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Inflammation induced loss of skeletal muscle

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Introduction

Inflammation is an important contributor to the pathology of diseases implicated in skeletal muscle dysfunction. A number of disorders including inflammatory myopathies and chronic obstructive pulmonary disorder (COPD) are characterized by chronic inflammation or elevation of the inflammatory mediators. While these disease states exhibit different pathologies, all have in common the loss of skeletal muscle mass and a deregulated skeletal muscle physiology. Pro-inflammatory cytokines are key contributors to chronic inflammation found in many of these pathologies. This section of the review focuses on some of the known inflammatory disorders like COPD, Rheumatoid Arthritis (RA) and inflammatory myopathies that display skeletal muscle atrophy and also provides the reader an overview of the mediators of inflammation, their signaling pathways, and mechanisms of action.

Myogenic Regulatory Factors

Skeletal muscle arises from mesodermal precursor cells whose differentiation is controlled by four highly conserved basic loop helix (bHLH) proteins known as Myogenic Regulatory Factors (MRFs). These MRFs, namely MyoD, Myf5, MRF4, and myogenin have overlapping patterns of gene expression. However, each plays a distinct role in myogenesis[1]. Myogenin is the only MRF required for viability[2; 3]. Mice lacking myogenin die at birth and have severe muscle defects. Although the absence of Myf5, MRF4, and MyoD is not lethal, each mutant nevertheless exhibits a distinct phenotype[4].

Signaling pathways involved in skeletal muscle development

In response to environmental cues, skeletal muscle activates a variety of signaling pathways to undergo remodeling and sustain a muscle performance. The Wnt pathway is required during embryonic muscle development as well as during muscle stem cell self renewal and differentiation in the adult[5]. Insulin-like growth factor (IGF-1) exerts a tremendous

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influence on skeletal muscle proliferation and myoblast differentiation. IGF-1 signaling also induces hypertrophy to skeletal muscle cells by stimulating the phosphatidylinositol-3 kinase (PI3K)/Akt pathway, which activates mTOR and other downstream targets that stimulate protein synthesis[6; 7]. Mice null for the IGF-1 receptor exhibit reduced skeletal muscle mass and growth retardation[8; 9], whereas muscle specific overexpression of IGF-1 causes muscle hypertrophy and increases protein synthesis.[10; 11; 12]. Fibroblast growth factor (FGF) is another signaling effector that plays essential roles in skeletal muscle development, as loss of FGFR1 signaling leads to reduced skeletal muscle mass and perturbed myofiber organization[13]. While some pathways positively influence the development of skeletal muscle, others act as negative modulators. During the induction of muscle atrophy, distinct transcriptional pathways are activated, which catalyze increased protein turnover and degradation[14; 15]. One such pathway is the ubiquitin-proteasome system[16]. In multiple models of skeletal muscle atrophy, E3 ubiquitin ligase genes, MurF1 and MAFbx/Atrogin-1 are significantly elevated[17; 18; 19; 20]. The inhibition of MuRF1 and MAFbx/Atrogin-1 involves FoxO family of transcription factors, which are phosphorylated by Akt [21; 22]. Upon dephosphorylation, FoxO transcription factors namely FoxO1 and FoxO3 translocate to the nucleus and upregulate MurF1 and MAFbx/Atrogin-1[21].

In addition, the nuclear factor kappa B (NF-κB) signaling pathway has also been implicated in regulating the atrophy of skeletal muscle. In cultured C2C12 myoblasts NF-κB is essential for TNF-α to mediate an inhibition of muscle differentiation[23]. Likewise, skeletal muscle specific over expression of the NF-κB pathway promotes severe atrophy via the regulation of MuRF1.

Regeneration of skeletal muscle post damage or injury

Skeletal muscle cells possess the remarkable ability to regenerate after injury. Whether the injury is inflicted on a day-to-day basis and involves normal wear and tear, or a direct physical trauma like extensive physical exercise, the process of muscle regeneration is divided into two main phases; a degenerative phase followed by a regenerative phase. The degenerative phase is characterized by extreme muscle necrosis and disruption of the muscular architecture. This early phase is also accompanied by accumulation of an inflammatory infiltrate and activation of quiescent, resident muscle stem cells called satellite cells, which are essential for efficient muscle regeneration[24; 25]. The signals generated from an injured muscle are thought to activate inflammatory cells residing within the muscle, which in turn provide chemotactic signals to other circulating inflammatory cells. Neutrophils promote revascularization in muscle cells and are amongst the first cells to arrive at the site of injury. Among the cells of the myeloid lineage, eosinophils and macrophages also positively influence muscle regeneration. Eosinophils promote muscle regeneration by removing cellular debris and activating fibroblastic/adipogenic mesenchymal progenitors (FAPs)[26]. Two distinct populations of macrophages, which are present at the site of injury at different times, play key roles in muscle regeneration[27]. The pro-inflammatory M1 subtype is present 1 or 2 days post-injury and coincides with the degenerative phase of muscle repair, marked by activation and proliferation of satellite cells. Conversely, the anti-inflammatory M2 subtype peaks at 4 to 5 days post-injury and is associated with the regenerative phase of muscle repair[27]. Targeted ablation of neutrophils,

monocytes, and macrophages severely disrupts muscle regeneration demonstrating their importance in the repair process. Recent studies have highlighted the role of non satellite cells in muscle regeneration. These include mesoangioblasts, which are associated with blood vessels[28; 29; 30] and interstitial cells that express PICs, PW1 interstitial cells (PW1)[31]. Furthermore, a permissive cellular environment that promotes interactions between FAPs and satellite cells helps regulate muscle homeostasis[32; 33].

The regenerative phase of muscle repair is characterized by cellular proliferation of the activated satellite cells, which re-enter the cell cycle and expand. Activated satellite cells express the transcription factor Pax7 which is required for expansion and cell survival, and further express MyoD that commits cells to a myoblast fate[34; 35; 36]. The process of differentiation is largely driven by MyoD and other MRFs such as myogenin, which in part regulate the decline of Pax7, which if left intact, signals cells to self-renew to satellite cells for a subsequent round of regeneration [37]. Committed myoblasts proceed through the differentiation program, characterized by fusion with neighboring myoblasts, to form terminally differentiated, multinucleated myotubes. A successfully regenerated, mature muscle fiber is almost indistinguishable from a non-injured, undamaged muscle fiber.

