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Review

A recipe for myositis: nuclear factor κB and nuclear factor of activated T-cells transcription factor pathways spiced up by cytokines

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Abstract: Nuclear factor κB (NF-κB) is a well-known pro-inflammatory transcription factor that regulates the expression of the tissue's immune-active components, which include cytokines, chemokines and adhesion molecules. In addition, the versatile nuclear factor of activated T-cells (NFAT) family of transcription factors plays a crucial role in the development and function of the immune system, integrating calcium signaling with other signaling pathways. NF-κB and NFAT share many structural and functional characteristics and likely regulate gene expression through shared enhancer elements. This review describes recent research data that has led to new insights into the involvement of NFκB- and NFAT-mediated pathways in the different idiopathic inflammatory myopathies. The general activation of NF-κB p65 in blood vessel endothelium, seems to flag down inflammatory cells that subsequently accumulate mostly at perimysial sites in dermatomyositis. The joint activation of p65 and NFAT5 in myofibers specifically at perifascicular areas reflects the characteristic tissue damage pattern observed in that particular subgroup of patients. In immune cells actively invading nonnecrotic muscle fibers in polymyositis and sporadic inclusion body myositis on the other hand, p65 activation is an important aspect of their cytotoxic and chemoattactant properties. In addition, both transcription factor families are generally upregulated in regenerating muscle fibers as components of the differentiation process. It can be concluded that the two transcription factor families function in close relationship with each other, representing two-edged swords for muscle disease: on the one hand promoting cell growth and regeneration, while on the other hand actively participating in inflammatory cell damage. In this respect, cytokines function as important go-betweens at the crossroads of the pathways. Beyond NF-κB and NFAT, many fascinating winding roads relevant to inflammatory myopathy disease management still lie ready for the exploring.

Keywords: nuclear factor κB; nuclear factor of activated T-cells; myositis; cytokines; dermatomyositis; polymyositis; sporadic inclusion body myositis; immune-mediated necrotizing myopathy; osmolytes

Abbreviations

AKR1B1	Aldose reductase
DM	Dermatomyositis
IIM	Idiopathic inflammatory myopathies
IMNM	Immune-mediated necrotizing myopathy
iNOS	Inducible nitric oxide synthase
IκB	Inhibitor κB
IKK	IκB kinase
LT-β	Lymphotoxin β
MCP-1	Monocyte chemoattractant protein 1
NF-κB	Nuclear factor κB
NFAT	Nuclear factor of activated T-cells
PM	Polymyositis
SLC5A3	Sodium/myo-inositol cotransporter
IBM	Sporadic inclusion body myositis
SLC6A6	Taurine transporter
TNF-α	Tumor necrosis factor α

1. Introduction

Chronic inflammation of skeletal muscle tissues, termed myositis, can have various origins. It can result from infection, tissue damage caused by inherited disorders, or an acquired autoimmune disease. In the muscular dystrophies for instance, muscle inflammation is secondary to tissue damage caused by deficiency of the dystrophin complex, yet represents an important pathogenic factor that contributes substantially to tissue deterioration [1]. In this review, focus will be on the involvement of pro-inflammatory transcription factors in the idiopathic inflammatory myopathies (IIM). The IIM comprise four main entities: dermatomyositis (DM), polymyositis (PM), sporadic inclusion body myositis (IBM), and immune-mediated necrotizing myopathy (IMNM). Each of these disease subgroups presents with distinct clinical and myopathological characteristics, with either the blood vessels or the muscle fibers as preferential immune-target. In DM, complement-mediated blood vessel destruction and perifascicular inflammation develop. PM and IBM are characterized by cytotoxic attack of nonnecrotic muscle fibers and mostly endomysial buildup of inflammation [2]. In IBM muscle fibers, additional degenerative phenomena occur, with rimmed vacuoles and inclusions that contain ectopic proteins [3]. IMNM is an increasingly recognized autoimmune myopathy, in subgroups of patients triggered by statin use and associated with autoantibodies directed against 3-hydroxy-3-methylglutaryl-coenzymeA reductase [4].

