Review

Matrix Metalloproteinases and Tissue Inhibitor of Metalloproteinases in Inflammation and Fibrosis of Skeletal Muscles

Hala S. Alameddine[a,*] and Jennifer E. Morgan[b]

[a]*Institut de Myologie, Groupe Hospitalier Pitié-Salpêtrière, boulevard de l'Hôpital, 75651 Paris Cedex 13, France*
[b]*The Dubowitz Neuromuscular Centre, Molecular Neurosciences Section, Developmental Neurosciences Programme, UCL Great Ormond Street Institute of Child Health, 30 Guilford Street, London, UK*

Abstract. In skeletal muscles, levels and activity of Matrix MetalloProteinases (MMPs) and Tissue Inhibitors of MetalloProteinases (TIMPs) have been involved in myoblast migration, fusion and various physiological and pathological remodeling situations including neuromuscular diseases. This has opened perspectives for the use of MMPs' overexpression to improve the efficiency of cell therapy in muscular dystrophies and resolve fibrosis. Alternatively, inhibition of individual MMPs in animal models of muscular dystrophies has provided evidence of beneficial, dual or adverse effects on muscle morphology or function. We review here the role played by MMPs/TIMPs in skeletal muscle inflammation and fibrosis, two major hurdles that limit the success of cell and gene therapy. We report and analyze the consequences of genetic or pharmacological modulation of MMP levels on the inflammation of skeletal muscles and their repair in light of experimental findings. We further discuss how the interplay between MMPs/TIMPs levels, cytokines/chemokines, growth factors and permanent low-grade inflammation favor cellular and molecular modifications resulting in fibrosis.

Keywords: MMPs, TIMPs, skeletal muscle, diseases, inflammation, fibrosis

ABBREVIATIONS

ACE	Angiotensin Converting Enzyme
ADAM	A Desintegrin And Metalloproteinase
α-SMA	Alpha-Smooth Muscle Actin
CA-MMP	Cysteine Array-MMP
CCL2	chemokine (C-C motif) ligand 2 (CCL2);
MCP1	Monocyte Chemotactic Protein 1
CCR2	C-C chemokine Receptor type 2
CD	Cluster of Differentiation
CTGF	Connective Tissue Growth Factor
CXC	Cysteine X Cysteine
CXCL	Cysteine X Cysteine Ligand
CXCR	Cysteine X Cysteine Receptor
DAMPs	Damage associated Molecular Patterns
EGF	Epidermal Growth Factor
EGFR	Epidermal Growth Factor Receptor
cGMP	Cyclic Guanosine Monophosphate
HE4	Human Epididymis Protein 4
HGF	Hepatocyte Growth Factor also known as Scatter Factor
IGF	Insulin Growth Factor

*Correspondence to: Hala S. Alameddine, PhD, Institut de Myologie, Bâtiment Babinski, Groupe Hospitalier Pitié-Salpêtrière, 47, boulevard de l'Hôpital, 75651 Paris Cedex 13, France. Tel.: +33 142165713; Fax: +33 142165700; E-mail: h.alameddine@institut-myologie.org.

IGFBP	Insulin Growth Factor Binding Protein
IGFR	Insulin Growth Factor Receptor
M-CSF	Macrophage Colony Stimulating Factor
MMPs	Matrix MetalloProteinases
MMPIs	Matrix MetalloProteinase Inhibitors
MT-MMP	Membrane Type- MMP
Musk	Muscle specific Kinase
NO	Nitric Oxide
NOS	Nitrogen Reactive Species
NOX	NADPH Oxidase
NRROS	Negative Regulator of ROS
PAMPs	Pathogen Associated Molecular Patterns
PDE5	PhosphoDiesterase 5
PDGF	Platelet Derived Growth Factor
PMN	Polymorphonuclear Leukocyte
Prss (23) or Prss (35):	Protease, Serine, (23) or (35)
RASI	Rheumatoid Arthritis Sign of Inflammation,
RECK	Reversion-inducing-Cysteine-rich protein with Kazal motifs
ROS	Reactive Oxygen Species
SDF-1	Stromal Derived Factor-1 or (CXCL12)
SMAD	Sma and Mad Related Protein
SOD	Super Oxide Dismuthase
TACE	Tumour necrosis factor Alpha Converting Enzyme
TGF-β:	Transforming Growth Factor beta
TIMP	Tissue Inhibitor of MetalloProteinase
TLR	Toll Like Receptor
TNF-α:	Tumour Necrosis Factor alpha
VEGF	Vascular Endothelial Growth Factor
XMMP	Xenopus MMP
PUMP-1	Plant Uncoupling Mitochondrial Protein 1

INTRODUCTION

The balance between hydrolytic activity and its inhibition regulates tissue and extracellular matrix (ECM) homeostasis. Disruption of this balance occurs as an integral part of tissue response to remodeling stimuli but its long lasting perturbation deregulates many biological processes and leads to the development of diseases. High MMP levels characterize acute or chronic disease situations and correlate with disease severity suggesting they have detrimental effects. Hardly appreciated however, is the possibility that these proteins serve essential or beneficial functions. MMPs are major determinants in remodeling events such as placental development, embryo implantation- a highly invasive but tightly controlled process involving ECM degradation and cell migration-, angiogenesis, bone development and mammary involution. They participate in ECM degradation by direct cleavage of connective tissue collagen, activation of latent enzymes and processing or liberation of structural or signaling molecules from the ECM.