Mediators of inflammation

During injury to adult skeletal muscle there are a number of key inflammatory mediators that govern the repair process. Both physiologic and pathogenic activities have been attributed to a selective number of inflammatory cytokines described below.

Interferon gamma (IFN-γ)

IFN-γ belongs to the type II IFNs and is secreted by $CD4^+$ T helper cells, CD8 cytotoxic T cells, and natural killer cells (NK) cells[38; 39]. Recent evidence suggests that macrophages, dendritic, B and professional antigen presenting cells (APCs) also secrete IFN-γ[40; 41; 42; 43]. Mice lacking IFN-γ are born normally, but are more susceptible to bacterial, viral, and parasitic infections[44]. IFN-γ acts as an antiviral factor and influences a myriad of cellular and physiological processes. In addition, IFN-γ provides cytotoxic immunity by upregulating the major histocompatibility complex (MHC) class I and class II antigens. IFN-γ and IL-12 are the main cytokines that direct the primary response to antigen towards Th1 differentiation, while IL-4 is responsible for directing the antigen response towards a Th2 differentiation. IFN-γ stimulates IL-12 production in phagocytes and inhibits IL-4 secretion[45; 46]. The cytokine also primes macrophages for a rapid and elevated response to lipopolysaccharide (LPS) and toll-like receptor (TLR) agonists[45], and contributes to multiple M1 macrophage dependent activities that include enhanced pinocytosis, increased microbial killing activity, induction of the NADPH-dependent phagocyte oxidase (NADPH oxidase) system, and priming for NO (nitric oxide) production[47].

IFN-γ primarily signals through the JAK (Janus kinase)-STAT1 (Signal transducer and activator of transcription) pathway. The IFN-γ receptor comprises of two signal transducing IFNGR2 chains, with associated signaling machinery, and two ligand binding IFNGR1 chains. Both the IFNGR1 and IFNGR2 belong to the class II cytokine signaling family[48]. When IFN-γ binds to its receptor, the receptor associated protein tyrosine kinases, JAK1 and

JAK2 are activated[49]. This leads to the phosphorylation of STAT1, which then dimerizes and subsequently translocates to the nucleus, where it binds to its target promoters, including the pIV promoter of *CIITA*[50], to activate gene expression. The JAK1-STAT1 pathway has been shown to play prominent roles in myogenesis[51]. JAK1 and STAT1 are required for myoblast proliferation and display a potent anti-differentiation effect, which appears specific to STAT1, as similar activities cannot be reproduced by family members, STAT2, 3, 5A, or 5B.

Numerous studies have also shown that IFN-γ influences skeletal muscle homeostasis and repair[52]. Transient administration of exogenous IFN-γ following injury has been shown to improve healing and limit fibrosis[53]. This response is consistent with the phenotype that IFN-γ null mice exhibit defective muscle regeneration and development of fibrosis[52]. During early stages of muscle regeneration, IFN-γ expression is upregulated in muscle itself [52] and its levels decline as the regeneration stage transitions from proliferation to differentiation. Mechanistically, IFN-γ improves muscle repair by regulating the migration of specific immune cells at the site of injury by upregulating chemokine and adhesion molecules that include chemokine C-C motif ligand 5 (Ccl-5, RANTES) and Ccl-2[54; 55; 56; 57] and intracellular adhesion molecule (ICAM).

Similar to inflammatory cytokines like TNF, where the effects on skeletal muscle differentiation appear to be dose dependent[58], IFN-γ is also able to impede myogenesis when administered in high doses *in vitro*. In addition, IFN-γ expression is elevated in *mdx* mouse muscles, which is a mouse model for muscular dystrophy, at a time of macrophage-mediated muscle damage[59]. Ablation of IFN-γ in the *mdx* animals improves muscle function and promotes muscle strength[60]. These types of studies reinforce the dose dependent effects of IFN-γ and show that at chronic levels this cytokine exhibits anti-myogenic properties. Recently, the mechanism by which IFN-γ inhibits muscle differentiation was resolved. The cytokine induces the expression of the MHC class II transactivator, CIITA, which acts by directly binding to and inhibiting the function of myogenin[61]. The absence of myogenin function leads to a reduction in muscle specific gene expression and transcription factors that drive terminal differentiation[61; 62; 63]. However, in IFN-γ treated myotubes, myogenin expression is unaffected. CIITA mediates the anti-differentiation activity of IFN-γ activity by catalyzing the initial recruitment of a Jumonji family protein JARID2, followed by the subsequent recruitment of the polycomb repressive complex 2 (PRC2) to the promoters of muscle specific genes[64]. Studies have shown that the PRC2 complexes are silenced during muscle differentiation[65]. However, elevated levels of circulating IFN-γ maintain the expression of PRC2 which silences muscle specific genes by methylating the DNA associated histone mark, H3K27[64].

Interleukin-17 (IL-17)

IL-17A and IL-17F belong to a six-member family of IL-17 cytokines[66]. Specialized T cells, known as Th17 cells, are the primary source of IL-17A and IL-17F in adaptive immunity[67; 68]. However, other sources such as lymphocytes and neutrophils also contribute to IL-17 production[69]. IL-17A, previously termed as CTLA8, signals via surface receptors

(IL-17R) on target cells. IL-17RA was the first receptor to be identified, followed by the subsequent identification of IL-17RB, IL-17RC, IL-17RD, IL-17RE[70; 71; 72].

IL-17 mainly mediates immune function by stimulating the production of pro-inflammatory cytokines TNF-α, IL-6, IL-1β, and chemokines C-X-C motif ligand 1 (CXCL1), C-C- motif ligand 2 (CCL2), CCL7, CCL20, as well as matrix metalloproteinase 3 and 9 (MMP3 and 9)[73; 74]. Albeit its importance in protecting the host from invasive pathogens, similar to IFN-γ, dysregulated IL-17 production can result in excessive cytokine production and chronic inflammation leading to tissue damage and autoimmunity. The IL-17 family has been implicated in several autoimmune diseases including multiple sclerosis (MS), RA and inflammatory bowel disease[75; 76]. Recent studies have shown that IL-17 mRNA is elevated in muscle biopsies from Duchenne muscular dystrophy (DMD) patients suggesting a possible pathogenic role[77].