In the IIM, progressive muscle damage is caused by an autoimmune response to skeletal muscle-derived antigens [5], yet many of the immunopathogenic processes underlying the diseases

remain poorly understood until today. It is, however, generally accepted that muscle fibers are active participants and that the interaction between immune cells, blood vessel endothelial cells and muscle fibers is requisite to the sustained inflammatory response.

2. NF-κB and Inflammatory Myopathies

Nuclear factor κB (NF-κB) is a ubiquitous yet inducible transcription factor and a key organizer of inflammatory processes. The transcription factor is encoded by a multigene family (Table 1). Functional NF-κB is a dimer that can be composed of different sets of subunits, with the most common cytoplasmic form of NF-κB a heterodimer composed of p50 and p65 subunits. Individual NF-κB dimers acquire different transcriptional properties and can recognize slightly different DNA targets.

Table 1. NF-κB and NFAT transcription factor families and their involvement in inflammatory myopathies.

	Subunits/subforms/names	Expression in IIM
NF-κB	p105-p50/NFκB1	Increased in blood vessels and muscle fibers, and expressed by infiltrating inflammatory cells
	p100-p52/NFκB2	Unknown
	p65/RelA	Increased and activated in blood vessels and muscle fibers, and expressed by infiltrating inflammatory cells
	cRel	Unknown
	RelB	Unknown
NFAT	NFAT1/NFATc2/NFATp	Unknown
	NFAT2/NFATc1/NFATc	Unknown
	NFAT3/NFATc4	Unknown
	NFAT4/NFATc3/NFATx	Unknown
	NFAT5/NFATz/NFATL1/TonEBP/CREBP	Increased and activated in muscle fibers

In most resting cells, NF-κB is retained in the cytosol in an inactive form sequestered through interaction with its inhibitor κB (IκB). Its major activation pathway starts with stimulation of the IκB kinase (IKK), which leads to IκB phosphorylation and subsequent proteosomal degradation of the inhibitor. Additional post-translational modifications of NF-κB subunits regulate the transcription factor's transactivation potential and includes phosphorylation of serine and threonine residues, with phosphorylation of the p65 subunit's Ser276, Ser468 and Ser536 residues as the best studied [6].

The importance of NF-κB pathways in human inflammatory diseases has long been recognized and cannot be overestimated. The transcription factor is indeed a key mediator of pro-inflammatory gene expression in the IIM, but is also involved in muscle tissue maintenance, regulating cell proliferation and differentiation. Under normal conditions, NF-κB activation is a transient process, which is stopped by IκB entering the nucleus, dislodging NF-κB from its DNA binding sites. In chronic inflammatory states however, which includes IIM, activation is sustained and transcription of responsive genes is continuously initiated. Myopathological data firmly corroborates an increased NF-κB transcriptional activity in the IIM. NF-κB-electrophoretic mobility shift assays reveal that

NF-κB-DNA binding activity is variably but consistently increased in DM/PM/IBM compared to control muscle [7,8].

Several studies are available typing NF-κB subunits p50/p65 in the different IIM, and have been reviewed in [9]. Protein levels of p65 are significantly increased in muscle tissue samples of DM, PM and IBM patients [8,10], and it can be concluded that p50/p65 activation is a more general phenomenon present in the IIM irrespective of patient subtyping. Genetic predisposition related to NF-κB could however not be observed. A study of 63 single nucleotide polymorphisms from NF-κB-related genes showed that NF-κB genes do not confer susceptibility to DM/PM [11].

