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Inception And Significance of Myoblasts

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Abstract

Adult mammalian skeletal muscle regeneration involves many proteins and signalling networks. Cytokines influence skeletal muscle development. Myofibrillar repair and regeneration depend on cytokines generated by cells of immune system, at injury site of muscle. Skeletal muscle is a key generator of cytokines. Muscle-released cytokines (myokines) may have endocrine effects on regulation of metabolism. Available reports suggest that myogenic differentiation and regeneration are governed by autocrine cytokines

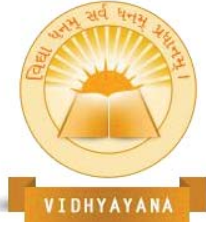
released by muscles. Present review focus on cytokines that (a) expression of muscle cells and (b) have a myogenic role. This group of cytokines controls the entire myogenic process. How cytokines create a regulatory network is an intriguing and crucial topic. To fully explore the therapeutic potential of cytokines, functional studies must pinpoint their in vivo source.

Keywords: Myofibril, cytokines, skeletal system, Hepatocytes, Myostatin

Introduction

One of the few adult mammalian tissues that may regenerate after injury is skeletal muscle due to a large number of stem cells. Satellite cells are myogenic progenitor cells that lie latent under myofibres' basal lamina until damaged by trauma, toxins, exercise, or disease. When an injury occurs, some activated satellite cells go into quiescence to allow the pool of stem cell of muscle to self-renew, whereas the activated remainder cells proliferate at the injury site to provide a place for the production of new myofibrils or the repair of damaged myofibrils [1].

Expression of embryonic myogenic genes, like MyoD and MEF2 transcription factors [2], is important for myoblast regeneration. The cells of Myoblasts should undergo cell-cell adhesion, migration, alignment, cytoskeletal rearrangement and fusion of membrane to form a multinucleated myofibre. Myocyte fusion is governed by two distinct molecular pathways [3]. Myotubes form from immature myoblasts during differentiation. Myofibres are formed when myoblasts and myotubes recombine. p38, PI3K/AKT, mTOR, JAK/STAT regulates this myogenic process. This review focuses on cytokines that are derived from muscle cells and their signalling roles in myogenesis. The first-discovered cytokines were thought to come from the blood and influence inflammation. Almost any cell type can secrete factors, and even the pioneering cytokines have activity outside the immune system. These secreted components have a variety of names, some of which overlap. Interleukins and interferons are considered genuine cytokines because they signal via JAK kinase-linked receptors. Most growth factors function through tyrosine kinases. G protein-coupled receptors have chemokines which are called "chemoattractant ligands" for attracting cells. TGFβ and TNF receptors bind these cytokines. "Cytokine" refers 30 kDa secreted protein which works via receptors that are present on cell surface. Nearly all members of the tumour necrosis factor



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(TNF) family exist in both transmembrane and extracellular soluble forms; both are physiologically active. Some cytokines like VEGF, IL-12 are greater than the 30 kDa.

Immune cells infiltrate injury sites to eliminate damaged tissue and enhance muscle repair [4]. Immune cells may emit chemicals that influence muscle repair after injury. Skeletal muscle's importance as a secretory organ has grown in the past two decades. Skeletal muscle cells produce myokines which are cytokines (during exercise) to exert metabolic and hormonal effects [5]. Myokine IL-6 is released by working muscles and has a variety of beneficial effects on metabolism (e.g., [5, 6]). Cytokines of endocrine system has little role in regulating myogenesis. Single-cell RNA sequencing (scRNAseq) allows for in-depth transcriptionomics of injured muscle, it has become obvious that there is a considerable degree of heterogeneity in gene expression among the many cell types and subpopulations that contribute to repair and regeneration [7-10]. Immuno-myoblasts are satellite cells in regenerated muscle that express immune genes. These cells may help regenerate cytokines. ScRNAseq findings from multiple groups [7-10] imply a cytokine-expressing satellite cell subpopulation. This review is just beginning to learn where cytokines come from and how cells react to them during regeneration. The current investigation focuses on cytokines released by muscle cells that influence skeletal muscle differentiation and regeneration to shed light on the myocyte lineage's role in myogenesis.