Interleukin-6 (IL-6)

IL-6 is a pleiotropic cytokine which controls and coordinates multiple immune responses[78]. IL-6, unlike other cytokines has a unique property of exerting both pro and anti-inflammatory effects depending on the local tissue mileu of the immune cells and the micro environment[79]. The IL-6 family of cytokines includes IL-11, IL-31, IL-27, leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary inhibitory factor (CNTF), andcardiotropin-1 (CT-1)[79]. In classical IL-6 signaling, IL-6 exerts its signaling activities by binding to the membrane bound IL-6R receptor on the target cells. Subsequently, IL-6/IL-6R complex associates with a membrane glycoprotein receptor and a signal transduction subunit, gp130, which homodimerizes to allow signal initiation and activation of the JAK-STAT3, PI3K and ERK signaling pathways[80; 81]. The membrane bound IL-6 receptor, however, is expressed on selected cells such as neutrophils, macrophages, hepatocytes, and some T cells. IL-6 signaling can also occur in trans via gp130 and the soluble IL-6 receptor (sIL-6R). The trans signaling is critical for lymphocyte trafficking during inflammation, regulation of adhesion molecule expression on endothelial cells, and T cell proliferation during colon cancer[82; 83; 84]. Studies have shown that an upregulation in circulating levels of IL-6 enhances fat oxidation and improves glucose uptake.

Increasing evidence suggests that muscle cells are a source of IL-6. This cytokine is detected in a contracting skeletal muscle after 30 minutes of exercise[85; 86; 87]. In cultured C2C12 myoblasts, IL-6 mRNA knockdown reduces muscle specific gene expression[88]. IL-6 has also been identified as an essential regulator of muscle stem cell mediated hypertrophy[89; 90]. IL-6 deficient mice exhibit severe muscle atrophy and loss of IL-6 results in proliferation and migration defects in myoblasts possibly due to reduced activation of STAT3[89]. In cases of muscle injury, IL-6 levels dramatically increase, but in control animals the levels return to normal unlike the age matched *mdx* mice, which exhibit persistently higher levels of IL-6[91]. In its heightened state, IL-6 has been linked to muscle wasting and chronic inflammation in *mdx* mice. Although the underlying mechanism remains to be elucidated, chronic levels of IL-6 have been shown to decrease the pro-myogenic factor, IGF-1 by directly acting on the liver and muscle IGF-1[92]. Elevated levels of IL-6 have also been associated with arthritis, Crohn's disease, and other inflammatory diseases[93; 94].

Interleukin-4 (IL-4)

IL-4 is produced by NK, activated T, mast, basophils, and eosinophil cells. This cytokine regulates a variety of immune functions including isotype switching in B cells and differentiation of T cells[95; 96]. IL-4 also induces the expression of MHC class II molecules and downregulates the expression of pro-inflammatory cytokines, TNF-α and IL-1[97; 98; 99]. IL-4 signals through two distinct cell surface receptor complexes IL-4R type I, specific for IL-4 and IL-4R type 2, which is shared by IL-13[100]. Both IL-4 and IL-13 utilize the JAK-STAT signaling pathway for signal transduction. However, IL-4Rα associates with JAK1 and JAK3 while IL-13Ra associates with JAK2 and not JAK3. During signal initiation, IL-4 binds to its receptor, IL-4Rα, which gets autophosphorylated. This leads to the phosphorylation of JAK, which in turn phosphorylates and activates STAT6. Phosphorylated STAT6 dimerizes, migrates to the nucleus, and binds to the consensus sequences located in the promoters of IL-4 target genes[101]. A second signaling pathway that can be activated by IL-4 through the IRS family of proteins is the phosphatidylinositol 3-kinase (PI3K) pathway. Binding of IL-4 to IL-4Ra leads to autophosphorylation of IL-4Ra. IRS proteins get recruited to IL-4Ra and then get phosphorylated. Tyrosine phosphorylated IRS proteins in turn associate with cytoplasmic signaling molecules containing SH2 domains including the p85 subunit of PI3K leading to the activation of the catalytic subunit of PI3K, p110[101; 102].

In muscle cells, induction of IL-4 by NFATc2 has been shown to promote myoblast fusion possibly by increasing the expression of cell adhesion[103]. In fact, IL-4 has been shown to regulate the expression of ICAM1 on myoblasts[104] and vascular cell adhesion molecule 1(VCAM-1), which is required for myotube formation *in vitro* in smooth muscle cells[60; 105]. IL-4 is expressed during early stages of muscle injury and is a dominant regulator of alternative macrophage (M2) activation that increases during the later stages of the muscle injury and promotes efficient muscle regeneration[106; 107]. IL-4 also facilitates muscle regeneration by controlling the functions of FAPS[26]. Stimulation with IL-4 directs the FAPs to proliferate as fibroblasts and support myogenesis by clearing out necrotic debris. In the absence of IL-4, FAPs differentiate into adipocytes, resulting into fatty degeneration of skeletal muscle[26]. Muscle biopsies from patients suffering from idiopathic in ammatory myopathies show an upregulation in IL-4 gene and mRNA expression[108; 109; 110].

Interleukin-10 (IL-10)

IL-10 also known as CSIF (cytokine synthesis inhibitory factor) was discovered through a screen for factors that inhibited cytokine production by Th1 cells[111]. IL-10 signals through IL-10R and IL-10R2 receptors, which belong to the interferon family[112; 113]. IL-10R1 (IL-10Rα) is expressed constitutively on most hemopoietic cells and exhibits an induced expression in non-hemopoietic cells[114; 115; 116; 117]. IL-10R2 (IL-10β) is expressed on most tissues[113; 118]. Like IFN-γ, IL-10 signals mainly through the JAK-STAT pathway with STAT3 being indispensible for IL-10 signaling in all IL-10 responsive cells[119; 120].

