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Muscle cell-derived cytokines in skeletal muscle regeneration

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Abstract

Regeneration of the mammalian adult skeletal muscle is a well-orchestrated process regulated by multiple proteins and signaling pathways. Cytokines constitute a major class of regulators of skeletal myogenesis. It is well established that infiltrating immune cells at the site of muscle injury secrete cytokines, which play critical roles in the myofiber repair and regeneration process. In the past 10–15 years, skeletal muscle itself has emerged as a prolific producer of cytokines. Much attention in the field has been focused on the endocrine effects of muscle-secreted cytokines (myokines) on metabolic regulation. However, ample evidence suggests that muscle-derived cytokines also regulate myogenic differentiation and muscle regeneration in an autocrine manner. In this review, we survey cytokines that meet two criteria: (a) evidence of expression by muscle cells; (b) evidence demonstrating a myogenic function. Dozens of cytokines representing several major classes make up this group, and together they regulate all steps of the myogenic process. How such a large array of cytokines coordinate their signaling to form a regulatory network is a fascinating, pressing question. Functional studies that can distinguish the source of the cytokines in vivo are also much needed in order to facilitate exploration of their full therapeutic potential.

Keywords

Cytokine; skeletal muscle; regeneration; myogenesis; myogenic differentiation

Introduction

Skeletal muscle is one of the few adult mammalian tissues that can undergo robust regeneration after injury, owing at least partly to a resident population of stem cells that imparts a great regenerative capacity. These myogenic progenitor cells, called satellite cells, exist in a quiescent state under the basal lamina of myofibers until stimulated to divide by muscle injury as a result of acute trauma, toxin, exercise, or diseases. A subset of

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Conflict of interest

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the activated satellite cells returns to quiescence, allowing for self-renewal of the muscle stem cell pool, while the remaining activated cells proliferate at the site of injury to allow for new myofiber formation or repairing of injured myofibers [1, 2] (Figure 1). Effective regeneration depends on the new myoblasts successfully completing a number of different processes, including expression of many of the same myogenic genes seen in embryonic development, such as the MEF2 and MyoD families of transcription factors [3, 4]. The differentiating myoblasts must also undergo massive cytoskeletal rearrangement, migration, cell-cell adhesion and alignment, and finally membrane fusion in order to form a multinucleated myofiber. Myocyte fusion occurs in two stages that are regulated by distinct molecular pathways [5, 6]. The first stage entails fusion between differentiated myoblasts, leading to small, nascent myotubes. The second stage of fusion occurs between myoblasts and these nascent myotubes, resulting in mature myofibers. This well-orchestrated myogenic process is regulated by numerous intracellular signaling pathways, including p38 [7], Jak/STAT [8], mTOR [9] and PI3K/AKT [10], to name just a few. This review will discuss the roles of cytokines and their signaling in regulating myogenesis, with a special focus on cytokines of muscle cell origin.

The exact definition of what constitutes a cytokine has been evolving since their discovery in purulent exudates in the 1940s [11]. The earliest identified cytokines were of hematopoietic origin and thought to be dedicated to modulating inflammatory responses. Today, it is well established that nearly every cell type can produce secreted factors to some degree, and that even the original cytokines have other sources and pleiotropic functions beyond the immune system. Biochemical, structural, and functional understanding of these secreted factors have led to various, sometimes overlapping, forms of nomenclature. For instance, most of the interleukins and all interferons signal through cytokine receptors associated with the Jak kinases and they are still considered by some to be the only bona fide “cytokines”. Most growth factors (e.g., EGF, IGF, FGF, VEGF, etc.) act through receptor tyrosine kinases. Chemokines, so named for their chemoattractant properties, are ligands for G protein coupled receptors. TGFβ’s and TNFs bind distinct families of receptors known as TGFβ receptors and TNF receptors, respectively. For all practical purposes, the term “cytokine” has been extended to include all small (<30 kDa) secreted proteins that function via cell surface receptors, although there are certainly exceptions to this already broad definition. For instance, almost all TNF family members exist in a transmembrane form in addition to the extracellular soluble form resulting from proteolytic cleavage, both biologically active; some cytokines are larger than the 30 kDa molecular weight cutoff (e.g. IL-12, VEGF).

A large number of infiltrating immune cells at the site of skeletal muscle injury play a critical role in not only clearing the damaged tissue but also promoting muscle regeneration [12, 13]. It is well accepted that these immune cells produce a milieu of secreted factors that modulate every stage of injury-induced muscle regeneration. However, in the past two decades the skeletal muscle has also gained increasing attention as a secretory organ. Originally coined by Pedersen et al. [14], the term “myokine” refers to a cytokine that is released by skeletal muscle cells (often as a result of exercise) into the circulation to exert endocrine effects and metabolic regulation [15, 16]. IL-6, for which the term myokine was first proposed [14], is secreted by exercising muscles and may exert a multitude of beneficial effects on metabolism [15]. At an ever-growing number, myokines have attracted

intense interest and been the subject of many excellent reviews (e.g., [15–17]). The autocrine and paracrine functions of muscle- or myogenic cell-secreted cytokines on modulating myogenesis have received less attention. With the advent of single-cell RNA sequencing (scRNAseq), which enables deep interrogation of the transcriptomics of the injured muscle, it has become evident that vast heterogeneity of gene expression exists in the many types and subpopulations of cells contributing to the regeneration process [18–21]. For instance, Oprescu et al. uncovered a subpopulation of muscle satellite cells enriched for immune gene expression in the regenerating muscle, which they termed “immunomyoblasts” [19]. It is reasonable to assume that these cells contribute to cytokine secretion during regeneration. scRNAseq data from other groups have also hinted at the existence of such a cytokine-expressing satellite cell subpopulation [18, 21]. The exact source of, and cell-specific responses to, each of the cytokines released during specific time points in regeneration are fascinating questions we are only just beginning to address. To help clarify the specific contribution of the myocyte lineage to the myogenic process, the current review focuses on muscle cell-derived cytokines that act in an autocrine manner to regulate skeletal muscle differentiation and regeneration.

