The Role of Cytokines, Chemokines, and Adhesion Molecules in the Pathogenesis of Idiopathic Inflammatory Myopathies

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Cytokines, chemokines, and adhesion molecules are important mediators in chronic inflammation and in immune regulation. In idiopathic inflammatory myopathies (IIM), increased expression of proinflammatory cytokines particularly interleukin (IL)-1α and IL-1β, tumor necrosis factor (TNF)-α and macrophage inflammatory proteins (MIP)-1α, as well as of the inhibitory cytokines transforming growth factor (TGF)-β was observed in muscle. There was no difference in cytokine and chemokine pattern between polymyositis, dermatomyositis, and inclusion body myositis, which could indicate that similar pathogenetic mechanisms are involved in these subsets of myositis. A prominent finding of IL-1α expression in endothelial cells, both in patients with active inflammtion and in patients with chronic persisting muscle weakness without inflammation, makes this an interesting molecule in understanding the mechanisms for the pathogenesis of muscle weakness. Involvement of the blood vessels in the pathogenesis of myositis was further supported by increased expression of adhesion molecules and by a phenotypical expression of endothelial cells, resembling high endothelium venules in all three subsets of IIM. The molecular studies to date indicate a role of the microvessels in the pathogenesis of IIM not only in DM, as was previously suggested, but also in PM and IBM. The studies also indicate that IL-1α could be a target molecule for new therapeutical interventions.

Introduction

The idiopathic inflammatory myopathies (IIMs) are chronic muscle disorders characterized by insidious onset of muscle weakness and by inflammatory infiltrates in muscle tissue. Based on different clinical as well as histopathologic features, the IIMs are further subclassified into dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM) [1,2]. The etiology and pathogenesis of these disorders is largely unknown. It is likely that features that are shared as well as features that differ between the subsets of the IIM could increase our understanding of the etiology and the pathogenesis of the chronic IIM.

The predominating clinical manifestations that are shared by the three subsets of IIM are muscle weakness, as well as decreased muscle endurance, with a symmetrical distribution in proximal muscles, and muscle pain at and after exertion. Another shared feature of the IIMs is the infiltration of mononuclear inflammatory cells in muscle tissue, which has also become a hallmark of these disorders. The most common infiltrating inflammatory cells are T-cells and macrophages [2,3]. Increased expression of major histocompatibility complex (MHC) class I on the muscle fiber membranes is another characteristic, but not specific, feature of untreated myositis patients [4,5]. The ability of the muscle fibers to express MHC class-I molecules on their membranes together with the observed infiltrates of $CD8^+$ T-cells in PM has formed the basis for the hypothesis of a cell-mediated immune response in PM [2,3]. The different clinical features in the subsets of the three IIMs are well known [1]. Particularly interesting in this perspective is resistance to treatment with corticosteroids usually evident in IBM patients. Through careful histopathologic studies, different features were also identified in the subsets of IIM with different localization of the inflammatory cells, as well as different ratios of $CD4^+$ and $CD8^+$ T-lymphocytes and macrophages. In patients with DM, the inflammatory infiltrates were predominantly localized to perivascular areas; whereas in patients with PM and IBM, the inflammatory infiltrates were mainly localized to the endomysium surrounding and sometimes invading non-necrotic muscle fibers [2]. In PM and IBM, a higher proportion of $CD8^+$ T cells was reported, compared with patients with DM [2]. IBM patients are also characterized by rimmed vacuoles and inclusions in the myofibers and patients with DM by a decreased number of capillaries [6]. Based on the descriptive histopathologic findings, an immunoreactivity directed toward the muscle fibers was suggested in PM and IBM and toward the blood vessels in DM, although no specific autoantigen has been identified. Thus, the primary event of the immune reactivity in muscle inflammation is still unknown as is the mechanism for perpetuating the chronic inflammation.