IL-10 is primarily known for its function in inhibiting the pro-inflammatory cytokines such as IFN-γ, TNF-α and IL-6[121]. IL-10 also inhibits the production of CSF, IL-1α, IL-1β, IL-12,IL-18, G-CSF, M-CSF, GM-CSF, as well as C-C and C-X-C cytokines[112]. IL-10

converts the cytolytic M1 macrophages to the more regenerative M2c phenotype, which express markers like CD206, arginase, IL-4α, and CD163[122; 123; 124; 125; 126]. IL-10 has a direct effect on muscle cells. Muscle cells express IL-10 independent of the myeloid cell population that resides in the muscle[127]. The role of IL-10 in inhibiting the pro-inflammatory cytokines could be deemed protective as IL-10 rescues the block on myogenin by IGF-1, which is induced by TNF-α[129]. IL-10 also prevents TNF-α induced phosphorylation of JNK and prevents upregulation of IL-6 expression by TNF-α in myoblasts[128; 129], all of which are considered anti-myogenic signals.

In an injured muscle, IL-10 is key in directing the switch between M1 to M2 macrophages[130]. A recent study from the Tidball lab demonstrated that the expression of IL-10 and its receptor are elevated in *mdx* mice at the onset of pathology as well as during the regeneration phase[131]. Therefore, unlike pro-inflammatory cytokines described above whose activities switch from pro to anti-myogenic in a dose dependent manner, persistent levels of IL-10, as shown in *mdx* mice, remain anti-inflammatory and pro-regenerative, a feature of this cytokine that might be exploited for therapy.

Transforming growth factor- beta (TGF-β)

The multifaceted TGF-β superfamily is crucial is regulating normal physiology and has also been described in a plethora of studies as a contributor to pathogenesis[132,133] The TGF-β superfamily consists of various signaling molecules including isoforms of TGF-β (1 to 3), Bone morphogenic proteins (BMPs 1 to 20), growth and differentiation factors (GDFs), activins (A and B) and inhibins (A and B)[133]. TGF1-β is synthesized as a precursor molecule which eventually upon getting cleaved into a mature, but inactive form, complexes with a portion of the precursor peptide known as the latency associated peptide (LAP)[134]. This inactive TGF1-β-LAP complex associates with latent TGF binding proteins (LTBPs), which release TGF1-β from the ECM. For the initiation of signal transduction, TGF1-β binds to its receptor, TGF1-βR type II or ALK (activin like kinase receptor) 1 or ALK5, which leads to the phosphorylation of two receptor-associated Smads, Smad2 and Smad3. Phosphorylated Smad2 and Smad3 proteins then heterodimerize with a common mediator Smad, Smad4, which as a Smad2/3 -Smad4 complex, translocates to the nucleus to activate the transcription of its target genes by cooperatively associating with other transcriptional factors and coactivators[135]. Apart from this canonical signaling pathway, TGF-β also signals in a non-canonical manner, which is Smad independent. Induction of this pathway leads to Ras and TGF-β activated kinase 1(TAK1) activation, which subsequently stimulates the MAPK kinases, p38/JNK [136]. Activation of the MAPK pathway however, can occur by both Smad dependent and independent fashion indicating that a possible cross talk exists between the TGF-β canonical and non-canonical signaling pathways[136; 137]. The TGF-β signaling is negatively regulated by the Smads, Smad6 and Smad7 or by a ubiquitin proteasomal degradation pathway mediated by Smad ubiquitin regulatory factors (SMURFs)[138]. In skeletal muscle, perhaps the most extensively studied ligand of TGF-β family is myostatin. Myostatin binds to the activin receptor type II A (ActR-IIA),ActR-IIB, or ALK 4 or 5. Both the pathways converge in the activation of Smad2 and 3 followed by the dimerization with Smad4[139]. Interestingly, Smad7, the inhibitor of the TGF-β/Myostatin signaling displays pro-myogenic functions through its interactions with MyoD1[140].

Studies have shown that TGF-β inhibits skeletal muscle differentiation and also modulates proliferation of satellite cells[141; 142; 143]. Smad3, which is the key mediator of the inhibitory effects of TGF-β on myogenesis, physically interacts with MyoD1 to inhibit MyoD1 dependent transactivation[141]. Furthermore, TGF-β not only inhibits the transactivation properties of MyoD1, but also inhibits the transcription of MyoD1[144]. TGF-β has also been shown to block the transcriptional activity of myogenin and thereby inhibit muscle differentiation[145]. Studies also demonstrate that TGF-β is upregulated in the skeletal muscle post-injury or following exercise. TGF-β is thought to participate in the inflammatory response involved in muscle repair and plays a key role in promoting the transformation of myoblasts into fibrotic tissue. This role of TGF-β as a driver of fibrosis is repeated in numerous pathologies, such as in idiopathic pulmonary fibrosis. This disease is characterized by the accumulation of inflammatory infiltrate and increased collagen deposition resulting in loss of alveolar architecture. Lung biopsies from these patients show activated fibroblasts expressing collagen and fibronectin and alveolar macrophages expressing excessive levels of TGF-β protein and mRNA[146].

GDF11 and myostatin are two highly related TGF-β family members, but have very distinct biological functions. GDF11 is more widely expressed and was recently identified for its 'rejuvenating' effects on skeletal muscle, suggesting that restoring systemic GDF11 levels may help prevent age related dysfunction in mice[147]. Myostatin however negatively regulates skeletal muscle mass during development. The *myostatin* gene is expressed in the heart, skeletal muscle, and adipose tissue. Mice homozygous null for *myostatin* exhibit hypermusculature due to increased muscle mass. Myostatin null animals also show decreased fat, increased muscle strength and change in fiber type distribution leaning more towards type IIb fibers[148]. In aged mice, short-term inhibition of myostatin enhances muscle regeneration and satellite cell activation. Not surprisingly, overexpression of myostatin leads to excessive muscle wasting, similarly to that observed in cancer cachexia[149].