In normal skeletal muscles, the steady state situation is characterized by basal activity of hydrolytic enzymes titrated by their inhibitors. Modifications of functional demands, trauma or disease disrupt this balance and trigger an adaptive response that includes MMPs/TIMPs regulation [1–12]. In turn, these proteins alter cell-cell and/or cell-matrix interactions thereby affecting cell proliferation, migration and differentiation. Nevertheless, "guidance cues", able to relocate and stop regenerating axons at original synaptic sites, are preserved during the denervation/reinnervation process [13] indicating that highly regulated and tightly controlled hydrolysis of ECM components characterize the accomplishment of a specific task.

The involvement of metallo-endopeptidase in myoblast fusion were published in the early eighties [14, 15] but their implication in pathophysiological processes [16–27] and therapeutic follow-up/perspectives [28–33] were published decades later. At present, we have indications of some of the functions accomplished by MMP-2, MMP-9, MMP-10 and MMP-14 but there is hardly a hint of the role played by other family members. However, considering the dysregulation of MMPs/TIMPs balance in disease situations, it seems important to identify the modification of expression pattern in identified muscle disease entities to sort out "IF" and "HOW" they affect clinical severity and determine potential targets for therapeutic interventions. By exploring the function(s) of each MMP and TIMP and identifying their degrading and regulatory actions one may depict the mechanism involved in their mode of action as described for MMP-9 and MT6-MMP [34, 35].

In a previous review, we have presented the involvement of MMPs/TIMPs in specific skeletal muscle diseases such as muscular dystrophies,

Table 1
Matrix Metalloproteinases: their alternative names, location within tissues and chromosomes and source of activation from a pro-form. MMP: Matrix Metalloproteinase; MT(n)-MMP: Membrane Type (n = 1,2,3,4,5,6)- MMP; RASI: Rheumatoid Arthritis Sign of Inflammation, XMMP: Xenopus MMP; CA-MMP: Cysteine Array-MMP; Pump-1: plant uncoupling mitochondrial protein 1

Enzyme	MMP	Location	Activation	Chromosomal Location
Collagenases				
Interstitial collagenase; collagenase 1	MMP-1	Secreted	MMP-3	11q22-q23
Neutrophil collagenase; collagenase 2	MMP-8	Secreted	MMP-3	11q21-q22
Collagenase 3	MMP-13	Secreted	MMP-14/TIMP-2/MMP-3	11q22.3
Collagenase 4 (*Xenopus*)	MMP-18	Secreted	Unknown	NA
Gelatinases				
Gelatinase A	MMP-2	Secreted	MMP-14/TIMP-2	16q13
Gelatinase B	MMP-9	Secreted	MMP-3/MMP-13	20q11.2-q13.1
Matrilysin				
Matrilysin 1; Pump-1	MMP-7	Secreted	MMP-3	11q21-q22
MMP-26	Secreted	Unknown	11p15	
Membrane-type MMPs				
MT1-MMP	MMP-14	Membrane	Furin	14q11-q12
MT2-MMP	MMP-15	Membrane	Furin	15q13-q21
MT3-MMP	MMP-16	Membrane	Furin	8q21
MT4-MMP, TACE	MMP-17	Membrane	Furin	12q24.3
MT5-MMP	MMP-24	Membrane	Furin	20q11.2
MT6-MMP	MMP-25	Membrane	Furin	16p13.3
Metalloelastase				
Macrophage Elastase	MMP-12	Secreted	Unknown	11q22.2-q22.3
Stromelysin				
Stromelysin 1	MMP-3	Secreted	MMP-14/TIMP-2	11q23
Stromelysin 2	MMP-10	Secreted	Unknown	11q22.3-q23
Stromelysin 3	MMP-11	Secreted	Furin	22q11.2
Others				
RASI	MMP-19	Secreted	Unknown	12q14
Enamelysin	MMP-20	Secreted	Unknown	11q22.3
XMMP (Xenopus)	MMP-21	Secreted	Unknown	ND
CA-MMP	MMP-23	Secreted	Furin	1p36.3
CMMP (*Gallus*)	MMP-27	Secreted	Unknown	11q24
Epilysin	MMP-28	Secreted	Furin	17q21.1

inflammatory myopathies and neurogenic muscular diseases [36]. Here, we chose to focus on MMPs/TIMPs involvement in inflammation and fibrosis that occur in several muscle diseases namely inflammatory myopathies and muscular dystrophies. In this respect, the emblematic Duchenne Muscular Dystrophy or its animal models, characterized by the occurrence of both components, have been widely used to investigate the functional consequences of MMPs/TIMPs balance modulation and will, therefore, be referred to in a specific section to illustrate these points.

Matrix Metalloproteinases (MMPs)

The MMP family is composed of 23 members in human (24 in mouse) [37, 38] most of which are secreted and six are membrane bound (Table 1). They are inhibited by TIMPs and, collectively, degrade all ECM components. Their general characteristics and regulation have been reviewed in [36]. The

regulation of MMPs activity and the modulation of MMPs/TIMPs activity/expression in inflammatory and wound conditions are schematically presented in Fig. 1.

