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Dermatomyositis and Type 1 Interferons

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Abstract

Dermatomyositis is a poorly understood multisystem disease predominantly affecting skin and muscle. This review focuses on the potential role of a group of related cytokines, the type 1 interferons, in the pathogenesis of dermatomyositis. Type 1 interferon-inducible transcripts and proteins are uniquely elevated in dermatomyositis muscle compared with all other muscle diseases studied to date. The endothelial cell tubuloreticular inclusions present in affected dermatomyositis muscle are biomarkers of type 1 interferon exposure. The cell-poor lichenoid reaction in skin with predominant involvement of the basal epidermal cell layer and its topologic equivalent in muscle, perifascicular atrophy, may be lesions that develop directly in response to type 1 interferon signaling.

Keywords

Dermatomyositis; Interferon

Introduction

Dermatomyositis is an autoimmune disease affecting the skin, skeletal muscle, and other tissues. The mechanisms resulting in tissue injury in dermatomyositis are poorly understood. The type 1 interferons are a class of molecules that include interferon- α and interferon- β . Their binding to the type 1 interferon receptor on target cells stimulates the transcription and translation of a set of genes, the type 1 interferon-inducible genes. Proteins abundantly produced from these genes' transcripts, such as MxA, ISG15, and OAS1, function inside of cells as defenses against viral infections through a variety of means, including inhibiting viral transcription, translation, or assembly of viral nucleocapsids. In contrast to the traditionally considered adaptive immune system's mechanisms of cellular- and antibody-mediated defense, these molecules are part of the innate immune system, highly effective at defending against certain infections from within cell cytoplasm. Evidence regarding the significance of type 1 interferons to dermatomyositis is reviewed here, with some of this material recently discussed elsewhere [1,2,3••].

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A second publication [Nakashima et al *Rheumatology* 2010;49:433–40] has independently identified IFIH1 as a dermatomyositis-specific autoantigen.

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Mechanistic Modeling: Histology Biomarkers

Early descriptions of dermatomyositis in the medical literature date back to at least 1866, with the current name of the disease originating no later than 1891 [4,5]. The clinical features of the disease were well-recognized for the next half-century, with little insight into pathogenesis. Although many features may be helpful in understanding disease pathogenesis, the most important in dermatomyositis have been its relatively specific skin and muscle histology.

Muscle Pathology

The unique pathological muscle biomarkers of dermatomyositis, perifascicular myofiber injury (widely called *perifascicular atrophy*) and capillary abnormalities that include endothelial tubuloreticular inclusions (TRIs), were emphasized starting in the 1970s [6–9]. Together with observations that complement components were immunohistochemically visible on muscle capillaries [10–12], a model of dermatomyositis myofiber injury in which circulating antibodies directed against an endothelial antigen damage blood vessels; lead to complement deposition; and result in ischemic myofiber injury visible as perifascicular atrophy and infarction has been advocated for more than 20 years. Within this literature, frequently cited to support this ischemic theory of perifascicular myofiber injury, lie two conflicting observations—that complement components were sometimes seen surrounding vessels rather than coinciding with the intraluminal endothelial surface [12] and that endothelial complement deposition was nearly absent in fascicles containing perifascicular atrophy, limited instead to other fascicles [10]. Other concerns about the ischemia hypothesis for perifascicular atrophy have been summarized elsewhere [13•,14]. Although both endothelial cell injury and perifascicular myofiber injury are present in dermatomyositis muscle, the central question for disease pathogenesis is how these two features relate: does the former cause the latter, or does some other mechanism cause both [13•]?

Skin Pathology

Skin pathology in which predominant injury occurs to the epidermal basal cell layer has been termed *lichenoid tissue reaction* [15•]; a related term that has been used is *interface dermatitis* [16•]. Diseases with a lichenoid tissue reaction have been further classified as cell rich or cell poor, depending on the presence of a visible cellular infiltrate in the dermis bordering this basal epidermal layer. Dermatomyositis usually has been classified as having a cell-poor lichenoid reaction. Prominent abnormalities of skin dermal blood vessels also have been reported [17]. Some observers have suggested that cytotoxic T cells cause keratinocyte death [18•] in dermatomyositis, although many images have been published of vacuolar keratinocyte injury in the absence of any nearby immune cells.