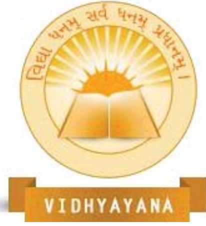
Skeletal muscle cells as cytokine factories.

Muscle-derived cytokines have long been suspected of playing a role in autocrine and paracrine modulation of myogenesis, and it's well recognised that components involved in skeletal myoblasts differentiation. Although cultured muscle cells are prolific cytokine secretors, muscle tissue homogenates may contain non-muscle proteins. Skeletal muscle secretome proteome view was provided 10 years ago by multiple research groups. Mouse C2C12 myoblast growth analysis was done by two research teams using SILAC and proteomic methods [11-13]. 34 secreted proteins were discovered by Chan et al. of which none were cytokines or growth factors. The two studies indicated that proteins changed their secretion pattern during differentiation, suggesting that the molecules may regulate

myogenesis. Yoonet al. studied 254 proteins in totally differentiated myotubes of rat L6 myoblast, another widely used myogenic cell line, where small up- or down-regulation observed by short-term (5 h) insulin administration [14]. Norheim et al. [15] analysed human myotubes and found 18 secreted proteins. 84 chemokines were analysed in mouse primary myoblasts by Griffin et al. The bulk of these genes surge during myocyte fusion, suggesting a function for chemokines in the cell mobility required for fusion [16]. Henningsen et al. discovered no clear link among quantities of cytokine proteins with their mRNAs [13], indicating that post-transcriptional regulation may play a major role in muscle cell cytokine secretion. Many muscle-secreted cytokines have not been linked to myogenesis. The evidence suggests that muscle cell-secreted proteins may influence myogenic differentiation and muscle regeneration. 29 potential regulators of myogenesis using an RNAi-based functional screen were identified after assessing 134 mouse cytokines for their effect on myogenic differentiation in C2C12 myoblasts [17].

Myogenic differentiation and autocrine cytokines

Muscle-secreted substances can regulate myogenesis. Within the following paragraphs, many primitive cytokines are overviewed. IGF1 and IGF2 are two of many cytokines shown to promote autocrine myogenesis [18-20], but they were discovered and studied first. Skeletal muscle cells respond positively to IGFs, increasing in size and proliferating [21, 22]. Over 30 years ago, myoblasts secreted IGF2, a growth factor essential for initiating differentiation [23]. Myogenin [18] is boosted by IGF1 and IGF2 [24, 25], which are produced by C2C12 myoblasts. Autocrine IGF2 is another growth factor that helps muscle cells in addition to PDGF from hepatocytes and PDGF from fibroblasts. In vitro, FGFs suppress myogenic growth, while IGFs stimulate it [19]. Direct inhibition of myogenic gene expression has also been postulated, but FGF2 (basic FGF) is more effective than FGF1 (acidic FGF) at preventing cell cycle withdrawal and reducing differentiation. Multiple fibroblast growth factors (FGFs) (FGF1, 2, 4, and 6) are expressed by satellite cells and have been shown to stimulate the growth of cultured satellite cells in an autocrine fashion [26]. During muscle regeneration, FGFs may inhibit myogenic differentiation and encourage the proliferation of satellite cells. The role of FGF in myogenesis has not been demonstrated in living organisms



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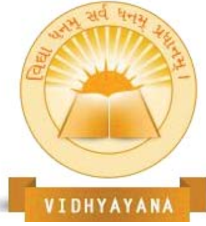
(to be discussed later). Myoblast-produced platelet-derived growth factor (PDGF) suppresses myogenic differentiation by preventing cells from entering a resting state after dividing [27-29]. During muscle regeneration in rats, hepatic growth factor (HGF) promotes satellite cell proliferation and suppresses differentiation [30]. Unlike FGF, PDGF, and HGF, IGFs boost myoblast proliferation without interfering with myogenic activity during differentiation. IGF2 in particular has a mitogenic activity that is unrelated to its myogenic effects.