MMP-2, MMP-10 and MMP-3 deficient mice are reported with no evident signs of malformation. Curiously, Mmp2-/- mice, originally characterized as overtly normal but with slower growth rate [39] revealed, upon closer examination, attenuated features of multicentric osteolysis and arthropathy [40] caused by MMP-2 mutations which lead to cardiac defects when the terminal hemopexin domain is deleted [41]. Such mutations may have phenotypic repercussions on skeletal muscles as well but has not been investigated in animal models. Mmp14 deficiency causes severe developmental defects and defective muscle maturation leading to premature death [42]; a phenotype aggravated by additional MMP-2 deficiency [43]. Mice deficient in MMP-3, known to degrade agrin, have high agrin levels and show increased size and number of AchR at
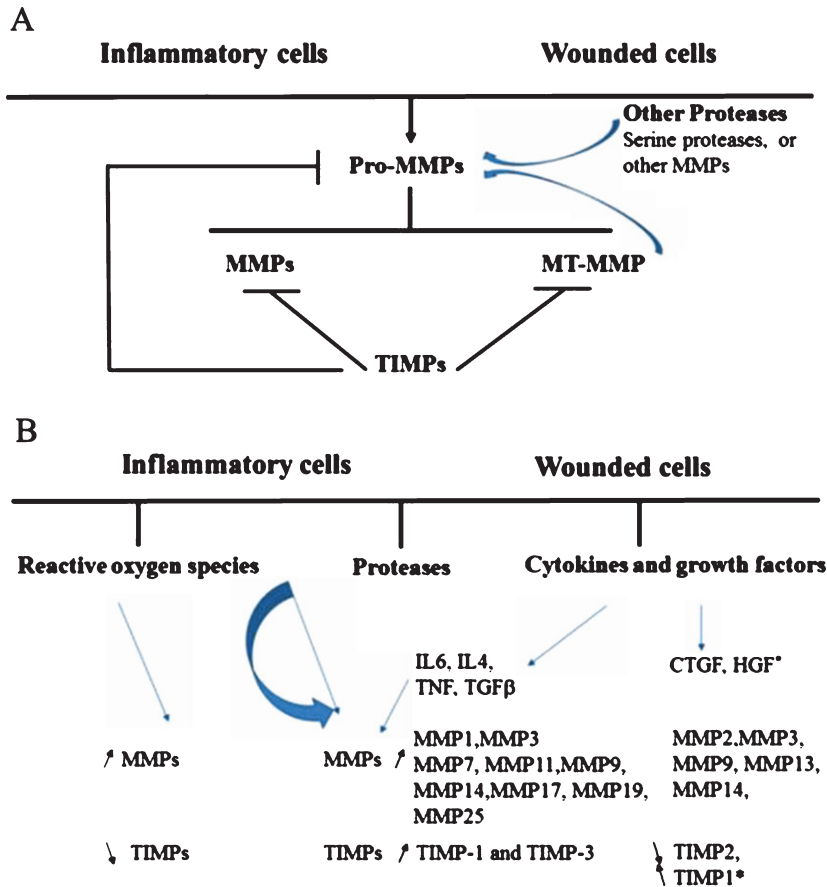
Fig. 1. Schematic representation of MMPs activation in inflammatory and wound conditions. Panel A: Overview of MMPs production, activation and their inhibition by TIMPs. Panel B: Modulation of MMPs/TIMPs production by reactive oxygen species, other proteases and by cytokines and growth factors released in inflammatory and wound conditions. These regulations are reported in the literature and may depend on cell types and tissue microenvironment. Pro-MMPs are the inactive MMPs forms; MT-MMPs membrane-type MMP; TIMPs, Tissue Inhibitor of Metalloproteinases. Thin curved arrow indicates MMP activation and ⊣ MMPs inhibition.

neuromuscular junctions [44, 45]. Upon prolonged denervation, they maintain a normal topography with preserved agrin and Musk at denervated endplates [5].

MMPs have an essential role as regulators of microenvironmental changes. They participate to cell migration by hydrolyzing ECM components and releasing cryptic fragments with different biological activities. MMPs and their related ADAMs (a disintegrin and metalloproteases) and ADAM-TSs (ADAMs with thrombospondin repeats) families are involved in shedding growth factors or cell-surface-adhesion molecules such as syndecan-1. From simple hydrolytic enzymes, MMPs have evolved to regulators of signal transduction, of innate and adaptive immunity, and modifiers of cellular/molecular phenotype [46, 47].

In skeletal muscles, MMPs have been involved in cell migration and fusion. On one hand, MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, and MMP-14 enhance myoblast migration [48–54]. On the other hand, MMP-7, MMP-9, MMP-14 are involved in cell fusion [48, 49, 52, 53, 55–58]. Further, MMP-2, MMP-10, MMP-14 proved to be essential for successful muscle regeneration: MMP-2 and MMP-14 act on the maturation of muscle fibers by controlling angiogenesis [42, 43, 59] whereas MMP-10 is involved in CXCR4/SDF1 signaling axis that is essential for efficient skeletal muscle regeneration [60, 61]. Finally, MMP-2 and MMP-9 may potentially be involved in muscular dystrophies and muscle atrophy. Indeed, α and β dystroglycan are ascertained and direct targets for MMP-2 and MMP-9

[62, 63] as originally proposed for β-dystroglycan processing by MMPs [64]. Furthermore, intracellularly localized MMP-2 [65] is involved in muscle fibers atrophy in various physiological and pathological situations [66–70]. This activity probably relies on MMP-2 ability to hydrolyze sarcomeric proteins such as troponin I, myosin light chain-1, titin, and α-actinin [71–73].

MMPs Inhibitors: The physiological (TIMPs) and synthetic inhibitors (MMPIs)

The TIMP family is composed of four members (TIMP-1,-2,-3 and -4) with significant homology that inhibit MMPs with some specificity [74, 75]. Originally, TIMPs are thought to function exclusively as endogenous inhibitors of MMPs thereby modulating MMP-mediated ECM degradation. However accumulating evidence indicate they are multifunctional proteins involved in various biological activities that may or may not depend on their inhibitory function and range from cell growth and differentiation, to cell migration, invasion, angiogenesis, survival and apoptosis depending on cell and tissue context [76–82]. TIMP-1 promotes cell proliferation in a wide range of cell types and regulates apoptosis. TIMP-2 is involved in MMP-2 activation through association with MMP-14. It contributes to ECM protection from proteolysis and increases both fibroblast proliferation and collagen production. TIMP-3 has pro-apoptotic activity whereas TIMP-4, the most recently identified and least studied, is reported to modulate angiogenesis. TIMPs and MMPs are regulated in a similar or reciprocal manner whereas cytokines and growth factors regulate TIMPs in tissue-specific, constitutive, or inducible manner [78].