Muscle fibers constitutively contain NF-κB subunits p50 and p65, but studies indicate their activation in the IIM. In PM and IBM sections, phosphorylated active p65 is found within the myonuclei, a pattern not observed in control tissues [8]. Activated p65 staining is also increased in the atrophic fibers at perifascicular sites of DM and scattered atrophic fibers in PM/IBM/IMNM tissues [12]. Necrotic fibers in IIM tissues are most often p50 and p65 positive, with only part staining for phosphorylated p65 [12,13]. The large majority of vacuolated fibers in IBM tissues contain p50 and p65 positive inclusions [13], with activated p65 observed in part of the vacuolated fibers [7,13]. This NF-κB activation may result in the endoplasmic reticulum overload response characteristic of IBM fibers, generating a self-sustained loop of cytokine release and amyloid precursor protein production [14]. This further illustrates how, in the IIM, muscle fibers are active participants in their own demise. They acquire major histocompatibility complexes on the sarcolemma [15], enabling them to present antigen to tissue-infiltrating immune cells. By producing various inflammatory factors, including adhesion molecules and cytokines, they mark themselves and their microenvironment as sites for autoimmune attack. As key regulator of pro-inflammatory gene expression, the pathological role of NF-κB activation in the muscle damage associated with IIM seems obvious. However, adding nuance to the culpabilization of the transcription factor, p65 and p50 are also induced in the regenerating muscle fibers within patient tissues [7,9], indicating a potentially protective role in myogenesis and repair is also at play.

DM is a systemic disease associated with blood vessel damage within the skeletal muscle tissue. The autoimmune response specifically targets the blood vessel endothelium, a process in which complement deposition is an early event [16]. The trigger that initiates complement activation still remains unclear. Further along, the affected blood vessels express a broad range of pro-inflammatory mediators, including adhesion molecules, cytokines and chemokines, attracting circulating monocytes and lymphocytes. The distribution of NF-κB reflects this particular endotheliopathic nature of DM. Generally enhanced expression of p65 and p50 can be observed in DM blood vessel endothelium, often with strong staining for phosphorylated p65 (Figure 1A). In PM/IBM, blood vessel p65 upregulation occurs more rarely [17]. It thus seems that endothelial NF-κB activation and subsequent expression of pro-inflammatory factors plays a pivotal role in the accumulation of perivascular inflammatory infiltrates in DM tissues in particular.

Inflammatory cells infiltrating IIM tissues broadly express p50 and p65, with part of muscle-infiltrating T-cells, B-cells, and macrophages of both the auto-aggressive M1 and regenerative M2 lineages, being positive [12,17]. Subsets also stain for phosphorylated p65 (Figure 1A–C). In immune cells actively invading nonnecrotic muscle fibers of PM/IBM tissues, most often cytotoxic T-cells or M1 macrophages, the activated form of p65 can be detected most frequently [12]. It can therefore be concluded that NF-κB activation is an important aspect of the cytotoxicity displayed by inflammatory cells infiltrating IIM muscle.