Transforming growth factor beta (TGFβ)

Three teams reported in 1986 that TGFβ suppressed differentiation of myogenesis in lab conditions [31-33]. These exploratory experiments found TGFβ's action was independent of cell growth. TGF-A increases myoblast proliferation by activating Smad2 [34, 35]. C2C12 cells confirm this effect. TGFβ-activated Smad3 may decrease MyoD and other myogenic regulatory factors' transcriptional activity [36]. Myoblasts synthesise TGF in vitro, and mouse skeletal muscles express TGF mRNA [37], indicating an autocrine role. Myostatin (GDF8) is a TGFβ family member that inhibits muscle hypertrophy in mice [38]. Myostatin gene deletion causes double-muscled mice, cattle, and humans [39]. Myostatin reduces muscle growth and myogenesis in several ways. Muscle cells secrete activin A and GDF11, TGFb family members that suppress myogenic differentiation [40, 41]. When they interact with muscle-released follistatin, they disrupt activin receptor binding [41-43]. Follistatin induces muscle growth [44,45] due to its anti-myostatin action, but a myostatin-independent mechanism has also been proposed [46].

Muscle-produced cytokines regulate myogenesis

Endogenous or synthetic cytokines regulate myogenesis and muscle cell expression in vitro or in vivo. Interleukins/muscle-derived cytokines in myogenesis, transforming growth factor beta (TGFβ), and transforming neurotrophic factor (TNF), chemokines, ligands for receptor tyrosine kinases, and chemokines. Interferons, discovered by R. J. Waldemer, relay the Streye signal through cytokine receptors. Although not all cytokines have been reported for their myogenic action, many articles detail the cellular processes of autocrine regulation in



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myogenesis by various cytokines. Numerous muscle-derived cytokines play multiple roles in regulating the myogenic process.

There was a rise in the number of satellite cells that had become active.

Examples include CCL2 [47], CXCL 16 , FGFs (1, 2, 4, 6, and maybe others) [30, 38], G-CSF [48], HGF [43, 44], IFNc [49], IGFs [29-31], IL-1 [50], IL-6 [51], LIF [52], NGF [53], PDGF [27-29], TGFβ [34,35], and Sonic hedgehog (SHH) [54,55]. By binding to receptors, these cytokines activate signalling proteins such as ERK, AKT, SMADs, and STATs, which in turn control cell proliferation. SHH is essential for myogenesis during development but is not found in mature muscles [56]. Blocking SHH signalling with medication hinders muscle regeneration [57]. Although Ptch1 and Gli1 are produced by C2C12 cells (derived from mouse primary myoblasts), SHH is not [55]. SHH is a muscle-derived cytokine since it is synthesised in vivo from damaged muscle fibres [57]. Specifically, myostatin suppresses satellite cell self-renewal and proliferation via influencing G1 cell cycle regulators p21CIP and Cdk2 [58, 59]. Proliferation and activation of satellite cells are stymied by activin A [60]. Epigenetic suppression of Notch1 and NF-kappaB signalling are the mechanisms by which TNFa suppresses satellite cell activation. [61, 62]

Leaving the Cell Cycle

To initiate myogenic differentiation, cells exit the cell cycle and begin to differentiate in response to cytokines. This makes sense, as distinction lasts forever. Knocking down Flt3L has a detrimental effect on myoblast growth in vitro and muscle regeneration in vivo [63]. Flt3L promotes G0/G1 transition in C2C12 myoblasts. When expressed on haemopoietin cells, Flt3L stimulates cell division by activation of extracellular signal-regulated kinase (ERK) signalling [64], but in myoblasts, Flt3L-Flt3 signalling activates cell cycle withdrawal via inhibition of ERK via a non-canonical p120RasGAP pathway [78]. Primary myoblasts from L6 [65], C2C12 [68], mice [66], and humans [67] have all been found to express brain-derived neurotrophic factor (BDNF). Delay in cell cycle exit and impaired differentiation are observed in primary myoblasts with BDNF knocked down or deleted in vitro [66 ,67], indicating a beneficial role for BDNF in promoting myoblast cell cycle exit. In the