There is another distant and divergent member of the TGF-β family known as GDF15 (also known as macrophage inhibitory cytokine (MIC-1)) that plays a role during chronic inflammation[150]. Elevated circulatory levels of MIC-1 are found in chronic inflammatory diseases like atherosclerosis and RA indicating endothelial activation and vascular inflammation[151; 152]. In patients with acute myocardial infarction, enhanced levels of GDF15 have been reported which are correlated with inflammatory biomarkers[153; 154]. GDF15 deficiency inhibits the progression of atherosclerosis and regulates IL-6 and TGF-β dependent inflammatory responses[155; 156]. However, studies have revealed that GDF15 also has broad anti-inflammatory and immune suppressive properties[157].

Tumor Necrosis Factor-α (TNF-α)

TNF-α, also known as cachectin is a prototypic ligand of the TNF super family. It plays central roles in inflammation, apoptosis and immune system development. TNF-α is produced by a wide variety of immune and epithelial cells[158] and activates a number of signaling pathways that mediate cell type specific, pleotrophic responses. At least 3 major pathways are activated by TNF-α including activation of c-Jun terminal kinase (JNK) and activator protein-1 (AP1), stimulation of apoptosis via TNF-α receptor complex, and Fas

associated protein with death domain (FADD) and activation of NF-κB, which is a primary mediator of transcriptional control and catabolic signaling. TNF-α signaling can be mediated by TNFR1 or TNFR2. Binding of TNF-α to its receptor, initiates a IKK-γ dependent signaling cascade that activates the inactive p50/p65 heterodimer and causes its translocation into the nucleus where it decreases the expression of the pro-myogenic transcription factor, MyoD[159].

In skeletal muscle, TNF-α influences satellite cell proliferation and accelerates the G1 to S phase transition[162]. Administration of neutralizing antibodies against TNF-α to *mdx* mice increases the number of $Pax7^{+ve}$ cells and decreases the inflammation based activation of p38/MAPK signaling[163]. The observed increase in Pax7 expression is due to the inhibition of association of the repressive PRC2 complex subunits with *Pax7* promoter[163].

TNF-α stimulates the production of catabolic cytokines and induces anorexia. In dystrophic muscle, elevated levels of TNF-α inhibit the regenerative potential of satellite cells by epigenetically silencing Notch 1[164]. TNF-α has been attributed to a number of inflammatory diseases like COPD and is associated with loss of muscle mass in COPD patients[165].

Tumor Necrosis Factor Like Weak Inducer of Apoptosis (TWEAK)

The cytokine tumor necrosis factor like weak inducer of apoptosis (TWEAK) is a member of the TNF superfamily. TWEAK is initially synthesized as a 249-amino-acid protein comprising of a C-terminal extracellular domain, a transmembrane domain, and a N-terminal intracellular domain, which gets proteolytically cleaved at its C terminal domain into an soluble form[166]. The soluble form trimerizes and functions as a homo trimer. While the specific conditions for the existence of both the forms of TWEAK have not been understood, TWEAK is fully functional both in its cell surface associated transmembrane form and its soluble form[166]. TWEAK has been detected as a membrane anchored protein in IFN-γ activated human monocytes[167] and in human $CD4^{+}$ cells[168].

TWEAK binds to the fibroblast growth factor inducible 14 (Fn-14) receptor, which also belongs to the TNF superfamily of receptors and is characterized as a type Ia transmembrane receptor lacking a cytoplasmic death domain[169; 170]. The unprocessed TWEAKR/Fn-14 contains a 27-aa N terminal signal peptide sequence and a highly hydrophobic region which functions as a plasma membrane spanning domain. The mature form of TWEAKR/Fn-14, which is produced after proteolytic cleavage is predicted to be 102 aa in length, making it the smallest member of the TNF family of receptors[169; 170]. Both the human and murine forms Fn14 contain a highly conserved 29 aa cytoplasmic tail and a putative TRAF binding site[171].

In cultured C2C12 myotubes, treatment with TWEAK leads to a reduction of MyHC, possibly through an upregulation of the muscle specific E3 ubiquitin ligases MuRF1 and MAFbx in a dose dependent manner[172]. In mice, the treatment with TWEAK results in reduction in body weight and fiber cross sectional area compared to the littermates[172]. Furthermore, transgenic overexpression of full-length TWEAK cDNA using a muscle creatine kinase promoter shows severe muscle wasting[172].

The TWEAK-Fn14 axis regulates a number of physiological processes like apoptosis, proliferation, differentiation, cell survival and angiogenesis. In various cell types including skeletal muscle, TWEAK has been shown to activate NF-κB, p44/p42 MAPK, JNK, and AP-1. However, the TWEAK-Fn14 axis is also often linked to the pathogenesis of systemic lupus, neuro inflammation, cardiac dysfunction, RA, MS, and a number of cancers [166]. Increased expression of TWEAK is also associated with the induction of fibrosis and a broad pro-inflammatory and cell death/tissue-damaging activity[173]. This could be through its direct action on fibroblasts and their progenitors, or the cooperation of TWEAK with other cytokines that become upregulated during various disease states[171].

The TWEAK/Fn14 pathway is well known for its involvement in modulating inflammation in auto immune and chronic inflammatory disorders. TWEAK induced pro-inflammatory responses stimulate the expression of chemokines, cytokines, adhesion molecules and MMPs, from endothelial, epithelial, and other non hematopoetic cell types [174]. TWEAK can also cooperate with other pro-inflammatory cytokines like TNF-α and IL-17, to name a few, to augment inflammatory response[173; 175]. In addition to TWEAK, a variety of Fn14 inducing stimuli like IFN-γ, TNF-α and IL-1β have been recently identified which could very well explain the diverse outcomes derived by the TWEAK-Fn14 pathway, alone or in combination with other cytokines[166].

Inflammatory disorders leading to muscle loss

Chronic obstructive pulmonary disorder (COPD)

COPD is one of the leading causes of morbidity and mortality all around the world. Primarily, COPD is a respiratory disease and is diagnosed based on abnormal lung function and symptoms such as dyspnea and chronic cough production. However, along with the symptoms described above, COPD presents itself with a low-grade systemic inflammation, which results in skeletal muscle dysfunction.