Perifascicular Atrophy: A Lichenoid Skin Reaction of Muscle

The characteristic pathological lesion of dermatomyositis muscle, called *perifascicular atrophy*, has important parallels to the skin lichenoid tissue reaction [19•]. Perifascicular atrophy is more precisely described as *perimysial perifascicular myofiber injury*, emphasizing the observation that injury does not occur equally in all the myofibers at the periphery of a fascicle, but rather those myofibers that border on the connective tissue of the perimysial spaces. Perifascicular myofibers adjacent to neighboring perifascicular myofibers of another fascicle tend to be less affected. This “border” effect, in which there is preferential injury to myofibers at the boundary of muscle fascicle and perimysial connective tissue, is the same arrangement as the lichenoid tissue reaction seen in skin, in which there is preferential injury to basal epidermal cells bordering the dermal connective tissue. This topology suggests speculation that soluble molecules present in these connective tissue regions injure the closest myofibers and keratinocytes.

Although muscle perifascicular atrophy has been stated dogmatically to follow from ischemia in many publications, the analogous injury to skin basal epidermal keratinocytes has never been attributed to ischemia. Indeed, attribution of this pattern in skin to ischemia would conflict with knowledge that the epidermis is avascular and the better preserved more superficial layers of keratinocytes lie further from blood supply than the affected basal layer.

Macromolecular Biomarkers of Type 1 Interferon Exposure: Tubuloreticular Inclusions

More than 25 years ago, TRIs (also known as *lupus inclusions*), macromolecular structures commonly visible with electron microscopy in dermatomyositis muscle endothelial cells [6, 7] and rarely seen in other forms of myositis, were recognized as downstream markers of type 1 interferon signaling. TRIs in circulating blood cells develop in patients treated with interferon- α [20] and in cultured endothelial and other cells directly in response to interferon- α and interferon- β [21,22], but not interferon- γ [23]. For uncertain reasons, for more than 20 years, no PubMed-indexed publication made a connection between this TRI literature and dermatomyositis [14]. However, the implications of this literature are compelling—dermatomyositis muscle endothelial cells have undergone type 1 interferon signaling.

Molecular Biomarkers of Type 1 Interferon Exposure: MxA, ISG15, and Other Interferon-Inducible Transcripts and Proteins

The marked overproduction of type 1 interferon-inducible transcripts and proteins in muscle is unique to dermatomyositis compared with all other muscle diseases studied [3•,24,25•, 26•]. Microarray gene expression studies of muscle biopsy specimens measuring about 18,000 transcripts in each of 113 muscle biopsy samples from patients with a wide range of myopathies showed that only dermatomyositis samples with perifascicular atrophy have marked elevation of type 1 interferon-inducible transcripts (Fig. 1) [3•]. In a combined microarray dataset of more than 200 muscle biopsies covering a wide range of diseases, the transcript for the type 1 interferon-inducible gene interferon-stimulated gene 15 (*ISG15*) was higher in muscle in all 28 biopsies from adults with dermatomyositis and perifascicular atrophy and children with juvenile dermatomyositis than in every one of 199 non-dermatomyositis biopsy samples from a wide range of neuromuscular diseases. Adult dermatomyositis samples without perifascicular atrophy usually do not show marked overproduction of these transcripts.

Two type 1 interferon-inducible proteins are similarly highly specific biomarkers of dermatomyositis muscle. MxA is impressively and uniquely (compared with other muscle diseases) abundant in dermatomyositis myofibers with perifascicular atrophy and in dermatomyositis muscle capillaries [24]. ISG15, a ubiquitin-like modifier, is furthermore attached to many other proteins in dermatomyositis muscle, the identities of which have not been determined [3•]. Exposure of human skeletal muscle cell cultures to interferon- α or interferon- β produces a similar picture of ISG15 conjugation present in human dermatomyositis samples [3•].