The cause of the muscle symptoms is another enigma. One would naturally assume that the inflammation per se, or that degenerated and necrotic muscle fibers, cause the muscle weakness and decreased muscle endurance. However, from previous studies based on muscle histopathology, a discrepancy between the degree of invading inflammatory cells or morphologic changes of muscle fibers and degree of muscular symptoms was observed. In some cases, in particular those with DM and IBM, inflammatory infiltrates can be absent in muscle tissue, despite impaired muscle function [7,8].

These findings suggest that factors other than the inflammatory infiltrates may contribute to the predominating clinical manifestations of weakness and myalgias. This hypothesis is further supported by the clinical observation of the very slow improvement of muscle strength and function despite treatment with corticosteroids in high doses and despite normalization of serum muscle enzymes indicating muscle repair, and by histopathologic studies confirming disappearance of the inflammatory infiltrates. In patients with DM, a decreased number of capillaries was observed and suggested to be part of the pathogenesis of the muscular symptoms [6]. Taken together, these observations suggest that events that are partly independent of the infiltrating inflammatory cells are of importance for the clinical manifestations. It seems likely that there could be different pathogenetic mechanisms that could be responsible on one hand for the inflammatory infiltration and on the other hand for the muscular symptoms.

Despite the careful descriptive characterization of the phenotypes of the inflammatory cells in muscle tissue in myositis, little is known about their function. Whether the different profiles of infiltrating inflammatory cells observed in the different subsets of myositis actually have divergent functional consequences is not known. To obtain increased knowledge of the function of the inflammatory cells as well as of other cells in the respect of clinical symptoms, there is an obvious need for further studies of functionally important molecules in the myositis lesions. Such studies can obviously be performed in animal models, as illustrated by rheumatoid arthritis and multiple sclerosis models [9,10]. However, no such animal model for chronic myositis has been developed [11].

In the absence of animal models, another possible way to investigate functions of the infiltrating cells is to continue previous descriptive studies that have carefully characterized the infiltrating cells, by determining which signal molecules are produced by these cells and, furthermore, to relate the molecular findings to the clinical symptoms. This is now feasible due to technical advances. Cytokines, chemokines, and adhesion molecules are such important signal molecules in chronic inflammation [12]. The production of these molecules at a protein level in tissue can be investigated by immunohistochemistry. The production can also be estimated by studies of mRNA expression in tissue by RT-PCR. Naturally, these techniques only give indirect evidence of the function of the cells in the investigated tissue but should illuminate mechanisms underlying the pathogenesis of myositis, as has been the case in the IIM. Several studies have been published on the expression of these molecules in the target organ, the muscle, and an additional few on the expression of these molecules in the peripheral blood [13]. To address the question of pathogenesis of myositis, concerning both inflammation and muscle weakness, investigations including histopathology, characterization of the inflammatory infiltrates and molecules expressed in muscle tissue should be taken into consideration and be related to the clinical symptoms. Furthermore, it could also be informative to investigate the molecular pattern in muscle tissues from patients during different stages of IIM (*eg*, acute and chronic) and during different therapies, and to relate the cellular and molecular expression to muscle function. Most of the studies to date have been performed on patients with untreated myositis with infiltrating inflammatory cells in muscle tissue. Follow-up studies in myositis patients are rare and have hitherto mainly been limited to investigations of inflammatory characteristics in muscle tissue [14,15]. Recently, a few studies have been published in which the effect of treatment on molecular expression of adhesion molecules and cytokines in muscle tissue was investigated, including our own studies on the effect of corticosteroids. In another study, we investigated the molecular expression in muscle tissues of patients with a chronic myositis with persisting muscle weakness. These studies will also be summarized in this review.