In skeletal muscles, different TIMPs have been implicated in myoblasts fusion and myofibers maturation. The involvement of TIMP-1 in cell fusion has been suggested by the concomitance between MMP-9 downregulation and TIMP-1 upregulation during cell fusion [83] whereas Timp2 can be involved in skeletal muscle maturation directly or via formation of the TIMP-2/MMP-14/MMP-2 complex leading to MMP-2 activation. Timp-2 Knockout mice have deficient motor function with abnormalities of neuromuscular junctions, increased sprouting of intramuscular nerves and decreased muscle mass [84, 85]. Timp-3 regulates myogenesis via miR-206-TIMP3-TACE-TNF-α−p38 signaling pathway and acts as an On/Off switch by regulating autocrine release of Tumor Necrosis Factor-α (TNF-α) [86].

Clinical trials have used synthetic MMP Inhibitors (MMPIs) to limit the progression of diseases. They have been unsuccessful [87, 88] but underscored the necessity for designing more selective inhibitors that discriminate between the different members of the MMP family [89, 90].

MMPs are involved in skeletal muscle inflammation

Several members of the MMP family have been involved in the inflammatory process occurring after injury or disease [91]. Inflammation is an essential step in the initiation and progression of tissue remodeling and entails the degradation and reorganization of the ECM scaffold to which MMPs are important contributors. Yet, despite its importance in host defense and tissue repair, if the inflammatory process becomes excessive or chronic, it associates with organ dysfunction and exacerbation of pathological features [92]. The pattern of MMPs/TIMPs regulation in non-pathological or pathological remodeling of skeletal muscles has been reviewed [36] and is summarized in (Table 2). Recently, experimental findings have characterized the involvement of MMP-10 (stromelysin-2) in muscle regeneration [61] and report transient MMP-13 upregulation during muscle injury [50].

MMP-9 is the most widely documented protease in the inflammatory process that characterizes the initial stages of muscle injury. MMP-9 increase correlates with the invasion of necrotic tissue by inflammatory cells, more particularly polymorphonuclear neutrophils (PMN) and activated satellite cells [7, 93]. Increased MMP-9 expression/activity quantitatively and qualitatively correlates with different stages of inflammation. An early phase of dramatic increase of MMP-9 protein corresponds to the initial flux of PMN into the necrotic tissue followed by a second phase of massive invasion by macrophages during which MMP-9 protein level is less intense but gelatinase activity more potent [7]. Such increase is predictable since white blood cells produce MMPs that facilitate their migration [94] and regulate their function [95, 96]. MMP-9 produced by these cells [97] is stored in granules [98–100] being, hence, immediately available for degranulation thereby facilitating transmigration through the vessel/capillary wall. These cells also regulate MMP-9 production in a time and phase specific manner [101] similar to sequential variations of MMP-9 at the early stages of muscle regeneration.

Table 2

MMPs and TIMPs expression in neuromuscular diseases and their animal models. *ALS TgSOD1 (G93A):* Transgenic mouse model of Amyotrophic Lateral Sclerosis carrying mutant Super Oxide Dismuthase gene, CSF: Cerebro Spinal Fluid; *CXMD*: canine x-linked muscular dystrophy; *mdx*: x-linked muscular dystrophy; ND: Not determined, *Neu1⁻/Neu1⁻* mice: Neuraminidase deficient mice

Inflammatory Myopathies	MMP expressed	MMP localisation	TIMPs expressed	Circulating	References
– Inclusion body myositis	MMP-2, MMP-9 ↗	MMP-9 in atrophic fibers & inflammatory cells		MMPs unchanged	[22, 25]
		MMP-1 and MMP-9 (mRNA)++		TIMPs unchanged	
– Sporadic inclusion body myositis	MMP-2 and MMP-9	MMP-2 in rimmed vacuoles		MMPs unchanged	[18]
		MMP-9 cytotoxic T cells		TIMPs unchanged	
– Polymyositis		MMP-2 and-9 MHC class1 + fibers		MMPs unchanged	[18]
		MMP-7 in inflammatory cells		TIMPs unchanged	[22]
		MMP-1 around sarcolemma & in fibroblasts			
		MMP-1 and MMP-9 (mRNA)+++			
– Dermatomyositis	MMP-2	MMP-9 in perifascicular atrophic fibers		MMPs unchanged	[22, 25]
		MMP-1 around sarcolemma & in fibroblasts		TIMPs unchanged	
		MMP-1 and MMP-9 (mRNA)+++			
Muscular Dystrophies *Human*					
– Duchenne muscular dystrophy	MMP-1, MMP-2, MMP-9	MMP-1 around individual or groups of muscle fibers	TIMP-1 & TIMP-2	MMP-9 and TIMP-1	[27, 33, 111, 214]
		MMP-2 surface of few myofibers and around blood vessels			
		MMP-9 in blood vessels, mononuclear cells and cytoplasm of regenerating fibers			
– Emery-Dreifuss muscular dystrophy *Animal models*	MMP-2, MMP-9, MMP-14			MMP-2, MMP-9, MMP-14, TIMP-1	[215]
– *mdx*	MMP-2, MMP-9, MMP-13	MMP activity in ECM around myofibers and in the sarcoplasm MMP-9 mRNA in inflammatory and satellite cells	TIMP1 (mRNA) ↗	MMP-9 ↗	[7, 203, 216]
			TIMP2,-3 (mRNA) ↗		
	MMP3,-8,-9,-10,-12,-14,-15 (mRNA) ↗ MMP11, ↘				[32, 61]
– *CXMD*	MMP-2, MMP-9, MMP-14				[20]