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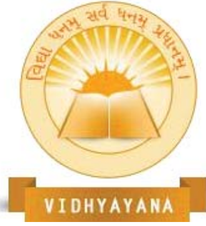
subventricular zone and the dentate gyrus of the hippocampus, BDNF promotes cell proliferation [68], while Flt3L does not. At the outset of differentiation, VEGF inhibits cell proliferation, making it a promising candidate for cell cycle exit [69]. Myogenic differentiation and cell cycle exit are adversely regulated by fibroblast growth factors (FGFs) [70, 71], PDGF], HGF, and TGFb, as well as tumour necrosis factor alpha (TNFa) [72], BMP4/7 [73-75], CXCL14 [76], and TNFSF10/TRAIL [77]. Despite the fact that individual cytokines belong to different classes and signal through different types of receptors, ERK signalling has evolved as a common downstream pathway responsible for changing the cell cycle.

Myogenic differentiation is slowed by pervasive mitogenic signalling via ERK [78, 79], which in turn requires the expression of the cyclin-dependent kinase inhibitor p21CIP [80,81]. Multiple cytokine signals may hypothetically converge on the cell cycle machinery after being transduced through distinct downstream pathways. Some cytokines may be influencing the exit from the cell cycle, albeit this aspect of their purported impacts on the first stage of differentiation was not investigated in all published publications. Myoblasts from a mouse embryo express LIF [82], recombinant LIF reduces myoblast differentiation early on, leading to decreased p21CIP expression and elevated ERK activation, and inhibition of ERK signalling rescues differentiation in LIF-treated cells [83]. Proliferation in primary mouse myoblasts was found to be increased by LIF in previous investigations [52]. When taken together, these findings strongly suggest that LIF hinders myogenic development by preventing cells from exiting the cell cycle. Using an RNAi screen, we identified ten new orso-cytokines (across several families) with the potential to suppress myogenic differentiation by inhibiting cell cycle withdrawal [28]. Is it desirable to maintain the satellite cell pool using the available arsenal of differentiation inhibitors, or is this not necessary for its function? Myoblast differentiation can proceed in the absence of all three of these cytokines, proving that they are not redundant



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Differentiation Begins

It's possible that cytokines play a role here, even if the cell cycle isn't involved., while in others, cell cycle withdrawal is a direct result of cytokine-regulated differentiation initiation. IGF-1 and IGF-2 activate myogenic differentiation via IGF1R and PI3K-AKT [21, 84]. mTOR serves multiple roles in IGF2's myogenic regulation. The AKT kinase mTOR complex 2 (mTORC2) is a positive regulator of IGF2, and mTOR regulates IGF2 expression in muscle cells in a rapamycin-sensitive and kinase-independent manner [85-87]. SHH has recently been shown to promote C2 myoblast development via the PI3K pathway [54], although recombinant SHH has been shown to decrease C2C12 differentiation. [70]. Possible explanations include differences between C2 and C2C12 [88]. SHH also increases myoblast and satellite cell proliferation; hence, the outcome of proliferation versus differentiation may depend on when SHH is added to cell culture [54, 55]. Myostatin blocks differentiation by reducing MyoD expression and activity via Smad3 [89]. Myostatin activates activin type II. Myostatin decreases myoblast development; mTORC1 and mTORC2 signalling may be involved [90]. TGFb1, GDF11, and Acti-Vin A may have a similar role to myostatin. Myogenin expression and myotube fusion are impaired in IL-6-knockdown C2C12 cells and mouse primary myoblasts [91, 92]. The different positive and negative regulators at different stages of myogenic differentiation are shown in table 1.

