiologic concepts of DM and PM, as can be observed by reading the most important review articles on the subject over the years [1–4]. However, in the past couple of years, many changes have occurred in the pathophysiologic models reflecting the extremely complex nature of the immune response in general. This increasing insight will hopefully result in better therapeutic strategies, but it should be remembered that selective inhibition or stimulation of certain pathways will inevitably result in unexpected side effects, indicating once again that it is not as simple as it appears.

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