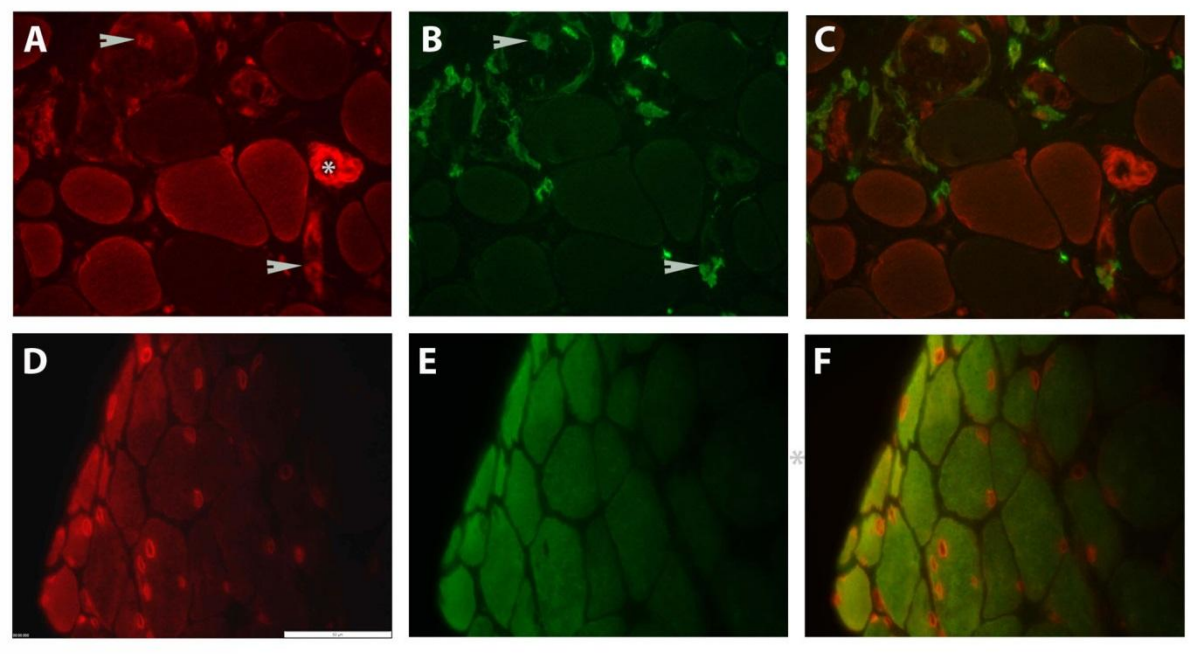

Figure 1. Immunofluorescent staining for NF-κB subunit p65 and NFAT5 in dermatomyositis muscle. (A–C): A subset of muscle fibers acquire sarcoplasmic Ser536 phosphorylated p65 staining (CY3, red), part of which are small regenerating or atrophic muscle fibers. Blood vessel endothelium is strongly positive (asterisk) and part of CD206+ (AlexaFluor488, green) M2 macrophages, both cells infiltrating necrotic muscle fibers (upper arrowhead) and interstitial cells (lower arrowhead), are positive. (D–F): Myonuclei stain strongly for NFAT5 (CY3, red) throughout the tissues, but perifascicular small muscle fibers acquire additional sarcoplasmic staining. In these regenerating or atrophic perifascicular muscle fibers, Heat Shock Protein 70 staining (AlexaFluor488, green) is concomitantly increased. Antibodies used: rabbit polyclonal anti-Ser536 phosphorylated p65, SantaCruz Biotechnology, 1 μg/ml; mouse monoclonal anti-CD206, Dako, 6.6 μg/ml; rabbit polyclonal anti-NFAT5, Acris, 20 μg/ml; mouse monoclonal anti-HSP70, Chemicon, 1/100 dilution. Scale bar = 50 μM.

3. NFAT and Inflammatory Myopathies

The Nuclear factor of activated T-cells (NFAT) transcription factor family, contains five members (Table 1) that are expressed in most cells of the immune system. In T-cells, NFAT proteins not only regulate activation but are also involved in cell differentiation and self-tolerance. These transcription factors possess, however, a much broader expression pattern, spanning many different cell types. NFAT regulate tissue development, including the buildup of skeletal muscle. The functional versatility of NFAT proteins can be explained by their complex mechanism of regulation and their ability to integrate calcium-regulated processes with other signaling pathways.

In the cytoplasm of resting cells, NFAT1-4 proteins are phosphorylated, and their nuclear import is opposed by maintenance kinases. In response to calcium signaling, they interact with calcineurin, a cytoplasmic phosphatase, which removes phosphates from multiple protein sites. Dephosphorylation of serine residues exposes the NFAT nuclear-localization signal and leads to

translocation of the transcription factor to the nucleus, that thus becomes transcriptionally active. In addition, the corresponding nucleus' export kinases become inactivated to achieve NFAT nuclear retention [18]. The fifth family member NFAT5 is differentially regulated. It is not stimulated by calcium, but activated by increased sodium concentrations, with hyperosmotic conditions inducing phosphorylation of the carboxy-terminal transactivation domain. NFAT5 is constitutively nuclear in many cell types [19].