The idea that skeletal muscle dysfunction could be an impairment in patients with COPD was first described in a study by Killian et. al[176], in which the exercise capability in patients with COPD was tested. Approximately 40% of the COPD patients exhibited early termination of exercise due to symptoms of leg fatigue, which was far greater than their rating of shortness of breath at the end of the exercise study. In addition to contributing to a reduced ability to exercise, decreased health status and diminished muscle function, muscle wasting is a determinant to morbidity in COPD, independent of the pulmonary disorders. Muscle wasting in COPD has been demonstrated as the loss of fat free mass at the whole body level and also at the level of the extremities[177]. In addition to the depletion of muscle mass, fiber type switching from type I to type II occurs resulting in decreased muscle oxidative capacity. This switch not only reduces endurance,[178] but also accelerates muscle atrophy[179]. Over the last two decades, research has focused on identifying the potential triggers of muscle wasting in COPD. Based on biochemical and immunohistochemical studies a number of factors have been identified as potential causes for muscle wasting in COPD. These include malnutrition, hypoxemia, disuse and inflammation. Low physical activity or a sedentary life style are common in COPD patients[180]. Inactivity and/or muscle disuse are well known triggers for muscle atrophy. Hypoxemia, i.e. reduced arterial oxygen

tension is prevalent in COPD patients. Currently, most of the evidence implying that hypoxemia and subsequent tissue hypoxia can trigger muscle wasting is purely based on observations made from healthy patients and experimental models. Studies in mountaineering expeditions in which subjects are exposed to high altitudes and hypoxia are reported to have decreased muscle mass[181] and reduced muscle fiber size despite of physical activity[182]. While being a potential trigger, the precise mechanisms by which hypoxemia induces muscle atrophy are still unknown. Malnutrition is reported in at least one third of the patients with COPD and the severity advances with the progression of the disease. Some data demonstrate that the positive effects of nutritional supplementation lead to preservation of fat free mass in COPD patients. However, for most patients increasing energy intake alone does not rescue muscle atrophy. The protein synthetic rate presumably goes down during starvation, which is supported by one study[183], but follow up reports have argued against such a mechanism[184; 185]. While malnutrition, hypoxemia, and inactivity have all been linked to muscle wasting in COPD, more recent attention has shifted to the relation between cachexia and inflammation.

Findings show that COPD is characterized by the elevation of inflammatory factors such as IL-6, TNF-α, IL-8, and C-reactive protein. In addition, COPD patients also show evidence of elevated expression of adhesion molecules in plasma and bronchoalveolar fluids, as well as an increase in the generation of ROS[186]. Possibly, muscle wasting in COPD results from bursts of ROS in combination with inflammatory cytokines. How downstream factors such as NF-κB are involved in COPD-induced muscle loss remains controversial. The variable levels of NF-κB that have been reported in COPD patients may reflect the different stages of disease progression that involve both stable and severe muscle loss. Results from animal models of COPD appear more consistent that NF-κB is activated and associated with acute pulmonary inflammation where there is a connection with muscle atrophy, but further evidence is required to validate the role of inflammatory factors and NF-κB in this pathology.

Rheumatoid arthritis (RA)

Rheumatoid arthritis is a chronic, autoimmune, debilitating disease that generally occurs within the fourth and sixth decade of life. The disease is more common in men than women. RA is primarily characterized by joint pain, swelling, stiffness, and accompanied by skeletal muscle wasting. RA is also characterized by sustained inflammatory synovitis[187]. Persistent synovial inflammation results in bone erosion and cartilage damage, due to the loss of functionality in individuals affected by RA[188]. Although RA is classified as a multi-system disease, inflammatory cytokines are recognized as key mediators in its pathology.

The synovial membrane in patients with RA is characterized by hyperplasia, increased vascularity, and infiltration of inflammatory cells, primarily of $CD4^+$ T cell origin[188]. Antigen activated $CD4^+$ T cells stimulate monocytes, macrophages, and synovial fibroblasts to release pro-inflammatory cytokines, IL-1, IL-6, IL-18 and TNF-α[188], which for the most part can be detected in the synovial fluid of RA patients [189]. Furthermore TNF-α and IL-1 act as potential stimulators of mesenchymal cells that release MMPs to destroy tissue and at the same time inhibit the production of TIMPs, inhibitors of MMPs[190]. Transgenic mice

over expressing TNF-α spontaneously develop inflammatory arthritis[191]. *In vitro* studies with synovial cultures from RA patients demonstrate that blocking TNF-α with antibodies drastically reduces the expression of pro-inflammatory cytokines[192]. This suggests that inhibition of TNF-α might have a more global effect in treatment of RA than neutralizing other cytokines.

IL-18 is another cytokine elevated in synovial fluids and synovial tissues of patients with RA. Within the RA joint, IL-18 contributes to the inflammatory process by stimulating leukocyte extravasation through the upregulation of endothelial adhesion molecules[193; 194] and the release of chemokines[195] from RA synovial fibroblasts through activation of NF-κB. Additionally, IL-18 acts synergistically with IL-12 to induce production of IFN-γ from T cells further aggravating joint inflammation and cartilage destruction. IL-32 is another inducer of pro-inflammatory cytokine produced from lymphocytes that infiltrate severely inflamed synovial tissues in patients with RA, and intensity of IL-32 staining correlates disease severity[196]. In mice models of inflammatory arthritis, studies have shown that recombinant IL-32 injections in naive mice result in joint swelling and infiltration of inflammatory infiltrates[196]. However, similar injections in TNF-α deficient mice did not show the same phenotype, suggesting that the ability of IL-32 to induce joint inflammation is in part dependent on TNF-α[167]. Due to its close relationship with TNF-α, IL-32 is being considered as a potential target for therapies against RA.