Skeletal muscle cells are prolific producers of cytokines during differentiation

It has long been known that conditioned medium of differentiating skeletal myoblasts or myotubes in culture contain factors that influence myogenic differentiation, implicating muscle-derived cytokines in the autocrine/paracrine regulation of myogenesis. Whereas muscle tissue homogenates can contain proteins from non-muscle sources, analyses of in vitro muscle cell cultures have provided definitive evidence for muscle cells as prolific secretors of cytokines. About 10 years ago, significant efforts by several research groups led to the first proteome-wide glimpse of the skeletal muscle secretome. Two groups independently performed stable isotope labeling by amino acids in cell culture (SILAC) followed by proteomic analysis of the conditioned media of mouse C2C12 myoblasts at various stages of differentiation [22–24]. While Henningsen et al. identified 635 secreted proteins among which 75 were cytokines/growth factors [24], Chan et al. reported 34 secreted proteins [22]. Both studies concluded that a large portion of the proteins were secreted differentially during the course of differentiation, providing potential support for the idea that those secreted factors may have regulatory roles in the myogenic process. Another commonly used myogenic cell line, the rat L6 myoblast, was studied by Yoon et al., and they identified 254 proteins in the conditioned medium of fully differentiated myotubes, a small subset of which were up- or down-regulated by short-term (5 hours) insulin treatment [25]. Myotubes differentiated from human myoblasts were also analyzed by Norheim et al. and 18 classically annotated secreted proteins were reported [26]. Around the same time as the cluster of proteomic studies, Griffin et al. examined the mRNA expression of 84 chemokines and genes encoding proteins involved in chemokine signaling during differentiation of mouse primary myoblasts. They found 80 of those genes to be expressed, with the majority peaking at the time of myocyte fusion, consistent with a potential role of these chemokines in cell migration necessary for fusion [27]. It is worth noting that Henningsen et al. did not observe a marked correlation between the levels of cytokine proteins in their secretome and the levels of the corresponding mRNAs [24],

suggesting that a significant part of regulation of cytokine secretion by muscle cells may be at a post-transcriptional level.

Many of those identified muscle-secreted cytokines remain to be characterized for their potential functions in myogenesis. Nevertheless, the collective evidence raised the intriguing possibility that muscle cell-secreted proteins might have a previously under-appreciated role in modulating myogenic differentiation and muscle regeneration. Our lab conducted a functional screen of 134 mouse cytokines for their impact on myogenic differentiation in C2C12 myoblasts using RNAi, which led us to identify 29 potential regulators of myogenesis in distinct functional groups [28]. Several of those candidates have since been characterized for their myogenic functions and mechanisms (discussed later).

Early discoveries of cytokines with autocrine functions in myogenic differentiation

The concept of autocrine regulation of myogenesis by muscle-secreted factors is not new. Below we briefly describe a few of such cytokines first reported. Where comprehensive reviews have been published, we will refer the readers to those reviews in lieu of citing primary literature.

IGFs

The insulin-like growth factors IGF1 and IGF2 were among the earliest characterized and most extensively studied cytokines that promote myogenesis in an autocrine fashion [29–31]. IGFs are critically involved in skeletal muscle development, hypertrophy, and regeneration [29, 32, 33]. The autocrine function of IGF was first reported 30 years ago in cultured myoblasts found to secrete IGF2 that was indispensable for the initiation of differentiation [34]. Indeed, C2C12 myoblasts secrete high levels of both IGF1 and IGF2 [35, 36], and both stimulate the expression of myogenin, an early marker of myogenic differentiation [29]. Autocrine IGF2 is also a survival factor for muscle cells [37].

FGF, PDGF, HGF

Around the time when IGFs emerged as positive regulators of myogenesis, it became clear that fibroblast growth factors (FGFs) were autocrine inhibitors of myogenic differentiation in vitro [30]. FGF2 (basic FGF) is more potent than FGF1 (acidic FGF) in this regard, both possibly acting as mitogens to prevent cell cycle withdrawal and consequently suppress differentiation, although direct inhibition of myogenic gene expression is also proposed [30]. Several FGFs (at least FGF1, 2, 4 and 6) are expressed in satellite cells and, not surprisingly, they can also stimulate cultured satellite cell proliferation in an autocrine manner [38]. It would therefore appear that FGFs could have dual roles in muscle regeneration – promoting satellite cell expansion and suppressing myogenic differentiation. However, in vivo evidence for FGF function in myogenesis is limited (to be discussed later).

Another growth factor, platelet derived growth factor (PDGF), is expressed by myoblasts and exerts inhibitory effects on myogenic differentiation by promoting cell proliferation and inhibiting cell cycle exit [39–41]. Likewise, hepatic growth factor (HGF) is found to be expressed in satellite cells during rat muscle regeneration [42], stimulate satellite cell proliferation, and inhibit differentiation [43, 44]. Although IGFs are also growth factors

that stimulate myoblast proliferation, unlike FGF, PDGF and HGF, the mitogenic activity of IGFs – especially IGF2 [45] – does not interfere with their myogenic activity at the time of differentiation [29].

TGFβ

In 1986 transforming growth factor β (TGFβ) was reported independently by three groups to be an inhibitor of myogenic differentiation in vitro [46–48]. Those initial reports concluded that the effect of TGFβ was independent of cell proliferation. However, it is now confirmed in at least C2C12 cultures that TGFβ stimulates myoblast proliferation through Smad2 activation and consequently suppresses cell cycle exit [49, 50]. On the other hand, TGFβ activation of Smad3 leads to direct suppression of the transcriptional activity of MyoD and possibly other myogenic regulatory factors [51]. Consistent with an autocrine function, TGFβ is found to be secreted by myoblasts in vitro and its mRNA is expressed in mouse skeletal muscles [52].

Myostatin

A member of the TGFβ family, myostatin (also known as growth/differentiation factor-8 or GDF8) was reported in 1997 to be an autocrine inhibitor of muscle mass in mice [53]. Deletion of the myostatin gene leads to drastic muscle hypertrophy, manifesting the double-muscled phenotype in mice, cattle, and humans [54]. The mechanism by which myostatin inhibits muscle growth and myogenesis is multifold and will be discussed later. Two other TGFβ family members closely related to myostatin, activin A and GDF11, are also secreted by muscle cells and inhibit myogenic differentiation [55, 56]. All three ligands signal through the same activin receptors, and the receptor binding is antagonized by these ligands' physical interaction with muscle-secreted follistatin [55, 57]. Consistent with its anti-myostatin function, follistatin is a potent inducer of muscle hypertrophy [58, 59], although a myostatin-independent mechanism has also been suggested for follistatin's hypertrophic effects [60].

Regulation of myogenic processes by muscle-derived cytokines—In our literature survey we have set two criteria to look for cytokines that are autocrine regulators of muscle differentiation/regeneration: (a) evidence of expression by muscle cells in culture or in vivo and (b) evidence of myogenic regulation by the cytokine – either endogenous or recombinant. To date, dozens of cytokines have met these criteria as summarized in Table 1. These cytokines encompass several major classes of extracellular ligands based on the types of their cognate receptors, including members of TGFβ family, members of TNF family, chemokines, ligands for receptor tyrosine kinases, and interleukins/interferons that signal through cytokine receptors. Although not all these cytokines have been defined for their mechanisms of myogenic action, there is a sizable number of reports on the cellular mechanisms of autocrine regulation in myogenesis by many of the cytokines. Remarkably, every stage of the myogenic process involves regulation by muscle-derived cytokines, and many cytokines contribute to myogenic regulation at more than one stage (Figure 2).