(Continued)

Table 2
(*Continued*)

Inflammatory Myopathies	MMP expressed	MMP localisation	TIMPs expressed	Circulating	References
Neurodegenerative Muscular disorders					
Human					
– Amyotrophic lateral sclerosis (affected patients)	MMP-2,-7,-9, MMP-14	MMP + in normal and atrophic fibers		MMP-1, -2, -9, -14	[105, 217, 218]
– Spinal muscular atrophy	MMP-7, -9	MMP + in normal and atrophic fibers		MMP-9 ↗	[102]
					[103]
– Chronic axonal neuropathies	MMP-9	MMP + in normal and atrophic fibers		TIMP-1 (CSF) ↗	[105]
– Guillain Barre				MMP-9 ↗ TIMP-1 ↗	[219]
Animal models					
– *Neu1⁻/Neu1⁻* mice	MMP-2,MMP-9 ↗			ND	[220]
– *ALS TgSOD1(G93A)* low copy number and low progression	MMP-2, MMP-9			MMP-2,-9 ↗ activity associate with disease onset	[221]
– *ALS TgSOD1(G93A)* high copy number and rapid progression	MMP-2, MMP-9			MMP-2,-9 ↗ activity associate with disease onset	[221]
Autoimmune Myopathies					
– Myasthenia Gravis: Ocular and Generalized subgroup (17% seropositive and 10% seronegative)	MMP-2, MMP-3, MMP-9 ↗			MMP-2,-3,-9	[217, 222–224]

MMP upregulation correlates with inflammation in muscular dystrophies and inflammatory myopathies

In a number of muscle pathologies, MMP overexpression correlates particularly but not exclusively with inflammation (Table 2). In muscular dystrophies and inflammatory myopathies, MMP elevation is due, at least in part, to inflammation whereas in motor neuron and peripheral nervous system diseases with secondary muscle manifestations, the evidence points towards an association with tissue remodeling [102–105]. In muscles of Duchenne Muscular Dystrophy (DMD) patients, the presence of inflammatory cells [106–109] correlates with high MMP-9 [17, 20, 110] in blood vessels, mononuclear cells and regenerating fibers [111]. MMP-9 is also elevated in the serum of dystrophic mice [36] and DMD patients [33]. Intense MMP-1 signal is reported around individual or small groups of necrotic muscle fibers and areas containing a high density of macrophages [111]. TIMP-1 is elevated in the serum, plasma, and muscle biopsies of DMD patients [27, 33] and increased immunolabeling is observed in the endomysium (unpublished results). TIMP-1 and MMP-2 mRNAs localize to areas of degeneration/regeneration whereas TIMP-2 transcripts distribute more homogeneously in mesenchymal fibroblasts [27].

In inflammatory myopathies, there is no evidence of elevation of MMP or TIMP levels in the serum [22] but MMP-9 up-regulation is found in muscles of Polymyositis, Dermatomyosistis, and Inclusion Body Myositis patients [22, 25, 112]. Immunolabeling localizes MMP-9 to atrophic myofibers or is restricted to CD8+ cytotoxic T cells [18]. MMP-1 transcripts are also upregulated in these pathologies, and the protein localizes around the sarcolemma and in cells resembling fibroblasts. MMP-7 strongly labels myofibers invaded by inflammatory cells in polymyositis cases only [25] and MMP-2 has a similar distribution but weaker intensity.

Effects of MMP modulation in Duchenne muscular dystrophy

Overexpression or inhibition of individual MMPs may deteriorate or ameliorate skeletal muscle structure and function depending on the specific outcome one is investigating. Examples of deleterious effects are provided by dystrophic and Amyotrophic Lateral sclerosis (ALS) mouse models in which MMP-9

overexpression has been incriminated in the aggravation of dystrophy in *mdx* mice [110] and selective denervation of fast muscles in the SOD1 ALS mouse model [113]. In this context, MMP-9 inhibition in *mdx* mice was reported to reduce necrosis, fibrosis, increase the levels of β-dystroglycan and improve muscle force production [31, 32, 110, 114]. It is thought to act by favoring satellite cell proliferation, emergence of M2 pro-myogenic macrophages, increase of the expression of Notch ligands, receptors and components of canonical Wnt signaling while decreasing non-canonical Wnt signaling [30]. These characteristics represent circumstantial evidence that fit well with structural and functional improvement but the effect of MMP-9 inhibition on satellite cell proliferation and improvement of muscle regeneration remains controversial. High MMP-9 levels in myogenic cells favored cell migration, differentiation and engraftment upon grafting into dystrophic mice [57] and its inhibition delayed myoblast proliferation and differentiation [115] causing, in the long term, impairment of muscle regeneration, reduction of muscle force and the development of fibroadipogenic tissue [26]. L-arginine, Nitric Oxide (NO) donors, Doxycycline (Dox) and Minocycline (Min) or other natural substances have the same beneficial effect. These substances decrease MMP-9 levels, orchestrate inflammation towards the "repair mode", favor preservation of structural integrity and reduce fibrosis in different mouse models [31, 116–118].

As far as we know today, the deficiency or inhibition of other MMPs have a detrimental effect on skeletal muscle regeneration/maturation. MMP-2 deficiency impairs the maturation of regenerating skeletal muscles by inhibiting angiogenesis [59] while MMP-10 deficiency is reported to worsen muscle dystrophy, delay muscle regeneration, impair the recruitment of endothelial cells and reduce the levels of ECM proteins by a mechanism associated with Vascular Endothelial Growth Factor (VEGF)/Akt signaling [61].