IL-6 has been regarded as a key player in promoting joint and systemic inflammation and inducing immunological abnormalities in RA. IL-6 promotes muscle wasting and joint destruction in RA by activating release of adhesion molecules and inducing the secretion of monocyte chemoattractant protein 1 (MCP-1) and IL-8[197; 198]. IL-6 and IL-1 can synergistically enhance the production of MMPs from synovial cells, which leads to joint and cartilage destruction[199]. Also, in synovial fibroblasts, IL-6 induces the secretion of vascular endothelial growth factor (VEGF), which leads to enhanced angiogenesis and vascular permeability of the synovial tissue[200]. The pathological effect of IL-6 has been well documented in animal models. Collagen induced arthritis is an established model for RA in which an injection of type II collagen in mice causes an immune response directed at connective tissue. In this model, activated T cells produce augmented amounts of Th1 and Th17 cytokines. Suppression of IL-6 through gene knockout experiments reduces cytokine production and ameliorates the symptoms of RA[201; 202]. Inhibiting IL-6 by antibody or gene deletion has yielded similar results in other models of RA[203]. Such results are consistent with findings documenting elevated levels of IL-6 in the serum and synovial fluid of RA patients[204].

More than two thirds of the people with RA suffer from loss of skeletal muscle mass or ‘rheumatoid cachexia’, a term coined by James Paget in 1873. Unlike the general definition of cachexia, which includes wasting of skeletal muscle and adipose tissue, rheumatoid cachexia is defined as a loss of body cell mass, predominantly in the skeletal muscle and with no or little weight loss in the presence of increased or stable fat mass[205]. While precise mechanisms for the cause are still under investigation, it is believed that elevated levels of pro-inflammatory cytokines are one of the leading causes of rheumatoid cachexia. TNF-α and IL-1 likely act as central mediators of muscle wasting in RA[206]. Studies in rat models of

adjuvant arthritis[207] show that TNF-α blockade alone rescues the loss of skeletal muscle, suggesting that TNF-α functions as an important contributor of cachexia in RA, but is also likely not the sole mediator. In support of this notion, inhibition of both IL-1 and TNF-α is more effective in reducing muscle wasting in cachexia[208] than individual blockage alone, thus reinforcing the concept that IL-1 and TNF-α act synergistically to promote cachexia in RA[208].

TNF-α has also been shown to reduce the action of peripheral insulin, which might be another mechanism by which this cytokine contributes to cachexia[209; 210]. Another peculiar characteristic of patients with RA is that they exhibit elevated resting energy expenditure[211]. Generally, under normal conditions, there is a balance between the rate of protein degradation and the rate of protein synthesis[212]. This balance regulates important physiological functions and enables adaptation to physiological and environmental cues. In RA, chronic inflammation alters this balance towards net protein catabolism causing an increase in the resting energy expenditure[211], a net efflux of amino acids from muscle to the liver, and an increase in the synthesis of acute phase proteins, fibrinogen and CRP, the sum of which is predicted to lead to cachexia.

Effective therapies for RA have concentrated on targeting the cytokines that mediate rheumatoid cachexia. For example, Tocilizumab, a humanized anti-IL-6 receptor antibody, is already in clinical trials[213]. Patients treated with Tocilizumab alone or in combination with methotrexate exhibit significant improvements[214]. TNF-α blocking antibodies like D2E7[215] or Infliximab[216] or the decoy receptor, Etanercept[217; 218], all demonstrate some form of clinical improvement for RA. In addition, in a randomized, double blind, placebo controlled trial of patients with RA, treatment with recombinant human IL-1 receptor antagonist resulted in moderate clinical improvement and decreased progression of erosions as assessed by radiography[219]. A drawback of using an IL-1 receptor antagonist therapeutically is its short half-life (6 hours)[220], which demands frequent injections and high concentrations. As opposed to the responses obtained with blocking IL-1, IL-6, and TNF, clinical trials undertaken to target IL-4 and IL-10[188] have met with limited benefit.

Inflammatory myopathies (Myositis)

Idiopathic inflammatory myopathies are autoimmune muscle disorders that involve inflammation of the muscle or the surrounding tissues such as blood vessels that supply blood to the muscles. Another term used to describe inflammatory myopathies is myositis- ‘myo’ meaning muscle and ‘itis’ meaning inflammation. These myopathies are considered to be auto immune in origin, due to their predominance of T and B cells in the affected muscle, the over expression of MHC class I and II molecules by muscle cells, and the association with myositis specific auto antibodies. Nevertheless, the exact nature of the antigens mediating these myopathies remains to be defined. Inflammatory myopathies are classified into three main types, polymyositis, inclusion body myositis, and dermatomyositis. Although each subtype presents with their own distinct clinical features, there are some common symptoms shared among all three subtypes including progressive muscle weakness, muscle atrophy, and vasculature damage surrounding muscle fibers.

Progressive muscle weakness leads to additional symptoms such as shortness of breath, difficulty in swallowing and speaking, heart arrhythmias, and fatigue.

Polymyositis (PM) and inclusion body myositis (IBM)

PM ('inflammation of many muscles') is generally regarded as a prototypic T cell mediated autoimmune myopathy whereas IBM on the other hand is classified by a more peculiar pattern of muscle wasting, longer clinical course, and a T cell dominant auto immune response in combination with myofiber degeneration. The degeneration aspect is characterized by the appearance of vacuoles in muscle cells, deposition of abnormal proteins, and filamentous inclusions, from which IBM derives its name. The existence of PM as a separate entity is controversial given the frequent coexistence of PM and IBM[221; 222]. The controversy relates to whether PM occurs as a muscle specific disease or an autoimmune disorder, given the similarities between IBM and PM and the more frequent occurrence of IBM[223].

In both PM and IBM, $CD8^+$ T cells are thought to be the primary effector cells causing muscle damage and weakness[224]. $CD8^+$ T cells proliferate and differentiate locally in the muscle. Because muscle presents antigen, these cells are targeted by autoinvasive $CD8^+$ T cells to induce their turnover [225; 226; 227]. This is thought to occur through the secretion of MCP1 by the T cells to recruit monocytes[228], which in turn express pro-inflammatory cytokines like TNF-α, IFN-γ and IL-1 to induce a toxic effect on skeletal muscle cells [229]. Yet another pro-inflammatory cytokine, macrophage inhibitory factor (MIF), is elevated in PM and thought to contribute to the turnover of muscle[230].

