Cytokine expression and secretion by skeletal muscle cells: regulatory mechanisms and exercise effects

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ABSTRACT

Cytokines are important mediators of various aspects of health and disease, including appetite, glucose and lipid metabolism, insulin sensitivity, skeletal muscle hypertrophy and atrophy. Over the past decade or so, considerable attention has focused on the potential for regular exercise to counteract a range of disease states by modulating cytokine production. Exercise stimulates moderate to large increases in the circulating concentrations of interleukin (IL)-6, IL-8, IL-10, IL-1 receptor antagonist, granulocyte-colony stimulating factor, and smaller increases in tumor necrosis factor-α, monocyte chemotactic protein-1, IL-1β, brain-derived neurotrophic factor, IL-12p35/p40 and IL-15. Although many of these cytokines are also expressed in skeletal muscle, not all are released from skeletal muscle into the circulation during exercise. Conversely, some cytokines that are present in the circulation are not expressed in skeletal muscle after exercise. The reasons for these discrepant cytokine responses to exercise are unclear. In this review, we address these uncertainties by summarizing the capacity of skeletal muscle cells to produce cytokines, analyzing other potential cellular sources of circulating cytokines during exercise, and discussing the soluble factors and intracellular signaling pathways that regulate cytokine synthesis (e.g., RNA-binding proteins, microRNAs, suppressor of cytokine signaling proteins, soluble receptors).

INTRODUCTION

Cytokines comprise a large family of polypeptides or proteins. This family includes interleukins, interferons, growth- and colony-stimulating factors, chemokines, members of the tumor necrosis factor group and transforming growth factors. Cytokines play an integrative and regulatory role as universal intercellular messengers. Once secreted, they can mediate intercellular communication locally or systemically. Alternatively, they can mediate intercellular contact even when bound to cell membranes (200). These characteristics distinguish cytokines from other intercellular messengers such as adhesion molecules, which require direct cell-to-cell contact, and hormones, which are produced by specialized endocrine organs and circulate throughout the body to exert their actions. Most cytokines are inducible mediators, are transported through the systemic circulation and are synthesized rapidly by multiple cell types in response to various stimuli. Individual cell types can express and secrete several cytokines simultaneously in response to a single stimulus (200). Cytokines are pleiotropic because they influence several cell types, and elicit different effects, depending on the type of target cells. They exert their pleiotropic actions in two phases. First, they bind to specific receptors expressed on cells with different origins and/or functions. Second, they mediate signal transduction through various intracellular messengers and transcription factors. The biological effects of cytokines depend on the presence and concentrations of other cytokines with synergistic, additive or counter-regulatory actions (200). Cytokines can act in an autocrine, paracrine or endocrine fashion to induce or suppress their own synthesis and regulate the production of other cytokines and their receptors. They possess an important characteristic of self-limiting synthesis through various auto-regulatory mechanisms (e.g., RNA instability) and negative feedback pathways. These pathways include synthesis of eicosanoids and corticosteroid hormones, expression of soluble receptors, and induction of intracellular transcription factors that block signal transduction (200).

The main function of cytokines is to regulate immune function. However, their wide-ranging effects on cell proliferation, differentiation, migration, survival and apoptosis allow them to play a role in homeostatic control of various tissues, organs and systems. For example, together with hormones and neuropeptides, cytokines mediate interactions between the nervous, endocrine and immune systems. Some cytokines also control body temperature, fatigue, appetite and metabolism. A link between cytokines and skeletal muscle was first established almost 50 years ago when researchers identified that an endogenous pyrogen was present in skeletal muscle (203). Cannon and Kluger (32) subsequently made another important discovery that endurance exercise induces the systemic release of a pyrogenic compound. These findings have since stimulated considerable interest in the biological significance and regulation of cytokine production in muscle during exercise and as a result of sepsis, aging, cancer cachexia and chronic inflammatory diseases.

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Initially, exercise research focused on the role of cytokines in mediating inflammatory responses to exercise-induced muscle damage. Evidence has accumulated over the past decade that cytokines play a much broader role during exercise. We now know that cytokines act in a hormone-like manner during exercise, mediating metabolism in working skeletal muscle, the liver and adipose tissue, angiogenesis and neurobiology (166). Following exercise, there is an increase in the circulating concentrations of assorted cytokines. Gene expression for some of these cytokines also increases within skeletal muscle. However, there appears to be a dissociation between local gene expression in skeletal muscle and the systemic concentration of other cytokines. For example, after exercise, tumor necrosis factor (TNF)-α and interleukin (IL)-1β expression in skeletal muscle increases, but the circulating concentration of these cytokines does not change (or only increases slightly). Conversely, the circulating concentrations of IL-1 receptor antagonist (IL-1ra) and IL-10 increase markedly, but these cytokines are not expressed in skeletal muscle after exercise.