MMPs/TIMPs are involved in muscle fibrosis

Fibrosis is a multifactorial process that integrates multiple cellular and biochemical events between different cell types, growth factors, inflammatory/fibrogenic cytokines and proteolytic enzymes resulting in the alteration of the tissue microenvironment. The build-up of fibrosis reflects a disruption of the balance between synthesis and degradation of ECM components, accomplished by MMPs and proteases of the plasminogen activation system [36, 55, 119]. Myofibroblasts, the key cellular mediators of fibrosis, are increased in fibrotic tissues [111, 120] and contribute to ECM and protease production. Their existence is still debated because we lack reliable markers to discriminate between myoblasts and myofibroblasts [121, 122].

Myofibroblasts arise from independent sources [123–127] and help in the repair process. They induce re-emergence of embryonic ECM proteins that favor tissue reconstitution [128]. The activation of myofibroblasts, necessary for tissue repair, involves paracrine signals derived from lymphocytes and macrophages, autocrine factors, pathogen- (PAMPs) or damage- (DAMPs) associated molecular patterns [129] and mechanosensing [130]. Fibroblasts respond to signals from immune cells that produce cytokines, growth factors and proteases that modify the phenotype of neighboring cells. Similarly, the behavior of different cells types sharing the same environment is profoundly influenced by the disturbance and remodeling of ECM. Increased tissue stiffness and decreased elasticity generate a mechanical stress that exacerbates tissue injury and perpetuates the activation of fibroblasts [128, 131].

Persistence of inflammation favors the transformation of wound healing to fibrosis

The wound healing response involves transitory, highly orchestrated events consisting of interrelated dynamic phases with overlapping time course that lead to tissue replacement [132]. They necessitate high levels of extracellular proteolytic activity attributed to MMPs, serine proteases and cysteine proteases [133]. The fibrotic response is initiated by innate wound healing mechanisms involving inflammatory myeloid cells and adaptive immune activation that modulate synthesis and deposition of ECM by myofibroblasts [134]. The accumulation of fibrin and fibronectin, immediately after trauma, forms a provisional matrix that serves to fill in the lesion and allow inflammatory cells to migrate into the wound [135, 136]. The platelets present in the clot participate in the recruitment of inflammatory cells, by releasing growth factors such as Platelet Derived Growth Factor (PDGF), potent chemoattractant for inflammatory cells and TGF-β1 which stimulates ECM synthesis [134]. Innate immunity is activated in response to molecular signals such as cryptic fragments, liberated by the digestion of ECM components, endowed with chemoattractant properties due

to structural relatedness to Cystein X Cystein (CXC) chemokines [137]. Endogenous myofiber proteins and mitochondrial-DAMPs, released into the circulation, generate a systemic inflammatory reaction and activate PMN through formyl peptide receptor-1 and toll-like receptor (TLR) 9 [138]. In turn, TLR activation initiates signaling cascades that converge at the NF-κB pathway activating the synthesis of inflammatory cytokines and β-defensins [139, 140]. TLR-9 activation by mitochondrial DAMPS induces the release of MMP-8, which, together with MMP-9, aid in PMN tissue penetration and recruitment [36, 138]. The second wave of inflammatory cells, the monocyte/macrophages, have a remarkable plasticity and ability to exacerbate, suppress or reverse fibrosis [141–143]. During the evolutionary phases of wound healing, macrophages with divergent functions arise progressively in response to exposure to fate determining mediators. Initial amplification of the inflammatory response is followed by a phase during which inflammation is resorbed and tissue repaired [144–146]. The neutrophil-specific protease Membrane-Type 6 Matrix Metalloproteinase (MT6-MMP/MMP-25) has a salient role in favoring monocyte chemotaxis and resolution of inflammation. It regulates the shift of macrophages from pro- to anti-inflammatory phenotype and contributes to efferocytosis by increasing phagocytic removal of neutrophils carrying "eat-me" signals [35]. Efferocytosis triggers specific downstream intracellular signal transduction pathways resulting in the production of anti-inflammatory, anti-protease and growth-promoting effects that favor the replacement of dead cells [147, 148]. Activated fibroblasts acquire a myofibroblast phenotype, synthesize and deposit ECM to replace the provisional matrix and contribute to the contraction and maturation of granulation tissue [149]. They also produce MMPs that disrupt the basement membrane allowing cell migration at the site of injury. Scar formation further involves progressive remodeling of the granulation tissue by proteolytic enzymes and their inhibitors, followed by a resolution phase leading to reconstitution of the damaged tissue and reduction of myofibroblast number by apoptosis [150]. Recurrent necrosis/regeneration, like in DMD, results in perpetuation of DAMPs release and chronic low-grade inflammation with persistence of neutrophils and monocytes at the injury site. These produce proteases, cytokines as well as reactive oxygen and nitrogen species (ROS/RNS) causing supplementary damage [151] and generating a prolonged inflammatory reaction, chemokine/cytokine production with consequent modifications of gene expression, cell functions and phenotype. In such conditions, wound healing is sustained with continuous degradation and deposition of ECM matrix resulting in fibrosis (Fig. 2).

Skeletal muscle fibrosis: The result of an interplay between cytokine/chemokines and growth factors which affect cell fate and levels of MMPs/TIMPs

Permanent induction of the wound healing response in muscles generates continuous exudation of plasma proteins, recruitment of inflammatory cells, activation of inflammatory mediators and increased expression of MMPs. These induce a cascade of molecular modifications that affect tissue reconstitution. During these modifications, the balance between hydrolysis of ECM components and their synthesis is deregulated in favour of hydrolysis in a first stage followed by a resolution phase during which inhibitors are upregulated. The end-result of these continuous cycles of necrosis-regeneration can, therefore, be associated with an increase of both MMPs and TIMPs, as occurs in DMD muscles.