Progression of Myoblast Fusion and Migrating Cells

Myotubes and myofibres are formed when myogenic gene expression is turned on and the cell cycle is halted in single-nucleated myocytes. Myocyte migration and proper cell placement or alignment are prerequisites for fusion. Myoblast migration and differentiation are both stimulated by VEGF, which is well known to be a cell migration driver [69,93]. Myoblast migration is stimulated by interleukin-6 and IL-7. Myocyte migration and fusion are impacted by CXCL12 and CXCR4 [16]. Migration of C2C12 cells is stimulated by CXCL14 [114]. The upregulation of chemokine mRNA expression during myoblast fusion was shown by Griffin et al. [16], which suggests that a network of chemokines may direct this process. Cell migration and actin cytoskeleton dynamics are governed by cytokine

signalling pathways that originate in muscle [94, 95]. Myoblast migration and myocyte fusion regulators may be associated with cytokine signalling [3]. In both embryonic and adult myogenesis, myoblast-myoblast fusion results in the formation of nascent myotubes, while myoblast-myotube fusion results in the formation of mature myotubes or myofibres [96]. Remarkably, the two fusion processes are driven by completely separate molecules and signalling pathways [3, 96]. The myocyte fusion-regulating cytokine IL-4 was first described by Horsley et al. [97]. The origin of cytokines in the body is still a mystery [98]. Although Heredia et al. [98] found no IL-4 expression in regenerating muscles in vivo, it is clear that fibroblasts and adipocytes are necessary for myofibre regeneration. Instead, IL-4 was discovered to regulate these cells after being secreted by recruited eosinophils. Motors regulate the fusion of second-stage myocytes by the secretion of a factor involved in myogenic differentiation [99]. The expression of follistatin in muscle cells is regulated by mTOR, which includes microRNA-1 and HDAC4. Follistatin is involved in both phases of myocyte fusion 100]. Maintaining viability of cells although essential, myocyte survival is not a direct step in the myogenesis process. Myoblast survival can be boosted by CNTF [101], IGF2 [37], SHH [70], TNFSF14 [102], and VEGF [69, 93]. Many different types of cells rely heavily on AKT signalling, which is regulated by Ser/Thr kinases [103,104]. AKT is involved in the signalling pathways that control myoblast survival by CNTF and TNFSF14 [101,102]. Pro-apoptotic cytokines could be produced in muscle. Myoblasts can be killed by exogenous IL-1 without any effect on their ability to divide or fuse [105]. IL-1 is expressed by myoblasts. Myogenesis cell number and density may be determined by opposing cytokine signalling.

Cytokines produced by muscles during myogenesis in vivo

It was previously thought that the primary source of cytokines was immune cells at the damage site [4]. Although cytokines have been related to inflammation and the immune system, they may also have a role in the development of muscle illnesses such muscular dystrophy, cachexia, and sarcopenia. Myogenesis is influenced by muscle-derived cytokinesin, and in vitro research have helped us better grasp this relationship. Surprisingly, studies that examine myogenesis in living organisms rarely alter the expression of cytokines

that are particular to muscles. During acute injury-induced muscle regeneration or in muscles that are undergoing satellite cell-dependent compensatory hypertrophy under mechanical strain, many of the cytokines mentioned in this review (that are expressed by muscle cells and have myogenic functions) are expressed in myogenic cells or myofibres. Muscles with Duchennes' muscular dystrophy (DMD) and other forms of dystrophy undergo spontaneous degradation and regeneration, and this process is accompanied by the expression of certain cytokines [106]. Muscle regeneration, hypertrophy, dystrophy, and development are all reflected in the expression of different cytokines. Some cytokines have been found to assist normal or dystrophic muscles repair.