Cytokines, Chemokines, and Adhesion Molecules in Patients with Active, Untreated Polymyositis, Dermatomyositis, and Inclusion Body Myositis

Cytokines

Cytokines are important molecules in inflammatory responses and immune regulation [12]. They can be produced by a wide variety of cells, act in a complex network, and can exhibit pro-inflammatory or anti-inflammatory effects. Increased expression of cytokines and chemokines in disease-affected muscle tissue, both at mRNA and protein levels, has been reported by several groups. The most frequently reported cytokines in IIM are the proinflammatory cytokines IL-1α, IL-1β, and TNF-α [13,16–23,24•,25•]. Another prominent molecule evident in muscle tissue was TGF-β<, which exerts downregulating effects on inflammation and could stimulate fibrosis [16-18,26]. T-cell derived cytokines such as IFN-γ were rarely observed despite the often pronounced infiltrates of T-cells [16–18,23]. IL-1α expression was observed not only in mononuclear inflammatory cells, but also in endothelial cells and smooth muscle cells, whereas IL-1β, TNF-α, and IFN-γ expression were restricted to mononuclear inflammatory cells [17]. TGF-β was expressed in mononuclear cells, as well as in endothelial cells, and in the extracellular matrix [17]. Another interesting observation from these descriptive studies was the phenotypical

expression of the IL-1α expressing endothelial cells in both capillaries and medium-sized blood vessels. A majority of the endothelial cells of the capillaries appeared clumsy and resembled the endothelial cells of high endothelium venules (HEV), which have a central role in lymphocyte homing (Fig. 1) [17]. These HEV-resembling endothelial cells were observed in areas exhibiting cellular infiltration, as well as in areas without inflammatory cells. Furthermore, these HEV-like blood vessels were detected in patients with all three subsets of myositis, indicating involvement of the small- and medium-sized blood vessels in the inflammatory process, not only in DM as was previously suggested, but also in PM and IBM [17].

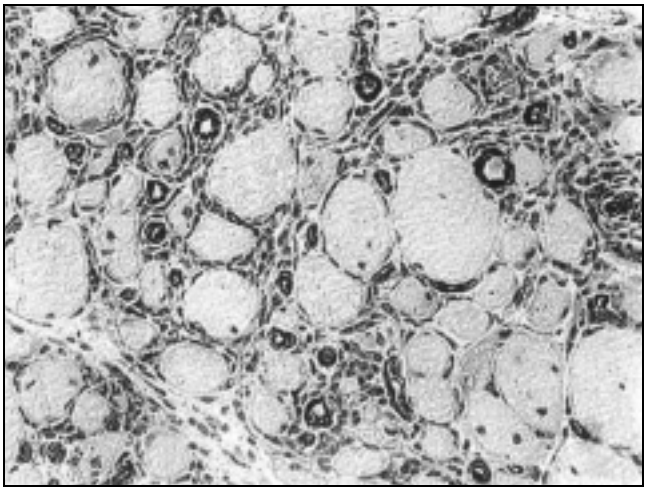

Figure 1. Immunohistochemical localization of interleukin-1a in endothelial cells of a patient with polymyositis. A majority of the endothelial cells both in capillaries and venules exhibit a high endothelial like phenotype.

Chemokines

Chemokines are inflammatory mediators that have a chemotactic function in attracting leukocytes to tissues [27]. They are produced by a number of different cells, including endothelial cells, fibroblasts, and lymphocytes. They are secreted and bound to receptors on target cells (*eg*, monocytes and lymphocytes). The main stimuli for chemokine production are early proinflammatory cytokines (*eg*, IL-1, TNF-α), bacterial products, and viral infections.

Increased mRNA expression of macrophage inflammatory protein 1a (MIP-1a) transcripts, a predominantly T- and B-cell attractant that enhances $CD8^+$ T-cell adhesion to extracellular matrix, was detected in 13 out of 14 PM and DM patients [18]. MIP-1b and RANTES, molecules that primarily attract $CD4^+$ cells, were less frequently detected. There was no difference observed between chemokine expression in patients with PM and DM in the single study presented so far [18]. The importance of chemokines in myositis can only be speculated on as no functional studies have been performed, but they may certainly have a crucial role in the attraction of lymphocytes and macrophages to muscle tissue. One of the proinflammatory cytokines evident in myositis, TNF-α, may stimulate MIP-1α production from fibroblasts. Besides its role as a chemoattractant, MIP-1α may also have a downregulatory effect on inflammation by enhancement of TGF-β production.