Satellite cell activation and proliferation

Cytokines that have been reported to positively regulate satellite cell activation and myoblast proliferation in a muscle-autonomous manner include CCL2 [61], CXCL16 [62], FGFs (1, 2, 4, 6 and possibly others) [30, 38], G-CSF [63], HGF [43, 44], IFNγ [64], IGFs [29–31], IL-1 [65], IL-6 [66], LIF [67], NGF [68], PDGF [39–41], TGFβ [49, 50], and Sonic hedgehog (SHH) [69, 70]. These cytokines signal through their cognate receptors and intracellular signaling pathways well established to regulate proliferation of various cell types, including ERK, AKT, SMADs and STATs (Figure 3). SHH plays a critical role in embryonic myogenesis [71] and its expression is absent in adult muscles. Muscle injury reactivates SHH signaling, and pharmacological inhibition of the signaling is reported to impair regeneration [72]. While its receptor Ptch1 and downstream target Gli1 are expressed in mouse primary myoblasts and C2C12 cells, SHH itself is not produced by those cells [70]. Instead, injured myofibers appear to be the source of SHH production in vivo [72], making SHH a bona fide muscle-derived cytokine.

Myostatin, among its many reported inhibitory functions in muscle, negatively regulates satellite cell self-renewal and proliferation by impinging on the levels of the G1 cell cycle regulators $p21^{CIP}$ and Cdk2 [73, 74]. Similarly, activin A is also reported to negatively regulate satellite cell activation and proliferation [75]. TNFα inhibits regeneration of mdx muscles by suppressing satellite cell activation via NF-κB signaling and epigenetic silencing of Notch1 [76, 77].

Cell cycle withdrawal

Two events during the earliest stage of myogenic differentiation – cell cycle withdrawal and initiation of differentiation – are regulated by a large number of cytokines (Figure 2). This is perhaps not surprising, as the commitment to differentiation is a point of no return for the cell fate. Muscle-derived Flt3L promotes C2C12 myoblast exit from the cell cycle, and knockdown of Flt3L impairs myoblast differentiation in vitro and muscle regeneration in vivo [78]. As an example of a ligand-receptor pair utilizing distinct signaling mechanisms in different biological contexts, Flt3L via its receptor Flt3 (an RTK) stimulates hematopoietic cell proliferation by activating ERK signaling [79], whereas in myoblasts Flt3L-Flt3 signaling activates cell cycle withdrawal by suppressing ERK through a non-canonical p120RasGAP pathway [78]. Brain derived neurotrophic factor (BDNF) is reported to be expressed in L6 [80], C2C12 [68], and both mouse [81] and human [82] primary myoblasts. Depletion or deletion of BDNF in primary myoblasts results in impaired cell cycle withdrawal and differentiation in vitro [81, 82], suggesting a positive role of BDNF in facilitating cell cycle exit of myoblasts. Similar to Flt3L, BDNF has an opposite effect in non-myogenic cells – it promotes cell proliferation in the subventricular zone and hippocampal dentate gyrus [83]. VEGF's effect on suppressing cell proliferation at the onset of differentiation also makes it a likely candidate as a positive regulator of cell cycle withdrawal [84].

Interestingly, a large number of muscle-derived cytokines have been found to block cell cycle withdrawal and negatively regulate myogenic differentiation including, not surprisingly, many of the growth factors that promote myoblast proliferation – FGFs [38, 85,

86], PDGF [39–41], HGF [43, 44] and TGFβ [49, 50], as well as TNFα [87], BMP4/7 [88–91], CXCL14 [92], and TNFSF10/TRAIL [93]. These cytokines belong to different classes and signal through different types of receptors, and yet, ERK signaling has emerged as a common downstream pathway responsible for modulating the cell cycle (Figure 3). It has been well established that the ubiquitous mitogenic signaling by ERK suppresses myogenic differentiation by preventing cell cycle withdrawal [94, 95], which requires the expression of cyclin dependent kinase inhibitor $p21^{CIP}$ [96, 97]. In principle, it is also possible that distinct downstream pathways can transduce the signals from different cytokines and converge on the cell cycle machinery.

Not all published studies reporting effects of cytokines on the early stage of differentiation directly examined their involvement in the cell cycle, but some of those cytokines may well be regulating cell cycle withdrawal. For instance, LIF is expressed in mouse primary myoblasts [98]; recombinant LIF inhibits myoblast differentiation at an early stage accompanied by reduced $p21^{CIP}$ expression and increased ERK activation, and inhibition of ERK signaling rescues differentiation in LIF-treated cells [99]. An earlier study in fact had reported LIF stimulating mouse primary myoblast proliferation [67]. These observations taken together strongly suggest that LIF negatively regulates myogenic differentiation through suppressing cell cycle withdrawal. Our RNAi screen [28] has led to the identification of additional 10 or so cytokines (belonging to several distinct families) that may negatively regulate myogenic differentiation by blocking cell cycle withdrawal (D. Kim & J. Chen, unpublished observations). It is not clear why myocytes secrete such a large number of distinct cytokines to modulate a single step of myogenesis. Do these cytokines support myoblast/satellite cell proliferation and simply need to be removed at the time of differentiation? The results of our unpublished preliminary studies do not seem to support this notion (R. Waldemer-Streyer, D. Kim, & J. Chen). Or is this arsenal of inhibitors of differentiation necessary for the maintenance of satellite cell pool? The knockdown of any one of those cytokines in myoblasts results in a differentiation phenotype, suggesting that these regulators are not redundant. How do they functionally interact? Do their signaling pathways interact and if so how?

Initiation of differentiation

Whereas the initiation of differentiation can be a direct consequence of cell cycle withdrawal regulated by the cytokines discussed above, some cytokines may regulate this process independently of cell cycle withdrawal. IGF1 and IGF2, through their receptor IGF1R, signal through the PI3K-AKT pathway to robustly activate the myogenic differentiation program [10, 100]. Mammalian target of rapamycin (mTOR) plays a multi-faceted role in the myogenic regulation by IGF2 [9]: (a) a rapamycin-sensitive and kinase-independent function of mTOR governs IGF2 expression in muscle cells [101–103]; (b) mTOR complex 2 (mTORC2) is a kinase for AKT [104] and hence a positive regulator of IGF2 signaling; (c) mTOR complex 1 (mTORC1) dampens PI3K-AKT myogenic signaling through serine phosphorylation of IRS1 [105, 106].

SHH was also reported to promote C2 myoblast differentiation through the PI3K pathway [69], although another study found recombinant SHH to *inhibit* C2C12 differentiation

[70]. The marked differences between C2 and its subclone line C2C12 [107] could have contributed to this discrepancy. Alternatively, since SHH also stimulates myoblast/satellite cell proliferation [69, 70], the timing of SHH addition to cell culture could determine the outcome of proliferation versus differentiation.

Myostatin, acting through the activin type II receptor, has been shown to reduce MyoD expression and activity via Smad3, hence inhibiting the initiation of differentiation [108]. Signaling from mTORC1 and mTORC2 may also be involved in mediating myostatin inhibition of differentiation of human myoblasts [109]. Several other TGFβ family members may have a similar role as myostatin, including TGFβ1, GDF11, and activin A [55, 56, 109].

In addition to regulating satellite cell proliferation as discussed earlier, the autocrine function of IL-6 is necessary for myogenin expression and myotube fusion, which is impaired in C2C12 cells with IL-6 knockdown and mouse primary myoblasts with IL-6 KO [110, 111].