BDNF

Muscle-regenerating mice produce more BDNF [81]. BDNF was discovered to be a myokine produced in human skeletal muscles in response to exercise that controls autocrine and paracrine muscle metabolism [107,108]. Healthy human skeletal muscles and immune cells near regenerated myofibrils express BDNF [67]. Exercise increases the number of BDNF+/myogenin+ cells, suggesting that human satellite cell produced BDNF may perform a myogenic role [109]. The lack of muscle regeneration in mice with targeted deletion of the BDNF gene, which was achieved by satellite cell-specific Myf5-Cre [66], provides strong support for the function that muscle-derived BDNF plays in myogenesis.

FGF6

FGF6 is expressed in embryonic skeletal muscle [110,111] and damaged muscles undergoing regeneration [112,113]. Contradictory results show that FGF6-null mice may have poor muscle regeneration upon injury due to lower satellite cell proliferation. Accelerated soleus muscle regeneration with intramuscular recombinant FGF6 [113] supports poor regeneration in FGF6-null animals. These data support a function for muscle-derived FGF6, although solid proof is missing until muscle-specific ablation is conducted.

IGF

IGF1 and IGF2 promote muscle regeneration [114,115]. Transgenic mice with muscle-specific IGF1 have hypertrophy, rapid regeneration after injury, and prevention of muscle degeneration in MDX animals [116-118]. IGF-binding growth factor receptor 1 deletion inhibits muscle growth [119,120]. No muscle-specific IGF1 or IGF2 deletions support autocrine IGF activity in vivo.

Mutations in the bovine myostatin gene cause double-muscled cattle. Systemic myostatin deletion in mice enhances muscle growth. Myostatin is expressed almost exclusively in mouse skeletal muscles, hence systemic deletion demonstrates muscle autonomy [53]. Myostatin antagonist follistatin enhances mouse muscle growth [121]. Mechanically strained hypertrophic muscles express increased myostatin [122]. Myostatin KO improves muscle regeneration and strength in the mdx mouse, a frequent (but poor) DMD model [123], making it a potential therapeutic target [124,125]. TNFα decreases myoblast development in human and animal cultures [126,127], suggesting it is a significant inflammatory mediator of age-related or disease-related muscle atrophy.

TNFα is expressed in mdx mice myofibres during regeneration [128]. TNFα may inhibit satellite cell activity in MDX dystrophic muscles [128]. Endogenous TNFα disruption decreases myoblast development [129-132]. Immune cells or dystrophic muscle TNFα may impair myogenic differentiation. Cytokine levels or downstream signalling may affect the outcome. TNFα signalling promotes myogenic development by targeting p38 MAP kinase, while inhibiting NF-kB [61, 62, 72].

Knocking down IL-6 in mice (known as KO) prevents satellite cell-dependent hypertrophy [51]. Another factor in compensatory hypertrophy is LIF, a close relative of IL-6 [122,133]. Muscles that are in the process of healing after an acute injury release IL-6 and LIF [134, 135] and it has been shown that endogenous LIF stimulates muscle regeneration in mice [135,136]. Muscle IL-6 expression is elevated in DMD [137] and young MDX mice [138]. There is a correlation between IL-6 and the severity of DMD in adult mice [139], showing that IL-6 worsens the disease. The severe DMD phenotype in humans is recapitulated in adult