Adhesion molecules

As mentioned above, the studies on cytokine expression indicated an involvement of blood vessels in the pathogenesis of not only DM, but also of PM and IBM. Further support for involvement of the blood vessels in the pathogenesis of myositis is the increased expression of vascular adhesion molecules, intercellular adhesion molecule type 1 (ICAM-1), and vascular cell adhesion molecule (VCAM-1) on endothelial cells (Table 1) [28–32,33••].

Adhesion molecules have a role in the homing of leukocytes, and allow trafficking of circulating inflammatory cells over the endothelial cells. A preferred site is the HEV, which, at least to some extent, has a role in homing to specific organs [34–38]. Specific homing molecules for muscle tissue have not been identified; however, ICAM-1 and VCAM-1 are both ubiquitously expressed molecules on activated endothelial cells. Increased expression of adhesion molecules can be induced by different stimuli such as cytokines (eg, IL-1, TNF-α, and INF-γ) or lipopolysaccarides [37]. The adhesion molecules act in a hierarchical fashion. E-selectin, belonging to the selectin family, is the first adhesion molecule to be induced on vascular endothelial cells within hours of stimulation with, for example, IL-1, whereafter E-selectin is rapidly downregulated. The selectins bind to sialylated and glucosylated ligands on leukocytes and initiate the "rolling" of leukocytes along the endothelial cells. E-selectin was not observed until recently on endothelial cells in muscle tissue in PM and DM cases [28,30,39], and in our own observations. This was not surprising as this molecule is rapidly downregulated after stimulation of the endothelial cells. However, in a recently published study, increased expression of E-selectin was detected in 13 of 18 patients with PM and DM [40•] The discrepancy in results compared with earlier reports could be due to methodologic differences.

The second phase of the adhesion involves the integrins and the Ig superfamily. Integrins are expressed on leukocytes and their level of expression varies with the cellular stage of differentiation and activation [37]. The integrin family includes leukocyte-function–associated antigen (LFA)-1 expressed on leukocytes and very late–activating antigen (VLA)-4 expressed on leukocytes and also on fibroblasts [34]. The third adhesion molecule family, the Ig superfamily, encompasses adhesion proteins (*eg*, ICAM-1, ICAM-2, VCAM-1), which are particularly expressed on endothelial cells [37]. The molecules of the Ig superfamily may bind to the integrins. ICAM-1 is constitutively expressed on endothelial cells but can be upregulated upon stimulation, whereas ICAM-2 is constitutively expressed on endothelial cells, but not upregulated with

Table 1. Adhesion molecules observed in tissue in idiopathic inflammatory myopathies

Adhesion molecule	Evidence for involvement in IIM	Comments	Study
ICAM-I	PM ↑ on EC, MNCs, MF	On capillaries, arterioles, venules [28,31]	de Bleecker *et al.* [28], Bartoccioni *et al.* [29], Tews *et al.* [30], Cid *et al.* [31], Iannone *et al.* [32],Carota *et al.* [39], Lundberg *et al.* [33••]
	DM ↑ on EC, MNCs, MF	On perimysial arterioles, venules and accicular capillaries [31]	
	IBM ↑ on EC, MNCs, MF	No difference between PM, DM and IBM [29,30,33] ICAM-I mainly in degenerating fibers of DM [31] Only PM patients investigated [32,39] anterioles, venules	
VCAM-I	PM ↑ on EC, MNCs	In PM on arterioles and venules, in DM on arterioles, venules and capillaries [28,31]	de Bleecker *et al.* [28], Tews *et al.* [30], Cid *et al.* [31], Carota *et al.* [39], Lundberg *et al.* [33••]
	DM ↑ on EC, in C, A, V	No differerence between PM, DM and IBM [30,33]	
LFA-Ia	PM ↑ on MNCs	No difference between PM and DM	de Bleecker *et al.* [28], Tews *et al.* [30], Iannone *et al.* [32], Carota *et al.* [39], Lundberg *et al.* [33••]
	DM ↑ on MNCs		
VLA-4a	PM ↑ on MNCs DM ↑ on MNCs	No difference between PM and DM	Cid *et al.* [31], Lundberg *et al.* [33••]
E-selectin	PM ↑ on EC of venules [40]	Some contradictory findings	de Bleecker *et al.* [28], Cid *et al.* [31], Carota *et al.* [39], Jimi *et al.* [40•]
	DM ↑ Neg [28,31,39]		
PNAd	IIM overlap ↑ on HEV	PNAd was absent in PM, DM and IBM	De Bleecker *et al.* [28]