Myoblast migration and fusion

Upon cell cycle withdrawal and activation of the myogenic gene expression program, mononucleated myocytes fuse to form multi-nucleated myotubes/myofibers. Proper positioning or alignment of the cells is necessary for this fusion, which likely requires myocyte migration. Known to induce cell migration in a number of cell types, VEGF is reported to stimulate myoblast migration and differentiation [84, 112]. Both IL-6 [66] and IL-7 [113] also play a positive role in myoblast migration. The chemokine CXCL12 and its receptor CXCR4 are demonstrated to be critical regulators of myocyte migration and fusion [27]. Another chemokine, CXCL14, is reported to stimulate migration of C2C12 cells as well [114]. In addition, Griffin et al. found a larger number of chemokines to be expressed at the mRNA levels during myoblast fusion, raising the possibility that a network of chemokines may regulate the fusion process [27]. Intracellular signaling pathways involving the Rho small GTPases are known to regulate actin cytoskeleton dynamics and cell migration [115, 116] and they can be downstream targets of muscle-derived cytokine signaling. Furthermore, it is possible that cytokine signaling can be linked to many of the regulators identified to control myoblast migration and myocyte fusion [5, 6].

There are two distinct phases of skeletal myocyte fusion during both embryonic and adult myogenesis in mammals – myoblast-myoblast fusion to form nascent myotubes and myoblast-myotube fusion to form mature myotubes/myofibers [6, 117]. Remarkably, the two fusion processes are separable at the molecular level, with a distinct set of molecules and signaling pathways regulating each [6, 117]. IL-4 was the first example of a muscle-derived cytokine that specifically regulates the second stage of myocytes fusion, reported by Horsley et al. [118]. However, the origin of this cytokine in vivo has been disputed [119]. Heredia et al., detected no IL-4 expression in regenerating muscles in vivo; instead, they demonstrated that eosinophils recruited to the muscle injury site produce IL-4 to regulate muscle resident fibro/adipocyte progenitor cells essential for myofiber regeneration [119]. mTOR is found to govern multiple stages of myogenic differentiation via distinct pathways, one of which is the regulation of second-stage myocyte fusion via a secreted factor [120]. Follistatin partially fulfills the criteria for this secreted factor as its expression in muscle cells is regulated by an

mTOR pathway involving microRNA-1 and HDAC4, although follistatin contributes to both stages of myocyte fusion [121].

Cell survival

Although not a direct step in the myogenic process, maintenance of myocyte survival is obviously necessary for the process. Among the muscle-derived cytokines, CNTF [122], IGF2 [37], SHH [70], TNFSF14 [123], and VEGF [84, 112] have been reported to support the survival of myoblasts. Signaling by the Ser/Thr kinase AKT is a major survival pathway in various cell types [124, 125] and, indeed, at least CNTF and TNFSF14 have been shown to signal through AKT to regulate myoblast survival [122, 123]. Other muscle-derived cytokines may exert pro-apoptotic effects. One example is IL-1, which has been reported to be expressed by human primary myoblasts; exogenous IL-1β induces myoblast apoptosis without affecting cell proliferation or fusion [126]. It is possible that optimal cell number/density is controlled by counter-acting cytokine signaling to regulate muscle size during myogenesis.

Muscle-derived cytokines in myogenesis in vivo—The critical role of cytokines in muscle regeneration is well established, but immune cells at the site of muscle injury have been traditionally considered the main source of those cytokines [12, 13]. Although cytokine involvement in muscle diseases, such as muscular dystrophy, cachexia and sarcopenia, has been widely known, the emphasis is again on inflammation and immune cell-produced cytokines [127, 128]. Much of what we know to date about muscle-derived cytokines in regulating myogenesis came from in vitro studies. In the literature there is surprisingly a paucity of in vivo studies of myogenesis that entail modulating cytokine expression in a *muscle-specific* manner. Nevertheless, many of the cytokines covered in this review (i.e., expressed by muscle cells and have demonstrated myogenic functions) are reported to be expressed in myogenic cells or myofibers during acute injury-induced muscle regeneration, or in muscles undergoing satellite cell-dependent compensatory hypertrophy upon mechanical overload. In addition, some of the cytokines are expressed in dystrophic muscles, in Duchenne muscular dystrophy (DMD) for example, which undergo spontaneous cycles of degeneration and regeneration [129]. In Table 1 we include information of cytokine expression in the regenerating muscle, hypertrophic muscle, dystrophic muscle, and developing muscle. Below we discuss selected cytokines with evidence of functional involvement in the regeneration of normal or dystrophic muscles.

BDNF

Initially identified as a myokine produced in human skeletal muscles in response to exercise and found to confer autocrine/paracrine regulation of muscle metabolism [130, 131], the expression of BDNF is also upregulated in mouse regenerating muscles after injury [81]. BDNF is expressed in normal human skeletal muscles as well as by immune cells located near regenerating myofibers from patients of inflammatory myopathies [82]. A myogenic role of BDNF produced by human satellite cells post-exercise has been implicated by an increase in the number of $BDNF^{+}$/$myogenin^{+}$ cells [132]. Muscle regeneration is impaired in mice with targeted BDNF gene disruption driven by satellite cell-specific Myf5-Cre

[81], providing definitive evidence for a physiological role of muscle-derived BDNF in myogenesis.

FGF6

The expression of FGF6 is restricted to developing skeletal muscle during embryogenesis [133, 134] and also found in regenerating muscles post-injury [135, 136]. It is reported that FGF6-null mice have impaired muscle regeneration upon injury, most likely due to diminished satellite cell expansion [135], although another study found no defect in injury-induced muscle regeneration with FGF6−/− mice [137]. The phenotype of impaired regeneration in FGF6-null mice is corroborated by accelerated regeneration of injured mouse soleus muscle upon intramuscular delivery of recombinant FGF6 [136]. While these observations combined provide support for a function of muscle-derived FGF6, definitive evidence is yet to come from muscle-specific ablation of the cytokine.

IGF

The expression of both IGF1 and IGF2 in regenerating muscles is associated with regenerative capacity [138, 139]. Muscle-specific transgene expression of IGF1 in mice has been well studied, the effects of which include hypertrophy, accelerated regeneration upon injury, prevention of muscle decline in mdx mice, and enhanced muscle maintenance and regenerative capacity during aging [140–143]. Muscle-specific deletion of IGFR1 (hence impairment of both IGF1 and IGF2 signaling) suppresses muscle growth [144, 145]. However, muscle-specific knockout of IGF1 or IGF2 has not been reported and hence definitive genetic evidence for the autocrine function of IGF in vivo is still lacking.

Myostatin

Systemic knockout of myostatin in mice leads to drastically enhanced muscle growth [53], and a mutation in the bovine myostatin gene is responsible for the double-muscled phenotype in cattle [146]. Since myostatin is almost exclusively expressed in skeletal muscles in mice [53], its systemic knockout provides sufficient evidence for a muscle-autonomous function. Muscle-specific expression of follistatin, which antagonizes myostatin, leads to enhanced muscle growth in mice to a similar degree as myostatin knockout [147]. The expression of myostatin is elevated in mechanically overloaded hypertrophic muscles but decreased in injury-induced regenerative muscles [148]. Nevertheless, myostatin KO may promote muscle regeneration and improve muscle strengths in the mdx mouse, a commonly used (albeit imperfect) model of DMD [149], making myostatin a potential therapeutic target for treating DMD [150, 151].