Skin gene expression profiling, reported in abstract format [27], has similarly shown marked abundance of type 1 interferon-inducible transcripts. The expression of MxA in skin endothelial cells and skin epidermal basal layer of keratinocytes [28•] is similar to that of MxA expression in muscle endothelial cells and muscle perimysial myofibers [24].

Plasmacytoid Dendritic Cells: Producers of Type 1 Interferons in Dermatomyositis Skin and Muscle

Plasmacytoid dendritic cells (pDCs), cells that produce high levels of type 1 interferons, have infiltrated dermatomyositis muscle [24,29] and skin [28•,30,31]. These cells have the capacity to rapidly produce large amounts of type 1 interferons over a 24-hour period after stimulation by Toll-like receptor-7 or Toll-like receptor-9 agonists. Through an autostimulatory type 1 interferon receptor-mediated mechanism, the accumulation of these cells in tissues exponentially amplifies their efficiency at producing type 1 interferons [32••]. Although pDC infiltration in dermatomyositis skin and muscle suggests they are a source of type 1 interferons, this finding does not exclude other potential sources, such as fibroblast-produced interferon- β .

pDCs were previously overlooked in dermatomyositis tissue specimens because they share certain surface markers widely but incorrectly interpreted as indicative of other cell types. pDCs may express CD4 [24] and be mistaken for T-helper cells, may express CXCR3 [33] and be mistaken for lymphocytes, or may express CD68 [34] and be mistaken for macrophages. Conversely, pDCs and endothelial cells express CD123, so care is required in interpreting CD123 immunoreactive material as pDCs [24]. Studies that have not determined accurately the identity of cells expressing CD4, CXCR3, and CD68 in muscle and skin biopsy specimens may have proposed inaccurate models. Whether the CXCR3⁺ cells seen in skin are lymphocytes, pDCs, or a mixture of the two is unknown [28•,30].

Lichenoid Skin Reactions: Increasingly Linked to Type 1 Interferon Exposure

Lichenoid skin reactions in several diseases (lichen planus, lichenoid actinic keratosis, cutaneous and systemic lupus erythematosus, and dermatomyositis) have been modeled as developing as a consequence of type 1 interferon exposure [15••,18•]. Evidence for such modeling includes varying degrees of pDC infiltration [18•,28•,30,31], upregulation of various type 1 interferon-inducible transcripts [27], and upregulation of MxA protein in skin biopsy samples [18•,28•,30].

Autoantibodies to a Type 1 Interferon-Inducible Protein: Autoantibodies May Follow Tissue Injury

Patients with dermatologic features of dermatomyositis who lack significant clinical evidence of muscle involvement have been called clinically *amyopathic dermatomyositis* (CADM). Recently, autoantibodies to a classic type 1 interferon-inducible protein IFIH1 (interferon induced with helicase C domain, also called MDA-5) have been identified [35••]. The presence of anti-IFIH1 antibodies among 262 patients with a range of connective tissue diseases was 69% sensitive and 99.6% specific for CADM. Anti-IFIH1 autoantibody levels above an optimized threshold were present in 22 of 32 patients with CADM but only one of 35 patients with classic dermatomyositis, and none of 53 patients with polymyositis. These remarkably strong data provide for a clinically valuable biomarker of CADM and mechanistic evidence for some abnormality related to type 1 interferons in CADM. The nature of this relationship is uncertain; one speculation is that IFIH1, a nuclear RNA helicase, is overproduced or altered in some way in CADM and evokes an autoantibody response.

These data further suggest that production of some autoantibodies in dermatomyositis may be downstream of the disease mechanism. Other autoantibodies that have been reported in dermatomyositis, including those against Mi-2 [36] and Jo-1 [37], have been emphasized as targeting proteins overproduced by regenerating myofibers. Because regeneration of myofibers implies previous injury to them (why else would they be regenerating?), such findings similarly

suggest that production of these autoantibodies is also a mechanistic event downstream of myofiber injury.