DM—Dermatomyositis; EC—Endothelial cells; IBM—Inclusion body myositis; ICAM—Intercellular adhesion molecule; IMM—Idiopathic inflammatory myopathies; LFA—Leukocyte-function-associated antigen; MNCs—Mononuclear cells; MF—Muscle fiber; PM—Polymyositis; PNAd—peripheral lymphnode addressin; VCAM—Vascular cell adhesion molecule; VLA—very late acitivating antigen.

inflammation. VCAM-1 is not constitutively expressed on endothelial cells but can be induced on stimulation [37].

Increased expression of ICAM-1 was observed both in microvessels and arterioles and venules in all three subsets of IIM, Table 1 [28–32,33••,39]. This was also true for LFA-1α and Mac-1α, ligands of ICAM-1 supporting migration of mononuclear inflammatory cells via the ICAM-1/LFA-1α and Mac-1α pathway [28,30,31,33••,39]. Data concerning VCAM-1 expression in myositis is more conflicting. In some studies, VCAM-1 expression was only detected in microvessels and medium-sized vessels of DM patients but not in PM patients, whereas in other studies no difference was detected between PM and DM patients [28,30,31,33••,39]. On the contrary, expression of VLA-4, a ligand of VCAM-1, was similarly expressed in PM and DM patients, suggesting that not only adhesion and migration by means of the ICAM-1/ LFA-1α pathway, but also by means of the VCAM-1/VLA-4 pathways are utilized in both PM and DM cases [31,33••]. In myositis patients with nodular infiltrates in muscle tissue, but not in PM, DM or IBM cases, an increased expression of the peripheral lymph node addressin (PNAd) was detected on HEV-resembling venules [41]. This indicates that at least in some myositis cases, lymphocyte extravasation could be facilitated by the PNAd expression on endothelial cells [41]. An indirect sign of activated endothelial cells in myositis was the increased serum levels of soluble ICAM-1 reported in untreated PM and DM patients [42]. Adhesion molecule expression in IBM is less well known.

Muscle cells are likely to be the target cells of chronic muscle inflammation, although the endothelial cells may also have a crucial role in the pathogenesis of myositis. Increased expression of MHC class-I molecule on the muscle fiber membrane was an early observation [4]. Immunohistochemical studies have determined that muscle fibers can express the adhesion molecule ICAM-1 and thus make it possible for lymphocytes expressing LFA-1α to adhere to the muscle fiber membrane [28,30,33••]. In a recent study, the costimulatory molecules CTL4 and CD28 were demonstrated on muscle fibers in PM and DM patients, suggesting that the muscle fibers are actively involved in the inflammation in both these subsets of myositis [43••]. These molecules could be induced in vitro on myoblasts by stimulation with IL-1α and IFN-γ. Expression of cytokines such as IL-1 and TNF-a in muscle fibers has also been observed; however (although in regenerating cells), the significance of this observation to the pathogenesis is not clear [20,21].