Several excellent reviews have discussed the evidence that skeletal muscle is a secretory organ (167, 168, 183, 232). Yet relatively few studies have specifically examined whether skeletal muscle cells themselves are the main source of cytokine gene expression in skeletal muscle during exercise. In this review, we examine this notion in more detail by (1) reviewing the findings from studies of cytokine expression and secretion in cultured skeletal muscle cells, and (2) summarizing the results of studies that have used histological staining of cytokine expression in cross-sections of muscle tissue. We also discuss other potential sources of cytokines both in skeletal muscle, other tissues and the systemic circulation. Most research to date has investigated the systemic factors and intracellular signaling pathways that stimulate cytokine secretion by skeletal muscle cells. By contrast, much less is known about the factors that restrict or inhibit cytokine translation in skeletal muscle cells, and cytokine release into the circulation during exercise. We propose some potential negative regulatory mechanisms that may govern cytokine expression and secretion by skeletal muscle cells. Considering the important role of cytokines as local and systemic mediators of various aspects of health and disease, we contend that continuing research is needed to determine the dominant sources and regulation of cytokine production in the body.

LOCAL AND SYSTEMIC CYTOKINE RESPONSES TO EXERCISE

Numerous studies have investigated changes in the circulating concentrations of cytokines following exercise. Cytokine responses are generally dependent on the combination of mode, intensity, and duration of exercise. In the case of IL-6, prolonged running produces the greatest increase in plasma IL-6 concentration (167, 184). Indeed, circulating IL-6 can increase up to 120× following endurance exercise. IL-1ra (up to 90×), IL-10 (up to 80×), IL-8 (15×) and monocyte chemotactic protein (MCP-1) (up to 3×) also consistently increase in the circulation following exercise (39, 64, 68, 102, 151-154, 164, 165, 208, 212, 219, 225) (Table 1). There is substantial individual variability in the magnitude of changes in these cytokines in plasma after exercise (Figure 1).