TNFα

Implicated as a major inflammatory mediator of muscle wasting in aging or disease [152–154], recombinant TNFα inhibits myoblast differentiation in human and mouse cultures [87, 155, 156]. TNFα is reported to be expressed in regenerating myofibers of mdx mice, although the source of this cytokine in DMD can also be immune cells [76, 128, 157]. The elevated level of TNFα in the mdx dystrophic muscles may suppress regeneration by inhibiting satellite cell activation [76, 157]. However, interfering with endogenous

TNFα expression or signaling leads to inhibition of myoblast differentiation in vitro and reduction of muscle regeneration in vivo [158–161]. A model to potentially reconcile these paradoxical observations is that normal muscle-derived TNFα has a positive role in myogenic differentiation whereas immune cell- or dystrophic muscle-derived TNFα has a negative role. Concentrations of the cytokine and/or activation of distinct downstream signaling pathways may determine the outcome. Indeed, the MAP kinase p38 is a relevant target of TNFα signaling that supports myogenic differentiation [160, 161], whereas NF-κB mediates the inhibitory function of TNFα [76, 77, 87] (Figure 4).

IL-6

A pro-myogenic function of IL-6 in vivo is supported by the observations that expression of this cytokine is induced in satellite cells and growing myofibers during load-induced compensatory hypertrophy [66, 162], and that satellite cell-dependent hypertrophy is impaired in IL-6 KO mice [66]. LIF, which is closely related to IL-6, also has a critical role in compensatory hypertrophy [148, 163]. In addition, IL-6 and LIF are expressed in regenerating muscles after acute injury [98, 148, 164, 165], and a positive role of endogenous LIF in muscle regeneration in mice has been reported [165, 166]. IL-6 expression is also upregulated in muscles of DMD [167] and young mdx mice [168], the latter manifest a disease phenotype similar to human patients. A decreased level of IL-6 accompanies lessened dystrophy in adult mdx mice [169], suggesting a detrimental role of IL-6 in DMD disease severity. Indeed, forced expression of recombinant IL-6 in adult mdx mice recapitulates the severe phenotype of DMD in humans [169]. Conversely, treatment of mdx mice with an IL-6 receptor-blocking antibody led to enhanced muscle regeneration and alleviated morphological and functional defects of the dystrophic muscle [168]. However, another study employing a similar strategy did not find statistically significant improvement in mdx muscles [170]. The discrepancy between the two studies may be attributed to differences in the antibody dosing regimen and/or functional analyses. Administration of the IL-6 receptor-neutralizing antibody also normalized gastrointestinal dysfunction in mdx mice [171]. Therefore, it appears that elevated levels of IL-6 may exacerbate the dystrophic phenotype in DMD and that IL-6 could be a therapeutic target. Currently it is believed that transient and local production of IL-6, such as during injury-induced regeneration or load-induced compensatory hypertrophy, is associated with pro-myogenic effects, whereas chronic and systemically increased IL-6 levels are coupled with muscle atrophy [172].
In vitro, IL-6 has been reported to play both positive and negative roles in myogenic differentiation. The autocrine function of IL-6 promotes satellite cell proliferation, myoblast migration and differentiation [66, 110, 111] as discussed earlier. However, exogenous IL-6 treatment of C2C12 cells suppresses myogenic differentiation, possibly through down-regulation of the kinases $p90^{RSK}$ and $p70^{S6K}$ [173]. This is reminiscent of the paradoxical roles of TNFα in differentiation discussed earlier (Figure 4).

IFNγ

Similar to TNFα and IL-6, paradoxical observations have been reported for the role of IFNγ in myogenesis. IFNγ is found to be expressed by both immune cells and muscle cells in regenerating muscles upon injury, and muscle regeneration is impaired in IFNγ KO mice or by the administering of an IFNγ receptor blocking antibody [64]. Clearly, IFNγ has a

positive function in myogenesis. However, administration of exogenous IFNγ also inhibits muscle regeneration in mice, whereas an IFNγ neutralizing antibody rescues regeneration in mice with elevated circulating levels of IFNγ and impaired regeneration as a result of KO of immunity-related GTPase family M1 protein (lRGM1) [174]. Consistent with these in vivo observations, antibody blocking of IFNγ receptor inhibits proliferation and fusion of C2C12 cells [64], and exogenous IFNγ also suppresses differentiation of C2C12 [175] and human skeletal myoblasts [176]. Again, all these observations can be potentially reconciled by considering muscle-derived IFNγ pro-myogenic and pathological levels of IFNγ anti-myogenic. It should be noted, however, a role of muscle-derived IFNγ is yet to be demonstrated in vivo.

Concluding remarks and future directions

Released by infiltrating immune cells at skeletal muscle injury sites, cytokines play critical roles in facilitating muscle repair and regeneration. Although autocrine functions of a few muscle-secreted cytokines have been known for a long time, only in the last 10–15 years has the muscle emerged as a significant source of a large number of cytokines from all families. Many of these cytokines have now been assigned functions in the well-orchestrated process of myogenic differentiation, although many more remain to be functionally characterized. However, very few studies thus far have directly examined the source of cytokines (i.e., muscle versus immune cells) for their contribution to muscle regeneration in vivo. Filling this knowledge gap not only is of intellectual intrigue but can also lead to more effective designs of stem cell therapy in muscular dystrophy and other muscle diseases. To that end, the advent of CRISPR/Cas9 gene editing technology should enable more rapid generation of mice with muscle-specific ablation of cytokines. For instance, the recently reported transgenic mice with Cas9 expression driven by human skeletal actin (HSA)-Cre [177] and muscle creatine kinase (MCK)-Cre [178] would offer a convenient way to knock out or knock down cytokine genes of interest in muscle by delivering specific sgRNAs. Muscle-specific activation of cytokine gene expression would also be informative and potentially applicable in therapeutics, and the CRISPR activation technology (CRISPRa) provides a powerful tool [179]. For instance, the dCas9-SunTag system [180, 181] can be combined with appropriate promoters [182] to drive Cre in order to achieve muscle-specific gene activation.

Many cytokines are detected at low levels in non-myeloid cell types including skeletal muscle cells. A potential implication is that individual cytokines may primarily contribute to fine-tuning mechanisms during differentiation and regeneration. Alternatively, it is possible that the local concentrations of muscle-derived cytokines are sufficiently high to support autocrine functions. To make matters more complicated, it is likely that many of the same cytokines are secreted by both muscle cells and immune cells, and that the source of a cytokine could determine its specific function, as we have seen with TNFα, IL-6 and IFNγ as examples. How does the muscle cell distinguish cytokines coming from different sources – what are the biochemical and cellular mechanisms for the differential signaling? How are muscle-derived cytokines regulated at the expression level and is there any inter-connectivity or hierarchy among them? Do these cytokines interact with each other at the signaling level to form a network in the regulation of the multiple processes of myogenesis? What would

be the heterogeneity, if any, within a muscle cell population in their production of and response to cytokines? Multi-pronged experimental approaches coupled with computational modelling may offer the best chance to delineate such a complex regulatory system.