Skeletal muscle can potentially express all isoforms, and NFAT regulate the transcription of a variety of muscle specific genes involved in skeletal muscle development and differentiation. NFAT2 is a key mediator of activity-dependent transcriptome regulation, with disuse reducing the NFAT2 content of the myonuclei [20]. Anabolic steroids activate calcineurin/NFAT signaling, with increased nuclear levels of NFAT3, resulting in hypertrophy in cultured myotubes and protection against denervation atrophy in rats [21]. For the control of fiber type distribution, the NFAT family also seems crucial. Type I or slow twitch muscle fibers utilize oxidative metabolism and are fatigue resistant, while type II or fast twitch fibers utilize glycolytic metabolism and fatigue rapidly. NFAT1 and NFAT4 are closely associated with the expression of fast twitch myofibrillar proteins [22], while NFAT2 induces slow twitch genes. NFAT are important regulators of myogenesis, and individual family members are activated only at specific stages [23], allowing them to regulate distinct subsets of genes. It appears also that different transcription factors display distinct co-activator/co-repressor interactions. NFAT2 has a negative influence on MyoD, the central regulator of the differentiation of myoblasts into functional multinucleate myotubes, whereas NFAT4 cannot block MyoD activity [24]. In damaged rat muscle, calcineurin and NFAT2 interact, and levels of activated NFAT2 are markedly increased in the first days after injury, gradually returning back to baseline levels [25]. NFAT5 levels are also increased in the regenerating fibers of mice exposed to experimental muscle tissue injury [26].

Despite their obvious involvement in muscle physiology, sparse data is currently available regarding the involvement of NFAT in the IIM, with only NFAT5 having been studied in some detail. The prominent myonuclear NFAT5 expression present in healthy skeletal muscle is increased further in IIM. In DM muscle, additional sarcoplasmic staining can be observed which is restricted mostly to perifascicular areas (Figure 1D). Possibly this changed intracellular expression pattern represents a regulatory mechanism, adjusting NFAT5 activity to the atrophic processes that in DM typically unfurl at the periphery of the muscle fascicle. An extra clue is that, in these perifascicular atrophic muscle fibers of DM muscle, otherwise absent staining for Ser1197 phosphorylated NFAT5 becomes prominent [10]. The precise role of this particular serine phosphorylation has not been elucidated in full, but phosphorylation appears to contribute to the protein's stability and activity in response to stress. In arterial smooth muscle cells, an NFAT5 increase and Ser1197 phosphorylation is observed in response to biomechanical stretch [27].

NFAT5 staining of part of blood vessels can be observed, which is no different from that in healthy control muscle. In arterial smooth muscle cells [27] as well as in endothelial cells [28], basal levels of NFAT5 are present, and expression promotes angiogenic processes.

So far, expression of NFAT5 could not be observed in the immune cells infiltrating the IIM muscle tissue [10]. This lack of immunoreactivity is somewhat surprising and could be due to technical reasons, variation of expression levels in different activation states and/or transient expression patterns that subside once immune cells penetrate the muscle tissue.

4. NF-κB and NFAT5 Interactions in Inflammatory Myopathies

The NF-κB and NFAT transcription factor families clearly are evolutionarily related. Respective promoter binding sites, κB for NF-κB and osmotic response elements or TonE for NFAT5, closely resemble one another. NFAT5 in particular can thus be regarded as a cousin within the subgroup of the large family of Rel/NF-κB proteins. Similar to NF-κB and unlike other NFAT family members, NFAT5 binds DNA as an obligate homodimer [29]. It is known that p50 and p65 can bind and activate TonE elements, and vice versa, hypertonicity promotes nuclear translocation and increases NF-κB activity. It is also known that NFAT proteins have weak DNA-binding capacity, achieving effective binding through cooperation with other nuclear resident transcription factors. In this story of cooperative binding, NF-κB could well be their privileged partner. Binding of p65-NFAT5 complexes to κB elements of NF-κB-responsive genes has been reported [30]. These authors propose a mechanism of interaction between NF-κB and NFAT5 mediated by mitogen-activated protein kinases and protein kinase B activation. Also, physical interactions between NFAT2 and NF-κB subunits cRel [31] and p65 [32] have been documented, the latter promoting proliferation of cardiomyocytes.