Inflammatory cells contribute to increased fibrosis by producing cytokines/chemokines [109, 122, 146, 152] that regulate MMPs. These in turn, modulate the activities of cytokines [153, 154], their receptors and ligands, which are abundant in injured muscles [155–159]. Among them, SDF-1/CXCR, CCL2(MCP-1)/CCR2 and M-CSF/M-CSFR axis have a beneficial effect on muscle recovery [160, 161]. The first one improves cell mobilization and migration by increasing MMP-2 and MMP-9 expression [162] and interferes in muscle regeneration by a mechanism dependent on MMP-10 [60]. The second two [163, 164] participate in the recruitment of monocytes/macrophages that help to repair the injury by producing Insulin Growth Factor-1 (IGF-1). The mitogenic IGF/IGF receptor autocrine loop is partly regulated by a family of six IGF Binding Proteins (IGFBPs) proteolyzed by MMP-1, MMP-3 and MMP-9 [165–167]. In contrast, the reduction of IGF-I/insulin signaling promotes fibrosis by regulating the interaction between p-Akt and Smad3. This allows the dissociation of Smad-3 and its nuclear translocation and results in increased TGF-β1 signaling and fibrosis [168].

Growth factors also influence satellite cell activation, (trans)-differentiation and muscle regeneration. TGF-β induces phenotypic transformation of
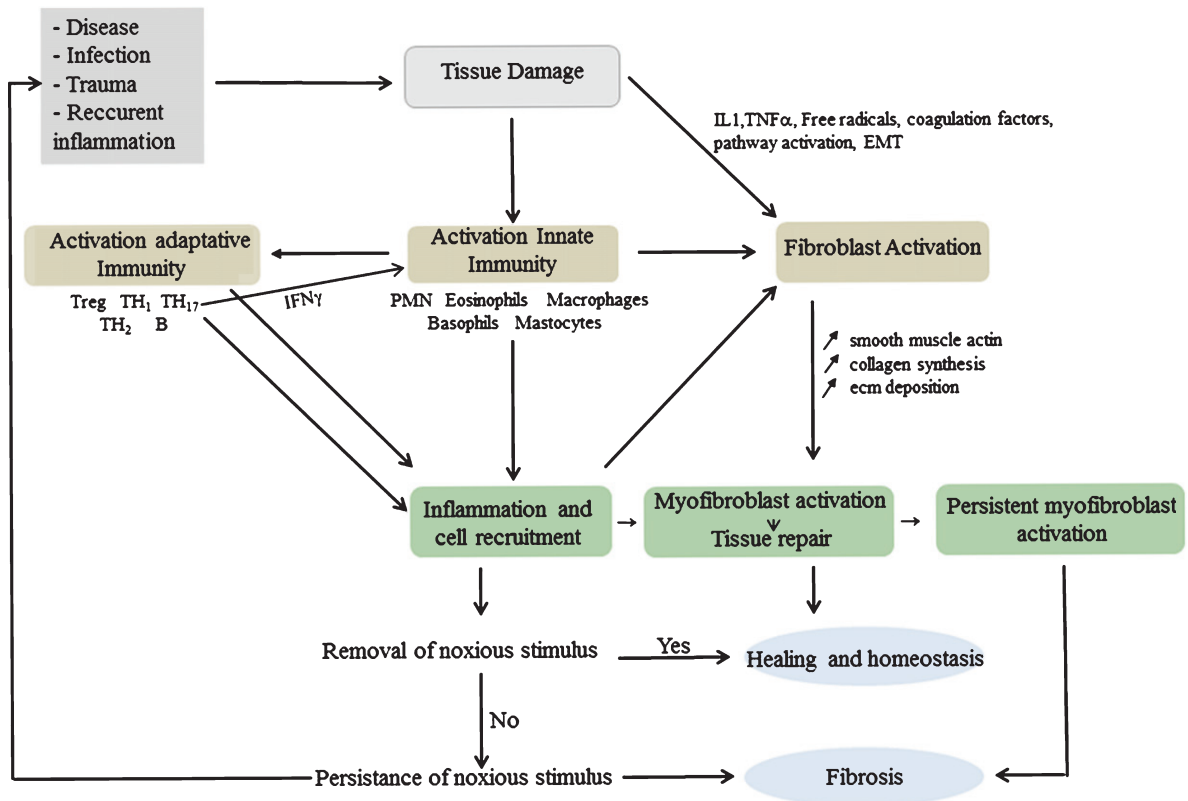
Fig. 2. Schematic representation showing the involvement of inflammatory cells in the regulation of myofibroblast activation in wound healing and fibrosis. Tissue injury triggers a cascade of interconnected steps to restore tissue homeostasis. The initial activation of coagulation pathway is followed by an acute inflammation and activation of innate immune mediators including macrophages, neutrophils and dendritic cells. Cytokines liberated by injured and inflammatory cells subsequently regulate the activation of adaptive immune response. Inflammatory cells and immune mediators attempt to eliminate noxious stimuli and activate fibroblasts into myofibroblasts that orchestrate angiogenesis and regulation of ECM components. Failure to eliminate factors causing the injury perpetuates wound healing and inflammation ultimately resulting in fibrosis.

myoblasts into myofibroblasts, downregulates myogenic regulatory proteins [126], stimulates collagen synthesis and inhibits its degradation [169, 170] by reducing MMP activity and promoting TIMP expression [132]. TGF-β is activated by MMP-9 [171] and it is neutralized by decorin. The latter is cleaved by MMP-2, MMP-3 and MMP-9 that release TGF-β from the complex [172]. The action of TGF-β is synergized by Connective Tissue Growth Factor (CTGF), incriminated in multiple fibrotic diseases [173, 174] and upregulated in DMD muscles [175]. The modular domains composing the protein have independent functions and can be cleaved by MMP-1, -2, -3, -7, -9, -13, elastase, and plasmin [176]. CTGF overexpression in normal skeletal muscles induces dystrophic features [177] possibly through the c-terminal module IV shown to have an immuno-modulatory function [178]. Its inhibition reduces skeletal muscle impairment, reverses fibrosis and

improves muscle strength without affecting TGF-β [179, 180] indicating that CTGF is, by itself, a critical modulator of fibrosis.