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Abbreviations

BDNF	brain-derived neurotrophic factor
BMP	bone morphogenetic protein
CCL	C-C motif chemokine ligand
CCN	connective tissue growth factor (CTGF), cystein rich protein, and nephroblastoma overexpressed gene (NOV)
CNTF	ciliary neurotrophic factor
CT-1	cardiotrophin-1
CXCL	C-X-C motif ligand
DMD	Duchenne muscular dystrophy
ERK	extracellular signal-regulated kinase
FGF	fibroblast growth factor
Flt3	fms like tyrosine kinase 3
Flt3L	fms like tyrosine kinase 3 ligand
G-CSF	granulocyte colony stimulating factor
GDF	growth differentiation factor
GPCR	G protein-coupled receptor
HGF	hepatocyte growth factor
IFN	interferon
IGF	insulin-like growth factor
IL	interleukin
LIF	leukemia inhibitory factor
mTOR	mammalian target of rapamycin
NGF	nerve growth factor

OSM	oncostatin M
PDGF	platelet-derived growth factor
PI3K	phosphoinositide 3-kinase
RTK	receptor tyrosine kinase
SHH	sonic hedgehog
STAT	signal transducer and activator of transcription
TGF	transforming growth factor
TNF	tumor necrosis factor
TNFSF	TNF superfamily
VEGF	vascular endothelial growth factor

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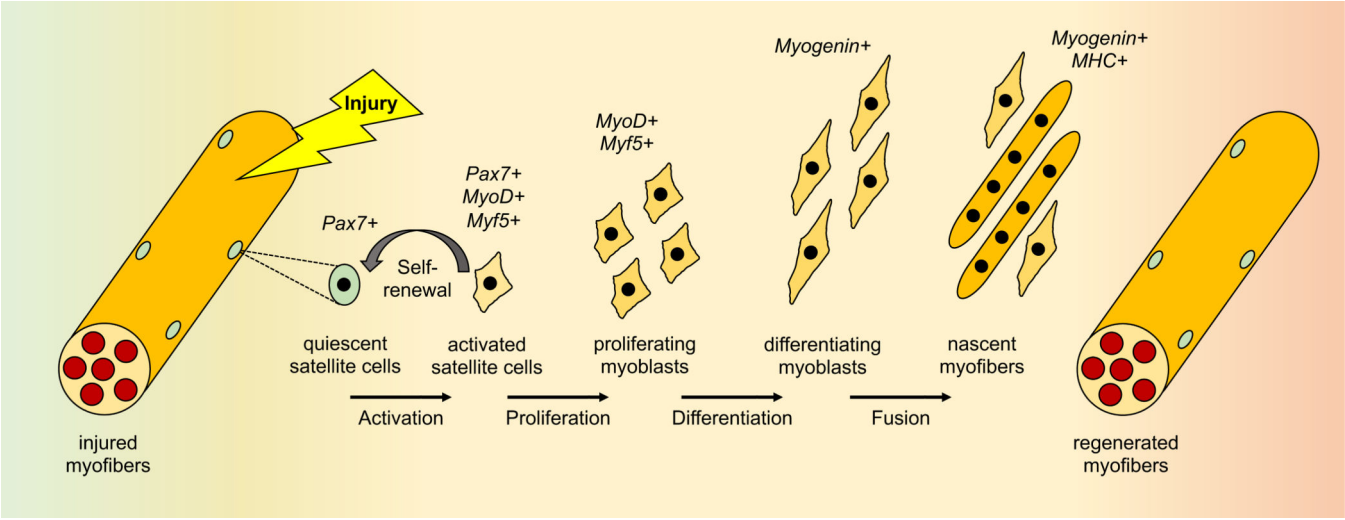

Figure 1. The sequential events of injury-induced muscle regeneration.

The expression of Pax7, MyoD, Myf5 and myogenin marks myocytes at different stages. MHC: myosin heavy chain.