In IIM NF-κB and NFAT5 signaling pathways seem indeed to be closely connected. In the perifascicular atrophic fibers of DM muscle in particular, p65 and NFAT5 staining and activation coincide [10], linking these pathways in this important pathological hallmark. Several pro-inflammatory mediators seem to act as important go-between in the communication between the two pathways. It is well known that NF-κB controls the expression of pro-inflammatory cytokines, by binding κB elements in their promoter regions. In addition, NFAT-regulated gene expression is an early event in lymphocyte activation following antigen-receptor-binding [33] and stimulates adhesion molecule and cytokine expression. Several genes involved in inflammatory processes share NFAT5 and NF-κB activation (Table 2). Importantly, NFAT5 is known to control the expression of tumor necrosis factor α (TNF-α), lymphotoxin β (LT-β) and monocyte chemoattractant protein 1 (MCP-1) genes, which all three happen to be key cytokines involved in the immunopathogenesis of IIM [34,35,36].

Table 2. Genes with documented combined NF-κB and NFAT5 transcription factor sensitivity.

Cytokines	**Osmolyte accumulators**
Tumor necrosis factor alpha (TNF-α)	Aldose reductase (AKR1B1)
Lymphotoxin β (LT-β)	Aquaporin 2
Monocyte chemoattractant factor-1 (MCP-1) (CCL2)	sodium/myo-inositol cotransporter (SLC5A3)
Chaperones	**Cytotoxic factors**
Heat shock protein family of 70 kd (HSP70)	Inducible NO synthase (iNOS)

4.1. Tumor necrosis factor α

The potent pro-inflammatory cytokine TNF-α plays a critical role in the immune responses that lead to the sustained inflammation characterizing the IIM, as reviewed in [34]. The TNF-α promoter contains binding sites for both NF-κB and NFAT family members, and expression is regulated in a

cell-type- and stimulus-dependent manner. NFAT1 and NFAT5 possess affinity to distinct TNF-α promoter sites, allowing the latter to specifically stimulate expression in response to hypertonic conditions [37]. NFAT5 binding to the TNF-α promoter has been shown in osmotically stressed T-cells [19]. In macrophages, NFAT5 promotes the M1 phenotype characterized by cytotoxic activities, through induction of inducible nitric oxide synthase (iNOS) and TNF-α gene expression, and suppresses the M2 phenotype and anti-inflammatory IL-10 gene expression [38]. iNOS immunoreactivity is most prominent in M1 macrophages actively invading nonnecrotic muscle fibers in PM/IBM tissues [39]. This raises the possibility of applying therapeutic strategies that selectively suppress this M1 activation, and this mode of action has already been put forward as an attractive strategy to combat inflammatory disease in general. Targeting CD64 for example, a high affinity IgG-binding receptor specifically overexpressed on M1 macrophages has proven to be an effective therapeutic target [40].

4.2. Lymphotoxin β

LT-β also belongs to the TNF-superfamily of cytokines, and is a key factor in the organization of immune cells into tertiary lymphoid organs. Especially in DM, organization of T-cells, dendritic cells and B-cells into follicle-like collections localized within the muscle tissue, can often be observed and puts LT-β forward as a possible regulator. In the IIM, LT-β is indeed expressed by subsets of inflammatory cells and by regenerating and necrotic muscle fibers. In addition, LT-β expression by muscle fibers of normal width appears to be an early event that precedes inflammation-induced tissue damage [35], putting the cytokine forward as one of the potential disease initiators. The LT-β gene promoter contains κB and TonE sequences, pointing the finger at both the NF-κB transcription factor family and NFAT5 as its regulators, with expression of LT-β being induced in T-cells both by inflammatory stimuli and NF-κB activation, as well as by osmotic stress [19].

4.3. Monocyte chemoattractant protein 1

An important role for the chemoattractant cytokine MCP-1 has been established in the IIM, exhibiting disease subgroup-related expression patterns [41]. Cytotoxic T-cells and M1 macrophages actively invading nonnecrotic muscle fibers in PM/IBM tissues are strongly MCP-1 positive. Specifically in the vicinity of the endomysial inflammatory infiltrates of PM/IBM tissues, the blood vessel endothelium is prominently positive for MCP-1. In contrast, endothelial MCP-1 staining is more homogeneously distributed in DM, with blood vessels staining strongly also remote from sites with perifascicular tissue damage and inflammation. In DM, perimysial inflammatory cell collections express lower levels of MCP-1 [42]. Both the NF-κB family and NFAT5 are important inducers of MCP-1 expression. In kidney cells, MCP-1 gene expression can be achieved via TNF-α induced NF-κB activation, but also by hypertonic conditions [30].