Immune Injury to Cells from the Inside: A Model of Dermatomyositis Myofiber and Keratinocyte Injury

How exactly are perimysial perifascicular myofibers and basal epidermal cells injured in dermatomyositis? These questions deserve intense attention. One possibility is that these cells are being injured by their own inappropriate and sustained overproduction of a class of immune molecules, the type 1 interferon-inducible proteins. For example, MxA is abundantly present in dermatomyositis perimysial perifascicular myofibers [24] and basal keratinocytes [28•]. The consequences of sustained intracellular production in myofibers, endothelial cells, or keratinocytes of molecules such as MxA, ISG15, OAS1, or many others in response to type 1 interferon signaling are largely unknown and have received very little attention. It is certainly known that type 1 interferons exert antiproliferative effects on a range of cells, including endothelial cells [22,38•,39•]. Interferon- α was the first discovered antiangiogenic factor [40]. How such effects result is unknown. Cell-poor lichenoid skin reactions and perifascicular myofiber atrophy in the absence of nearby immune system cells are lesions compelling consideration of injury due to the intracellular production of these innate immune system molecules.

Potentially Useful Biomarkers: A Blood Type 1 Interferon-Inducible “Signature”

Separate from the mechanistic implications of the type 1 interferon pathway in dermatomyositis, the measurement of aspects of this pathway may prove to be useful in the diagnosis and management of patients with myositis. Blood gene expression profiling has demonstrated marked abundance of these transcripts in patients with active dermatomyositis (eg, untreated patients) but also in polymyositis [25••]. In a study of 23 patients with dermatomyositis and polymyositis, all except one of the highest-expressed 25 genes among about 38,000 studied are known to be highly inducible by type 1 interferons [25••]. If therapeutic development proceeds with targeting the type 1 interferon pathway, these blood measurements may be useful in selecting appropriate therapies.

Conclusions

Substantial attention has recently turned to the presence of biomarkers of type 1 interferon signaling in dermatomyositis muscle and skin. The attribution of perifascicular atrophy to impaired blood supply seems likely to be incorrect. The next set of questions to be answered involve how exactly type 1 interferon signaling might result in injury to myofibers and keratinocytes, and what drives interferon signaling in dermatomyositis skin and muscle. Although the effects of these cytokines on other immune cells, which then act as effectors of tissue injury, have been suggested, it seems more likely that sustained inappropriate intracellular production of type 1 interferon-inducible molecules will turn out to be the mechanism giving rise to endothelial injury, perimysial perifascicular myofiber injury, and the vacuolar changes of basal epidermal keratinocytes seen in dermatomyositis. If so, conventional concepts of cellular and humoral autoimmunity would not apply in dermatomyositis; rather, dermatomyositis disease mechanism would provide a new concept in autoimmune disease modeling—the injury of cells by their own intracellularly produced innate immune system molecules.

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Fig. 1.

Genomic identification of type 1 interferon (IFN)-inducible pathway activation in dermatomyositis muscle (DM). **a** Analysis of 22,283 gene transcript probesets (4904 shown after filtering; one per row) in 113 muscle biopsy samples (one per column) disclosed a cluster of type 1 IFN-inducible genes specifically and highly upregulated in dermatomyositis with perifascicular atrophy (PFA) (*thin stripe marked by an arrow*). Enlargement of this arrowed region is shown on the right. *Red* and *green* indicate high and low expression. **b** High expression of transcripts for IFN-stimulated gene 15 (*ISG15*) and myxovirus resistance protein A (*MxA*) are extraordinarily specific to dermatomyositis. **c** Examples of *ISG15* Western blots show free *ISG15* (the ~15-kDa band) and multiple *ISG15*-conjugated proteins (the discrete bands and smear shown at higher molecular weights) in dermatomyositis, but not in other muscle biopsy samples. Cultured human skeletal muscle cell lines exposed to interferon- β develop the same pattern of free and conjugated *ISG15* as occurs in dermatomyositis. *Vertical axis* indicates molecular weight (kDa). **d** *MxA* staining of DM is sometimes evident on glass slides viewed without the aid of a microscope. *MxA* is preferentially located in perifascicular myofibers and in blood vessel walls. *IBM*—inclusion body myositis; *JDM*—juvenile dermatomyositis; *PM*—polymyositis; *Tx*—treatment. (*Adapted from* Salajegheh et al. [3•])