Activated metalloproteinases from both MMPs and A Desintegrin And Metalloproteinase (ADAMs) families signal through their receptors and downstream mitogen-activated kinases to activate the transcription of immediate-early genes, mediators of fibrosis [181]. Two ADAMs, notably ADAM-17 (Tumour Necrosis Factor-α Converting Enzyme TACE, or MT4-MMP) and ADAM-12 are key players in the pathogenesis of inflammatory and fibrous connective tissue diseases. TACE overexpression and activation in dermal fibroblasts, activates Epidermal Growth Factor Receptor (EGFR) by its ligands and stimulates type I collagen expression [182]. In a model of cardiac fibrosis induced by angiotensin II [183], TACE overexpression induces transcriptional regulation of MMP-2 and ADAM-12 that activate

TGF-β signalling independently of its protease activity [184]. This leads one to question whether the blockade of fibrosis in dystrophic *mdx* mice by ACE inhibitors inhibits only CTGF expression as hypothesized [180] or whether it also affects TACE expression and activation. TACE release of TNF-α activates the myogenic program [185] and stimulates collagen synthesis in fibroblasts [186] exerting direct adverse effects on skeletal muscle function and regeneration. Its blockade reduces necrosis and contractile dysfunction in response to eccentric exercise [187, 188] and significantly reduces the levels of TGF-β1 and type I collagen mRNA in *mdx* mice [189].

TIMPs and other protease inhibitors interfere in the fibrotic process. Exposure of cardiac fibroblasts to any of the four TIMPs stimulates cell proliferation and induces a significant increase of α-SMA but only TIMP-2 increases both fibroblast proliferation and collagen production [81]. The occurrence of a similar process in skeletal muscles needs to be investigated. We also need to, precisely, define the effects of all four inhibitors on fibroblast and myoblast proliferation, differentiation and ECM production. Finally, a putative serine protease inhibitor *HE4* (encoding human epididymis protein 4), that inhibits serine proteases Prss23 and Prss35 as well as collagenase, MMP-2, MMP-9 and trypsin, is upregulated in fibrosis-associated fibroblasts of mouse and human kidneys and in serum of patients with chronic kidney diseases [190]. Its inhibition accelerates collagen I degradation, inhibits fibrosis and restores higher levels of Prss23 and Prss35 indicating that *HE4* serves as biomarker and therapeutic target for the treatment of renal fibrosis. To date, *HE4* expression is still unexplored either in skeletal muscles and serum of dystrophic patients or in other fibrotic diseases.

CONCLUDING REMARKS

Although we have gained some insight about the expression and role of certain MMPs and TIMPs in skeletal muscles, we still have much to learn before being able to use them for therapeutic perspectives. Clearly, MMP-2 and its activator MMP-14 are linked to angiogenesis and vessel growth [59] and MMP-2 contributes to satellite cell activation by mediating HGF shedding from extracellular matrix in response to NO [191]. Furthermore, MMP-9 and MMP-10 are important for muscle regeneration and one can assume, although it remains to be experimentally proven, that deficiency of MMP-25, MMP-28 or

MMP-24 would have a deleterious effect on muscle regeneration because MMP-25 and MMP-28 influence macrophage progression [35, 192] and MMP-24 regulates stem cell quiescence [193].

Another observation concerns the specific issue of inhibiting proteases in general and MMPs in particular as a complementary therapeutic approach to cell or gene therapy. Many reviews have highlighted the potential benefit of inhibiting diverse classes of proteases in muscular dystrophies placing "MMPs" among potential therapeutic targets [194–196]. This can be misleading in the absence of a comprehensive view of the role played by these proteins in skeletal muscles. Clearly, it is only short term inhibition of MMP-9 or its signaling cascade that was proven to improve skeletal muscle and tendon healing and ameliorate structure and function of dystrophic muscles [30, 32, 110]. What MMP-9 inhibition is, most likely, doing is limiting **"excessive/prolonged"** inflammation and attenuating its micro-environmental consequences possibly by cooling-off inflammation [197]. Alternatively, reduction of hydrolytic enzymes reduces inflammation and ROS production causing a reduction of pro-MMP-1, -8, -9 activation and oxidative cell injury [198, 199] expected to limit DAMPs release, reduce the activation/perpetuation of the immune response and decrease MMP-9 levels [198, 199]. Several substances that modulate p38-MAPK, NF-kB, NO-cGMP [116, 118, 200–203], inhibit TGF-β [204], reduce oxidative stress [205] or inflammation [206, 207] have had beneficial effects in muscular dystrophies and deserve to be tested, in preclinical settings, in combination with *short-term, transitory* MMP-9 inhibition. With the exception of MMP-9 that plays a dual role in skeletal muscle regeneration/dystrophy [110, 208, 209], the inhibition of other MMPs proved they are essential for efficient muscle regeneration -this review and [210]-, reduction of fibrosis [211] and amelioration of myoblast engraftment following implantation into dystrophic mice [212]. This confirms the necessity for questioning long-term inhibition of MMPs not only in cancer and inflammation [213] but also in muscular dystrophies and other muscle diseases.

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