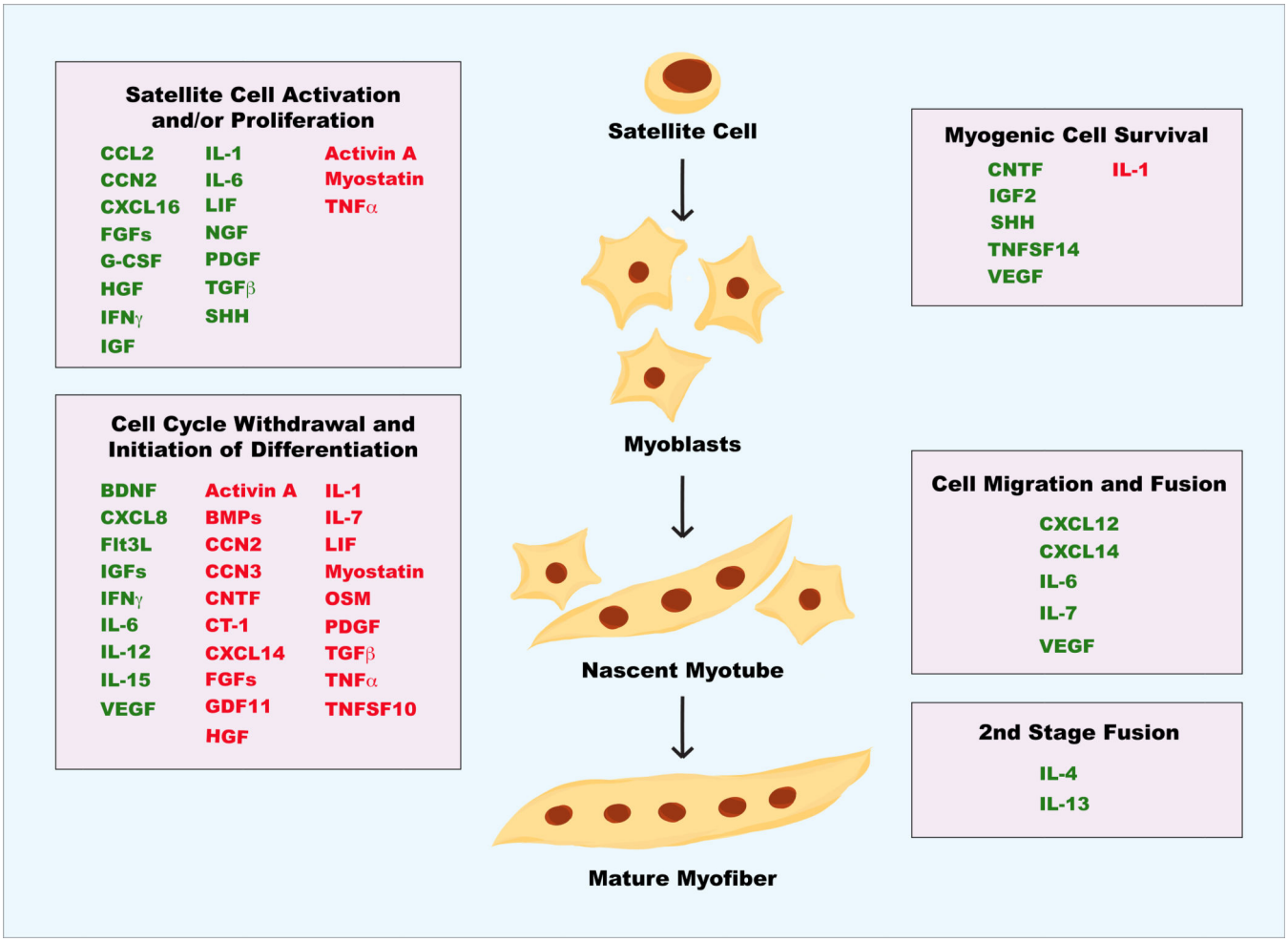

Figure 2. Muscle-derived cytokines involved in various stages of myogenesis.
Green: positive regulators; red: negative regulators.

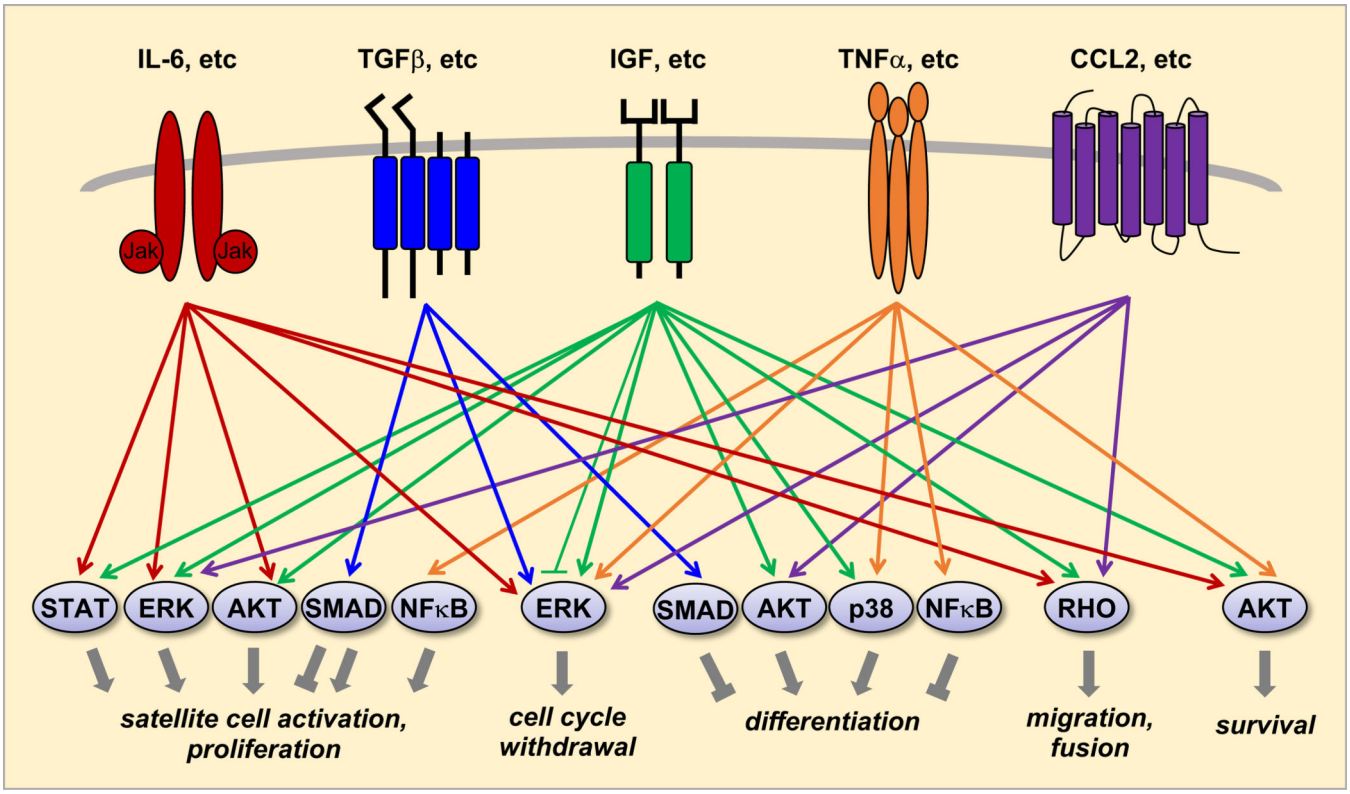

Figure 3. Schematic diagram of muscle-derived cytokine signaling regulating myogenic processes.

Five classes of cytokines and receptors are represented, and only the most downstream components of signaling pathways are shown. A major omission is SHH, which signals through its receptor Ptch1 and regulates satellite cell activation and proliferation, differentiation, and survival.