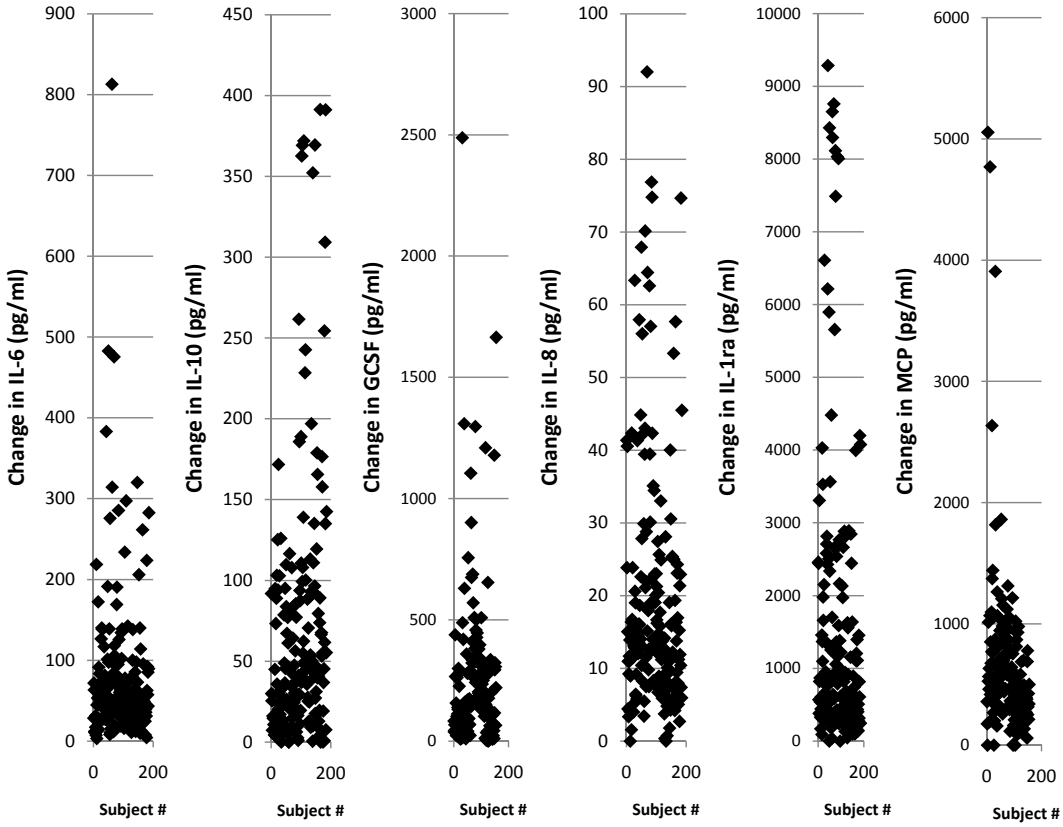

Figure 1. Individual variability in plasma cytokine responses to the Western States 160 km Endurance Run. Data indicate the change (in pg/ml) from pre- to post-exercise. Data are combined from *Int J Sports Med* 24:541-547, 2003; *Brain Beh Immun* 19:398-403, 2005; *Brain Beh Immun* 20:578–584, 2006.

Table 1. Cytokine and chemokine expression in muscle and responses to mechanical strain and exercise.

	Expression in human muscle		Responsive to *in vivo* cyclic strain and EPS of C2C12 or human myotubes		Responsive to exercise		Change in plasma	
	mRNA	protein	mRNA	protein	mRNA	protein		
IL-1β	✓	✓	✓	✓	✓		↑	↔
IL-1ra			×	×			↑↑↑	
IL-2		✓		✓				↓
IL-4	✓			✓				↔
IL-5				✓/×				↔
IL-6	✓	✓	✓	✓	✓	✓	↑↑↑↑	
IL-7	✓	✓		✓/×	✓			
IL-8	✓		✓	✓	✓		↑↑	↔
IL-10	✓ (low)			×	✓		↑↑↑	
IL-12p35	✓			×	×		↑	
IL-13				✓				
IL-15	✓	✓		✓/×	✓	×	↑ ↓	
IL-18	✓	✓						
IFN-γ	✓	✓		×				↔
TNF-α	✓	✓		✓/×	✓/×		↑	↔
MCP-1	✓	✓		✓	✓	✓	↑	
LIF	✓	✓		✓	✓	×		↔
VEGF	✓	✓		✓/×	✓	✓		
BDNF	✓	✓		✓	×	✓	↑	↔
TGF-β	✓	✓			✓			↔
uPA	✓				✓			

✓ or × indicate positive or negative evidence (respectively) of cytokine mRNA or protein expression/secretion in muscle and muscle contraction.
↑ or ↓ indicate an increase/decrease in plasma cytokine concentrations (more arrows denotes a greater increase). ↔ indicates no increase in plasma cytokine concentrations. (Inclusion of two symbols indicates conflicting data.)
N.B. Blank cells indicate no data are currently available. EPS, electromagnetic pulse stimulation. IFN, interferon; TNF, tumor necrosis factor; MCP, monocyte chemotactic protein; LIF, leukemia inhibitory factor; VEGF, vascular endothelial growth factor; BDNF, brain-derived neurotrophic factor; TGF, transforming growth factor; uPA, urokinase plasminogen activator.

Some of this variability appears to be related to variation in exercise intensity (156) and the extent of exercise-induced muscle damage (157, 228). By contrast, the plasma/serum concentrations of TNF-α (4×), brain-derived neurotrophic factor (BDNF) (2.5×), IL-1β (2×), IL-12p40 (0.3×), IL-15 (0.05×) increase to a smaller extent, whereas leukemia inhibitory factor (LIF) and transforming growth factor (TGF)-β remain unchanged following exercise (25, 29, 39, 137, 153, 154, 186, 190, 220, 225).