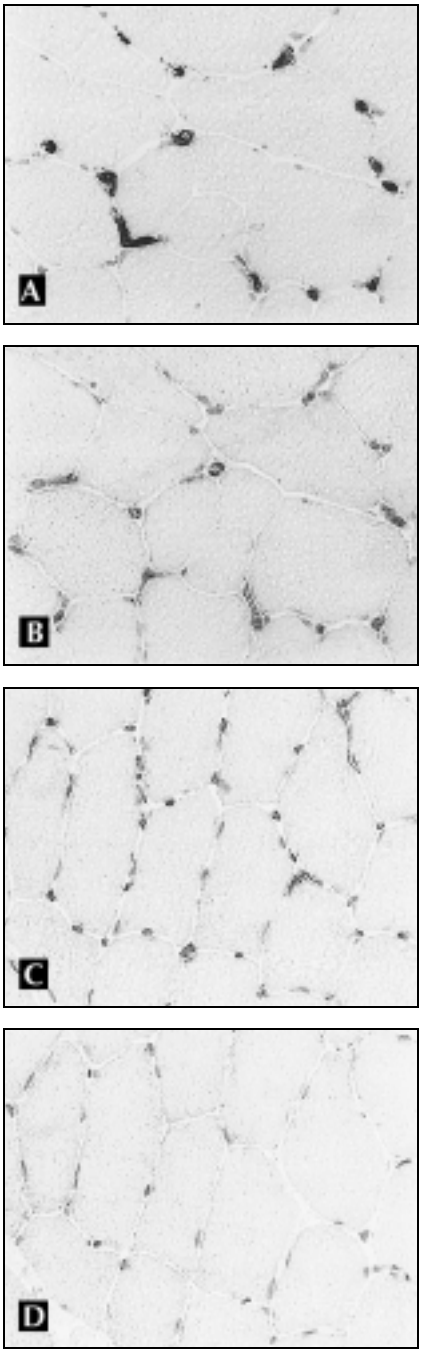

Figure 2. Immunohistochemical localization of IL-1a and human endothelium, visualized as dark staining in muscle tissue from a chronic inactive polymyositis patient and from a control individual. **A**, Identification of endothelial cells with a antihuman endothelium antibody (EN4) in muscle tissue from a polymyositis patient. **B**, In a consecutive section, notice IL-1a expression in endothelial cells of capillaries. **C,** Control muscle stained with anti-human endothelium antibody (EN4). **D,** Consecutive section from that in C, stained with anti-IL-1a, in which no IL-1a positive cells were evident

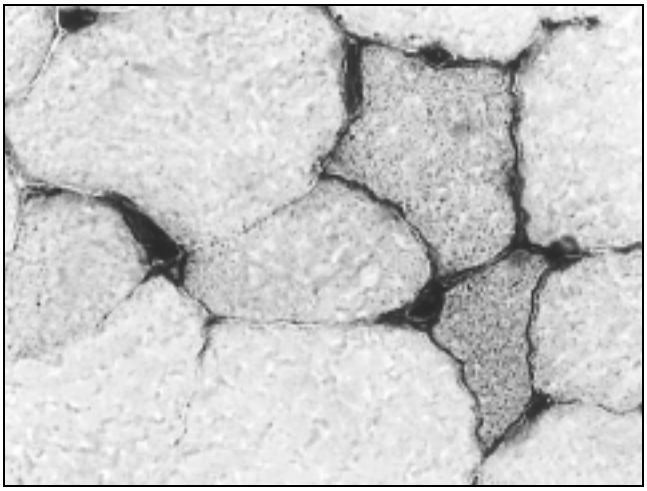

Figure 3. Immunohistochemical localization of MHC class I in muscle tissue from a patient with chronic inactive polymyositis. Positive staining for MHC class-I molecules was detected in endothelial cells, on the sarcolemma and in the muscle fiber cytoplasm.

Effect of Immunosuppressive Treatment on Adhesion Molecule and Cytokine Expression in Muscle Tissue

The clinical improvement of muscle function and skin changes in DM is typically insidious over several months, with a maximal improvement occuring often as late as 3 months or longer, despite the use of high doses of corticosteroids [44]. Whether this slow response in improved muscle function is due to a limited effect on the inflammatory infiltrates or depends on a slow recovery of muscle fiber function is not clear. Few follow-up studies have been published to date in which cellular and molecular expressions were related to muscle function. Persisting, decreased muscle strength was reported despite a decrease of inflammatory cells, suggesting that factors other than the inflammatory cells could affect muscle function [14,33••].