MDX mice that have been engineered to produce recombinant IL-6 [139]. Muscle regeneration and dystrophic muscle defect reduction in MDX mice were both improved by blocking IL-6 receptors [138]. A second study aiming to find muscle improvement with MDX failed to do so [140]. Different antibody dosage techniques and/or functional analysis might account for the disparity. Normal gastrointestinal function can be restored in MDX mice by administering an anti-IL-6 antibody [141]. The dystrophic phenotype of Duchenne muscular dystrophy (DMD) may be worsened by elevated IL-6 levels; hence, this cytokine may be a therapeutic target. Muscle atrophy is associated with persistently high systemic IL-6 levels [142], whereas IL-6 production is linked with pro-myogenic effects during injury-induced regeneration and load-induced compensatory hypertrophy. Myogenic differentiation is affected both positively and adversely by IL-6 when studied in vitro. Satellite cell proliferation, migration, and myoblast differentiation are all stimulated by autocrine IL-6 [66, 110,111]. By inhibiting p90RSK and p70S6K, exogenous IL-6 inhibits myogenic development in C2C12 [143]. Like the contradictory function of TNFa in differentiation. There is some debate about whether or not IFNc has a role in myogenesis, similar to that of TNFa and IL-6. IFNcKO animals or IFN receptor-blocking antibodies hinder muscle regeneration [49]. Regenerating muscles produce IFNc from immune and muscle cells. Myogenesis is promoted by IFN. Negative effects of high IFNc on regeneration caused by lRGM1 deletion can be reversed with an IFNc-neutralizing antibody in mice [144]. IFNc receptor-blocking antibodies suppress C2C12 cell proliferation and fusion [49], and exogenous IFNc attenuates differentiation of C2C12 cells [145] and human skeletal myoblasts [146]. Considering muscle-derived pro-myogenic and pathological anti-myogenic IFNs may help reconcile these observations. There is no evidence that IFNc generated in muscles serves any function in the body.

Final thoughts and directions for the future

Cytokines, secreted by invading immune cells at muscle damage sites, aid in muscle healing and regeneration. Muscle has been recognised as a major source of cytokines across all families in the past 10–15 years, despite the autocrine activities of a few muscle-secreted cytokines being known for much longer. Recently, several cytokines were classified. Source

and concentration determine TNFa's signalling pathways and myogenesis effects. Myogenic differentiation is a well-orchestrated process that uses muscle-derived cytokines. Few studies have examined the contribution of muscle-derived cytokines to muscle regeneration in vivo. This information gap is academically intriguing and could hinder the development of more effective stem cell treatments for muscle illnesses like muscular dystrophy. CRISPR/Cas9 gene editing should speed up the production of animals with cytokine ablation in skeletal muscle. Some transgenic mice express Cas9 driven by human skeletal actin (HSA)-Cre [147] and muscle creatine kinase (MCK)-Cre [148], which could be exploited to knock out or downregulate cytokine genes in muscle via sgRNAs. Muscle-specific stimulation of cytokine gene expression can be informative and therapeutically beneficial [149]. Combining dCas9-SunTag [150,151] with Cre promoters can activate muscle-specific genes. Skeletal muscle cells release cytokines like other non-myeloid cells. Distinct cytokines may play different functions in differentiation and repair. Muscle-derived cytokines may assist autocrine activities. The source of a cytokine can affect its activity, as observed with TNF, IL-6, and IFN. How does the muscle cell use biochemical and biological processes to signal distinct cytokines? How are muscle-derived cytokines expressed, and do they have a hierarchical structure? Does cytokine signalling regulate myogenesis? How varied is a muscle cell population's cytokine production and reaction? Combining computational modelling and multi-pronged experimental approaches may help unravel a complex regulatory system.

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Table 1: Positive and Negative regulators at different stages of myogenic differentiation

STAGE	POSITIVE REGULATORS	NEGATIVE REGULATORS
Satellite cell activation	CCL2 CCN2 CXCL16 FGFs G-CSF HGF IFNγ IGF IL-1 IL-6 LIF NGF PDGF TGFβ SHH	Activin A Myostatin TNFα
Myogenic Cell Survival	CNTF IGF2 SHH TNFSF14 VEGF	IL-1
Cell Migration and Fusion	CXCL12 CXCL14 IL-6 IL-7 VEGF	--

2nd Stage Fusion	IL-4 IL-13	--
Cell Cycle Withdrawal and Initiation of Differentiation	BDNF CXCL8 Flt3L IGFs IFNγ IL-6 IL-12 IL-15 VEGF	Activin A BMPs CCN2 CCN3 CNTF CT-1 CXCL14 FGFs GDF11 HGF IL-1 IL-7 LIF Myostatin OSM PDGF TGFβ TNFα TNFSF10