Dermatomyositis (DM)

DM is characterized by the presence of a typical DM rash on the face (heliotrophe rash), hand, elbows (Gottron's papules), and torso[231]. DM can be classified into various subgroups based on its childhood or adult forms (Juvenile DM or adult DM), or based on whether it is associated with malignancy or a part of an overlapping syndrome (Cancer associated DM). DM can be further classified based on cutaneous manifestations and the severity of muscle weakness (DM with systemic manifestations or amyopathic DM)[231; 232; 233]. DM is thought to be initiated by the activation of the complement pathway leading to depletion of muscle fibers [229]. However, how the complement pathway is activated in DM, is still unknown. One notion is that immunoglobins accumulate on intramuscular capillaries, which causes the activation of the complement cascade, and in turn triggers the production of pro-inflammatory cytokines and chemokines. These pro-inflammatory molecules, then upregulate adhesion molecules on endothelial cells that go on to stimulate B, T, and dendritic cells, leading to muscle necrosis[229; 232]. This inflammatory cascade within the perivascular and perimysial mileu is comprised of B and $CD4^+$ T helper cells, IFN-γ producing Th1 cells, IL-17 secreting Th17 cells, and IFN-α producing dendritic cells[234; 235]. IL-17 is believed to be one of the factors responsible for upregulating MHC class I molecules in muscle cells as well as for facilitating the migration of mononuclear cells to muscle cells[236].

In summary, while there are other causal factors to muscle wasting chronic inflammatory diseases, pro-inflammatory cytokines act as major contributors to muscle loss in these diseases (Fig. 1). While therapies targeting the cytokines are already in clinical trials, efforts are being focused on generating more efficient strategies to better target and reduce the deleterious effects of inflammation in these diseases.

The concept of skeletal muscle and myokines

The term ‘myokine’ was initially coined to strictly include proteins that were secreted by skeletal muscle cells. Nevertheless, the recent extended definition of a myokine includes proteins that are synthesized by skeletal muscle tissue and exert either paracrine or autocrine effects[87]. Chronic diseases like type 2 diabetes, cardiovascular diseases, colon cancer, breast cancer, to name a few, have highly different phenotypical presentations[237]. However, they share a few common pathogenic mechanisms such as physical inactivity. Chronic systemic inflammation goes hand in hand with physical inactivity, independent of obesity[238]. Evidence suggests that physical inactivity can lead to visceral fat, which can result in obesity and health consequences. Obesity coupled with lack of exercise subsequently results in activation of inflammatory pathways that lead to deleterious effects such as neuro degeneration, atherosclerosis, and development of insulin resistance. It has been long known that adipose tissue can function as an endocrine organ to release pro-inflammatory factors to promote obesity induced cardiovascular diseases and metabolic disorders. Recent studies have introduced the concept of ‘myokines’ which are released by skeletal muscle cells and predominantly function to counter the pro-inflammatory factors released by adipocytes[239].

To date, IL-6 is perhaps the best recognized myokine. IL-6 was shown to be released in high amounts from contracting skeletal muscle following prolonged exercise, without exhibiting prominent muscle damage[240]. Besides IL-6, FGF2 can also be secreted from cultured C2C12 myoblasts[241], but whether this factor qualifies as bonafide myofiber releasing myokine awaits further study. Although muscle derived IGF-1 is not detected in circulation, it is considered a myokine that functions in regulating muscle hypertrophy in an autocrine/paracrine manner, in response to exercise[242; 243]. Several activities of IGF-1 are regulated by muscle derived IGFBPs (IGF- binding proteins), which modulate IGF-1 availability and biological activity[244]. The cytokine, IL-15, also falls in the myokine category due to its anabolic activity on muscle cells and its possible role in reducing adipose tissue mass as part of a muscle, fat cross-talk[245]. Similar to IL-6, IL-15 is elevated in skeletal muscle cells post-exercise. Interestingly, administering IL-15 has also been found to improve glucose homeostasis and insulin resistance in obese mice[246]. Additional myokines include Fstl1 (also known as TSC36), which when secreted from skeletal muscle, exhibits an anti-apoptotic activity on endothelial cells[247] through an Akt-eNOS signaling pathway[247]. This can be manifested under conditions of ischemic stress, where the addition of Fstl1 has been seen to accelerate revascularization[247].

The myokine field is one that continues to emerge (reviewed in[239; 248]), as more recent candidates, such as IL-7, myonectin, and BDNF, have been proposed to be produced from skeletal muscle cells and act in a paracrine and autocrine fashions to maintain skeletal muscle homeostasis.

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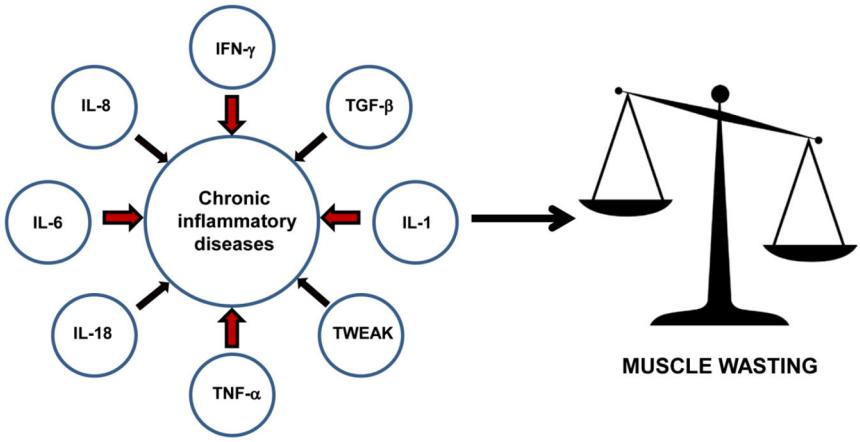

Figure 1. The drivers of muscle wasting in chronic inflammatory diseases

The figure depicts the inflammatory cytokines that contribute to muscle wasting. The degree of involvement of a particular cytokine is denoted by the width of individual arrows. Due to elevated expression of cytokines in these diseases, the balance is tipped towards hypercatabolism resulting in loss of muscle mass