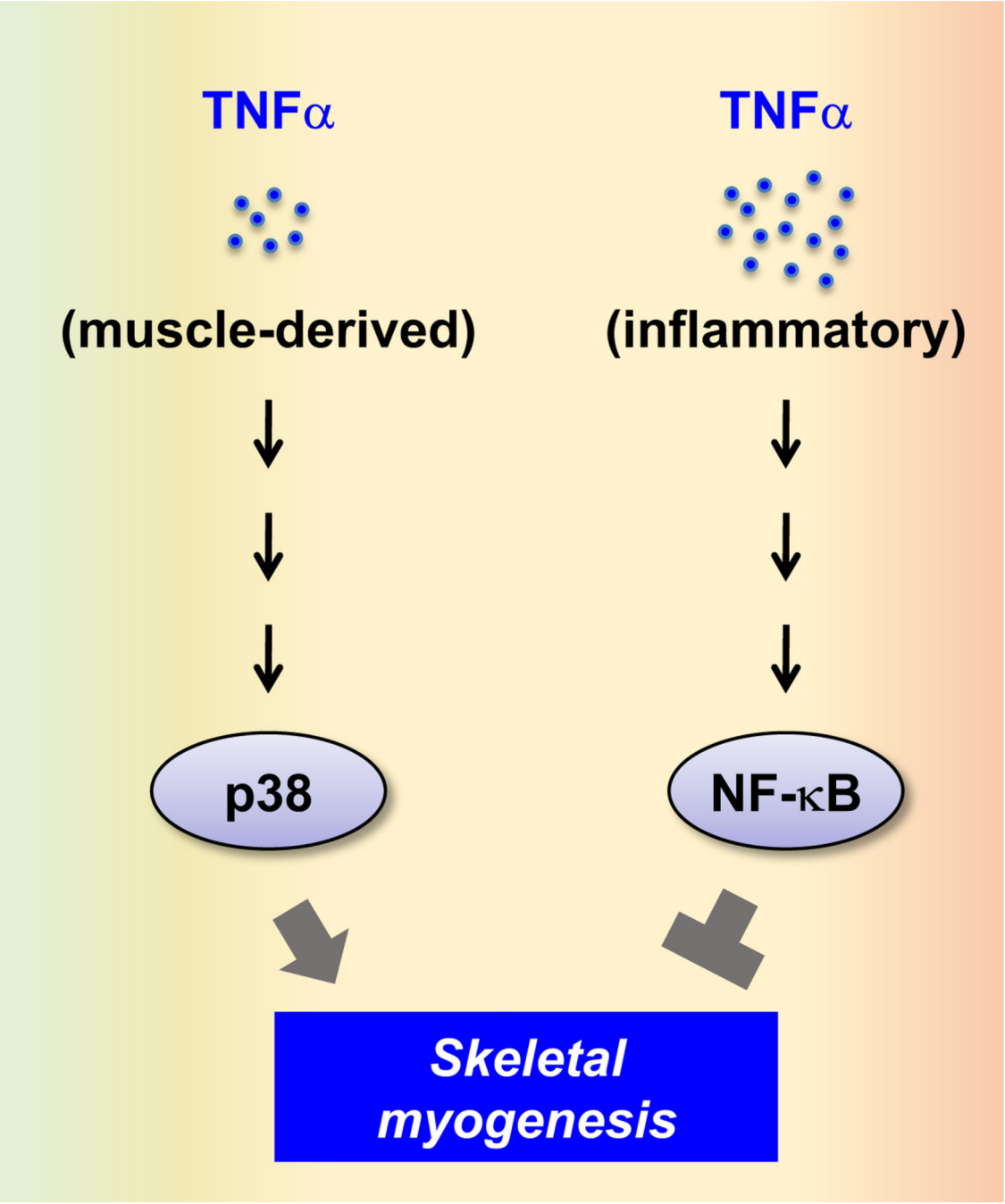

Figure 4. Context-dependent TNFα signaling in myogenesis.
The source and concentration of TNFα can determine its downstream signaling pathways and effects on myogenesis.

Table 1.

Muscle-derived cytokines and their reported functions in myogenic regulation.

Cytokines reported to be expressed in muscle cells and have a myogenic function are listed. "+" indicates positive regulation of the process whereas "–" indicates negative regulation. Differential expression of these cytokines in muscles or muscle progenitor cells in vivo under the following conditions are indicated: Dev – developing muscle; Reg – regenerating muscle after acute injury; Hyp – satellite cell-dependent compensatory hypertrophy; Dys – DMD or mdx.

Cytokine	Function in myogenic differentiation	Expression in vivo
Ligands for RTKs:		
BDNF	+ cell cycle withdrawal; + differentiation [81, 82]	Dev [183, 184]; Reg [81]
FGF1,2,4,6	+ proliferation; − cell cycle withdrawal; − differentiation [30, 38]	Dev [133, 134, 185]; Reg [135, 136]; Hyp [188]; Dys [186, 187]
Flt3L	+ cell cycle withdrawal; + differentiation [78]	
HGF (Scatter factor) [191]	+ proliferation; − cell cycle withdrawal; − differentiation [43, 44]	Dev [189]; Reg [190]; Hyp [188]; Dys
IGF1, IGF2 [193];	+ proliferation; + initiation of differentiation; + survival [29–31, 37]	Dev [192]; Reg [138, 139, 190]; Hyp Dys [191]
NGF	+ satellite cell activation/proliferation [68]	Dev [194]; Dys [195]
PDGF	+ proliferation; − cell cycle withdrawal; − differentiation [39–41]	Dev [196]; Reg [196]; Dys [197]
VEGF	+ cell cycle withdrawal; + migration; + differentiation; + survival [84, 112]	
		Reg [198]; Hyp [199]; Dys [187]
Ligands for cytokine receptors:		
CNTF	+ survival; − differentiation; + dedifferentiation [122, 200]	
CT-1	− initiation of differentiation [201, 202]	Dev [203]; Reg [204]; Hyp [204]
G-CSF	+ proliferation [205–208]	Dev [209]; Reg [209]; Hyp [210]
IFNγ	+ proliferation; +/− differentiation [64] [87, 155, 156, 158]	Reg [64]
IL-4	+ second-stage fusion [118]	Hyp [162]
IL-6	+ proliferation; + migration; + differentiation [66, 110, 111, 173]	Hyp [66]; Reg [164]; Dys [187]
IL-7	+ migration; − differentiation [113]	
IL-12	+ differentiation [211, 212]	
IL-13	+ second-stage fusion [118, 213, 214]	
IL-15	+ differentiation [215, 216]	
LIF	+ proliferation; − cell cycle withdrawal; − differentiation [67, 98, 99]	Hyp [148]; Reg [148, 164]; Dys [98, 187]
OSM	+ satellite cell quiescence; − differentiation [217, 218]	Dys [187]

Cytokine	Function in myogenic differentiation	Expression in vivo
Ligands for GPCRs:		
CCL2 (MCP1)	+ proliferation [23, 61, 219]	Reg [219, 221]; Dys [187, 220]
CXCL8 (IL-8)	+ differentiation [222]	Dys [223]
CXCL12 (SDF1)	+ migration; + fusion [27, 224, 225]	Dev [224]; Reg [226]; Dys [227]
CXCL14 (BRAK)	− cell cycle withdrawal; + migration [92, 114]	Reg [92]; Dys [220, 227]
CXCL16	+ proliferation; + modulating immune cells [62]	Reg [62]
TGFβ family:		
Activin A	− proliferation; − differentiation [55, 58, 75]	Dev [55]; Reg [75]
BMP4, 7	− cell cycle withdrawal; − differentiation [88–91]	Dev [228, 229]
GDF11	− differentiation [56, 109]	Dev [230]
Myostatin (GDF8) [187]	− proliferation; − initiation of differentiation [73, 74, 108, 109]	Dev [231]; Reg [148]; Hyp [148]; Dys
TGFβ	+ proliferation; − cell cycle withdrawal; − differentiation [46–50]	Dev [232]; Reg [235]; Dys [233, 234]
TNF family:		
TNFα (Cachectin)	− satellite cell activation; − cell cycle withdrawal; −/+ differentiation [87, 155, 156, 158–161]	
		Dev [236]; Reg [159]; Dys [187, 237]
TNFSF10 (TRAIL)	− cell cycle withdrawal; − differentiation [93]	
TNFSF14 (LIGHT)	+ survival; + differentiation [123]	Reg [123]
Others:		
CCN2 (CTGF)	+ proliferation; − differentiation; + dedifferentiation [238, 239]	Dev [240]; Dys [241, 242]
CCN3 (NOV)	− myogenic cell lineage; − cell cycle withdrawal; − differentiation [243]	
		Dev [244]
IL-1	+ proliferation; − differentiation; − survival [65, 87, 126]	Reg [235]
SHH	+ satellite cell activation and proliferation; +/− differentiation; + survival [69, 70, 72]	
		Dev [245]; Reg [72]