We recently determined a persisting, increased expression of MHC class-I molecules on muscle fibers, as well as increased expression of IL-1α, ICAM-1, and VCAM-1 in endothelial cells after an average of 4 months of treatment with high doses of corticosteroids, despite a marked reduction of the inflammatory infiltrates in muscle tissue [33••]. At the time of rebiopsy, all patients had persisting muscle weakness, or in one case, persisting skin lesions of DM, implying that these molecules are central in the pathogenesis of the clinical symptoms. This hypothesis was further supported by the presence of IL-1α in the endothelial cells (Fig. 2A–D), and by MHC class-I molecules on the muscle fibers (Fig. 3), in patients with chronic but otherwise inactive PM and DM [45••]. Thus these patients, despite treatment for more than 1 year with immunosuppressive drugs, still had persisting, decreased muscle function but without signs of ongoing inflammation as measured by routine histopathologic assessments or by magnetic resonance imaging (MRI) scans [45••]. Extensive replacement of muscle tissue by fat or connective tissue was also excluded as a cause of defect muscle function. In the cases with chronic myositis, an increased number of capillaries with phenotypically changed endothelial cells resembling high endothelial cells were still observed, but there was no increased expression of ICAM-1 or VCAM-1 compared with normal controls. A similar finding of a decreased, but not abrogated, expression of ICAM-1 and MHC class I was observed in muscle tissue after 3 weekly pulses of intravenous methylprednisolone in two patients with myositis [46].

The slow response to corticosteroids regarding functional improvement in patients with IIM is unique compared with other chronic inflammatory disorders (*eg*,

rheumatoid arthritis), in which an almost instant improvement of function with introduction of high dosages of corticosteroids is achieved. The reason for the lag in response to high doses of corticosteroids in PM and DM is unknown, as is the cause of persisting muscle weakness despite regression of inflammation in the muscle tissue. It is noteworthy that in our study, the persisting muscle weakness was in most cases accompanied by persisting upregulation of the molecules IL-1α, VCAM-1, and ICAM-1 in the capillary endothelial cells, despite the lack of detectable inflammatory infiltrates. These studies also support a role for the capillaries in the pathogenesis of the muscle weakness in the chronic phase of myositis. Such a role for the capillaries in causing muscle weakness has previously been suggested by the observation of an increased number of capillaries in patients with DM after treatment with intravenous gammaglobulin, coinciding with improvement of muscle strength [47]. Most patients with IBM do not improve concerning muscle strength and function during corticosteroid or other immunosuppressive treatment [48]. There is even a controversy as to whether corticosteroid treatment affects the inflammatory infiltrates in muscle tissue, [49,50]. The expression of molecules such as cytokines and adhesion molecules after corticosteroid treatment is less well known. In one study including four patients with IBM, no significant changes were observed concerning cellular infiltrate or cells expressing cytokines or ICAM-1 after 3 months of corticosteroid therapy [23].

Functional Implications of Cytokines, Chemokines, and Adhesion Molecules in the Pathogenesis of Idiopathic Inflammatory Myopathies

The descriptive studies of cellular and molecular expression in muscle tissue presented so far suggest that proinflammatory cytokines have a central role in the pathogenesis of myositis, in particular IL-1α, IL-β, and TNF-α. IL-1 is a well known product of endothelial cells and known inducers include lipopolysaccarides (LPS), TNF, and IL-1 itself [51]. A continuous upregulation of these molecules in the muscle tissue could thus be perpetuated despite the absence of inflammatory infiltrates. IL-1 has a variety of effects on endothelial cells, acting in a proinflammatory and prothrombotic sense by upregulating molecules in the endothelial cells (*eg*, ICAM-1 and VCAM-1). IL-1α also has the potential to upregulate expression of MHC class-I molecules on various cells [52,53] and as recently reported, on myotubes in vitro [54••]. Thus, it seems likely that IL-1α could have a central role in the upregulation of MHC class I on muscle fibers in myositis patients and is a more likely candidate molecule in this aspect than the previously suggested IFN-γ [55].