4.4. Osmolyte pathways

NFAT5 not only activates pro-inflammatory cytokines, but in addition regulates the expression of protective genes. As one of its main cellular functions, the transcription factor mediates the

intracellular accumulation of small organic osmolytes in response to changing osmotic conditions. Osmolyte pathway genes contain TonE elements, and include aldose reductase (AKR1B1), taurine transporter (SLC6A6), and sodium/myo-inositol cotransporter (SLC5A3), of which only AKR1B1 is expressed in high amounts in normal skeletal muscle. In the perifascicular atrophic fibers of DM muscle however, strong staining for AKR1B1, SLC6A6 and SLC5A3 is induced [10]. In these fibers, upregulation of HSP70 is also present (Figure 1E), a chaperone of the heat shock protein family under control of NFAT5 [43]. Also, the related molecular targets MCP1 and iNOS are induced in the perifascicular atrophic muscle fibers [10]. But it should be noted that AKR1B1, SLC6A6 and SLC5A3 are also induced in the regenerating muscle fibers, possibly as a protective mechanism aiding the buildup of the cell's renewed proteome.

In addition to an involvement in tissue damage and regeneration, osmolytes have been shown to be potent immune regulators. They influence immune cell function and regulate cell volume as an important aspect of their phagocytic activity. A subset of macrophages and T-cells infiltrating IIM muscle have been shown SLC5A3 positive [10], but SLC6A6 and AKR1B1 could not be detected. If a pivotal role in chronic inflammation is played by specific members of the osmolyte pathway, this could evolve into an attractive target for therapy. The plausibility of an anti-inflammatory approach targeting osmolyte accumulators has already been shown with AKR1B1 inhibitors put forward as a novel therapeutic strategy [44]. This seems an amenable approach, as the beneficiary effects of the pathway members appear to be based mostly on redundant cytoprotective activities that can be compensated when individual partners are targeted. There indeed is a definite need to develop novel therapies, as classical broad range immunosuppressive compounds that are most often used to treat DM and PM can present with severe side effects. In addition, treating IBM remains a challenge to date, as these patients generally do not respond to the available immunomodulatory drugs, and trials with immunoregulatory biologicals have generated mostly discouraging results [45].

5. Conclusions

From the data gathered so far, it is clear that transcription factor NF-κB and NFAT families are both involved in the regulation of muscle tissue protection and damage repair. Both transcription factors contribute to myoblast migration and differentiation into functional myotubes, and are therefore imperative to muscle regeneration. These transcription factors do, however, also possess potent pro-inflammatory properties. In the IIM, the delicate balance between their anabolic and catabolic activities seems seriously disturbed and these transcription factors become important mediators of the chronic and tissue-damaging inflammatory response. A role for NF-κB in the endotheliopathic processes of DM and the cytotoxic muscle fiber damage in PM/IBM, and for both NF-κB and NFAT5 in the perifascicular muscle fiber atrophy in DM comes forward. Key cytokines in the underlying context-dependent communication between transcription factors seem to be TNF-α, LT-β and MCP-1. The expression patterns of these cytokines are indeed reflective of the differential targeting displayed in different disease entities: blood vessel and perifascicular damage in case of DM on the one hand, and muscle fiber and endomysial damage for PM/IBM on the other hand.

It is crucial to further unravel signaling and interaction between the pathways in order to gain insight into the precise sequence of events responsible for sustained inflammation. Table 1 illustrates how limited our knowledge still is on the involvement of the transcription factor families and how badly needed proliferation of insight is to help identify novel therapeutic targets for the future.

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Conflict of Interest

The author declares no conflicts of interest in this paper.

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