Endothelial cells of the HEV phenotype observed in IIM were characterized by an increased expression of IL-1α and often by ICAM-1 and VCAM-1. In in-vitro systems another vascular adhesion molecules, mucosal addressin cell adhesion molecule (MAdCAM)-1 expressed in mucosal lymphoid organs, was upregulated by IL-1 and TNF‴α [56]. Thus, there is a possibility that the observed HEV-like endothelial cells observed in patients with active IIM could be induced either by IL-1α produced by the endothelial cells themselves or by IL-1α, IL-1β, or TNF-α produced by inflammatory cells. The increased expression of vascular adhesion molecules and IL-1α in endothelial cells as well as the phenotypically, HEV-like, endothelium indicate a role of the microvasculature in the inflammatory process, promoting migration of lymphocytes to muscle tissue, not only in DM as was previously suggested, but also in PM and IBM. Whether the primary target for the inflammatory process of myositis is muscle fibers or the blood vessels, is still unknown.

A Potential Role of Cytokines and Adhesion Molecules for the Clinical Problems

The common molecular findings in patients with impaired muscle function were increased expression of IL-1α in the endothelial cells in muscle tissue, as well as increased expression of MHC class-I molecules on the muscle fibers [33••]. These findings were observed regardless of detectable inflammatory infiltrates, and indicate that these molecules could have a role in causing muscle weakness. One could speculate that involvement of the blood vessels of the muscle tissue could cause metabolic disturbances, as has been suggested for dermatomyositis [57]. The hypothesis of a disturbed circulation in muscle tissue could also have an implication for the upregulation of molecules observed in the inflamed muscle tissue. Interestingly, hypoxia can upregulate both IL-1 and TGF-β, the cytokines most often detected in muscle tissues of myositis patients [58,59], and in a small pilot study hypoxia was observed in muscle tissue in myositis patients [60]. To our knowledge, this finding has not been pursued. It has also been confirmed in an in-vitro model that hypoxia can dynamically modulate endothelial function [61]. In another experimental study, induction of hypoxia in endothelial cells was associated with increased IL-1 expression followed by increased ICAM-1 expression [58]. Hypoxia-mediated IL-1 expression in muscle tissue was further supported by the findings of positive IL-1 expression in muscle fibers undergoing ischemic damage, as well as in regenerating muscle fibers observed in patients with DM and in some patients with PM [21]. IL-1α could also affect muscle function by exerting a metabolic effect on muscle cells through the inhibition of glucose transport and lactate production by means of blocking the effect of insulin-like growth factor [62]. Another functional implication for IL-1α is its ability to induce atrophy of human myocytes in culture [63].

Conclusions

From the descriptive studies performed to date on cytokine, chemokine, and adhesion molecule expression in idiopathic inflammatory myopathies, we can conclude that there is a common molecular profile in PM, DM, and IBM, indicating similar functional effects of the inflammatory process in the IIMs. These studies also suggest a central role of the microvasculature in the pathogenesis of not only DM as was previously suggested, but also in PM and IBM in causing extravazation of the leukocytes to the muscle tissue and in causing the muscular symptoms of weakness and pain. Furthermore, the common features in muscle tissue shared by myositis patients with decreased muscle function were phenotypically changed endothelial cells with increased expression of IL-1α and muscle fibers with increased MHC class-I expression, regardless of degree of inflammatory infiltrate. Thus, it remains uncertain whether the inflammatory cells actually cause the clinical symptoms or if they are a secondary phenomenon to muscle cell damage. To achieve increased knowledge on which molecules are important in the pathogenesis of myositis, further studies that should be focused on molecular expression and changes related to changes in muscle function are required. Such investigations should naturally be included in new drug trials.

Acknowledgements

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