The gene expression of IL-1β, IL-6, IL-8, IL-10, IL-15, TNF-α, MCP-1, LIF and TGF-β in skeletal muscle increases following endurance exercise (39, 64, 68, 82, 102, 124, 147, 151, 152, 154, 208, 212) and resistance exercise (25, 50, 94, 124, 149, 150, 192) (Table 1). BDNF mRNA expression also tends to increase (non-significantly) in response to endurance exercise (137). Similar to plasma cytokine responses, exercise-induced changes in cytokine gene expression in muscle can also be highly variable, possibly due to variation in single nucleotide polymorphisms within cytokine genes (52, 186). However, less is known about changes in the protein abundance of these cytokines in skeletal muscle after exercise. IL-6 and BDNF protein expression increases in working skeletal muscle following endurance exercise (68, 89, 137), while the protein abundance of IL-6, IL-8 and MCP-1 also increases after resistance exercise (50, 51) and eccentric exercise (94). Changes in IL-1β are inconsistent (66, 129, 130), whereas IL-15 and LIF protein content does not change following exercise (25, 26, 130, 149).

In contrast with pro-inflammatory cytokines, exercise-induced changes in the anti-inflammatory cytokines IL-4 and IL-13 are less well characterized. We recently reported that IL-4 protein expression in muscle tended to decrease 2 h after resistance exercise in young men. However, following 12 weeks of resistance training, IL-4 protein expression increased when the same individuals performed another bout of resistance exercise (51). This finding suggests that IL-4 may play a role in muscular adaptations to training. In the same study, we observed that IL-13 protein expression in muscle did not change significantly after either bout of exercise (51).

CYTOKINE EXPRESSION AND SECRETION BY SKELETAL MUSCLE CELLS

Most of the evidence for cytokine expression in skeletal muscle is derived from the analysis of isolated RNA or protein extracts from homogenized muscle. However, muscle homogenates reflect contributions from intracellular, sequestered and interstitial sources of cytokines (23). This makes it difficult to identify specific cellular sources of cytokines in vivo. An extensive body of research has explored

Table 2. Expression of cytokines by skeletal muscle cells.

	Constitutive expression in myoblasts		Constitutive expression in myotubes		Change with differentiation	Stimulatory agents	Dose effect	Time effect
	mRNA	protein	mRNA	protein				
IL-1β	H ✓(low) / ✗	H ✓		H ✓(low)	↑ (late)	TNF-α		
IL-1ra	C ✓			H ✗		LPS		+
IL-4	H ✗			H ✓(low)				
IL-6	H ✓/ ✗	H ✓(low)	C ✓ (low)	H ✓	↑ (early)	LPS	+	+
	C ✓ (low)	C ✓		C ✓ (low)				
						TNF-α	+	+
						IL-1β	+	+
						IFN-γ	↔	↔
						TGF-β		
						HSP60	+	
						H_2O_2	+	
						pyrogallol	+	
						X/XO	+	
						epinephrine	+	+
						MG-132		
						AP-1		
						HSF-1		
						Dithiothreitol		
						Thapsigargin		
						Tunicamycin	+	
						Castanospermine	+	
						ATP		+
IL-7			H ✓(low)	H ✓(low)	↑	LPS		
IL-8	H ✓	H ✓(low)	H ✓	H ✓		TNF-α		
						IFN-γ		
						IL-1β		
						'Hyper IL-6'		
						LPS		
						HSP60	+	
IL-10	H ✗			H ✓(low)		TNF-α		
IL-12				H ✓(low)		LPS		+
IL-13				H ✓(low)		IGF-1		
IL-15				H ✗	↑	TNF-α		+
IL-17				H ✓(low)				
IL-18	C ✓							
TNF-α	H ✓/ ✗	H ✗		H ✓(low)	↑ (early)	LPS	+	+
	C ✓ (low)							
						TNF-α		
						IFN-γ		
MCP-1	H ✓/ ✗	H ✗			↑ (early)	LPS		
						TNF-α		
						IFN-γ		
						IL-1β		
						'Hyper IL-6'	+	+
						HSP60	+	
LIF			H ✓(low)	H ✓	↑ (early)	ionomycin		
IFN-γ	H ✓			H ✓				
BDNF			C ✓	C ✓	↓			
VEGF-A				H ✓				
TGF-β	C ✓			H ✓	↑	LPS		↔
						IL-1α		+
						TNF-α		+
						IFN-γ		

✓ indicates constitutive expression. ✗ indicates no constitutive expression. H, human muscle cells. C, C2C12 muscle cells. + indicates positive/additive response. ↔ indicates no effect. N.B. Blank cells indicate no data are currently available. MCP-1, monocyte chemotactic protein-1; LIF, leukemia inhibitory factor; IFN, interferon. BDNF, brain-derived neutrophic factor; VEGF, vascular endothelial growth factor; TGF, transforming growth factor. LPS, lipolysaccharide; HSP, heat shock protein; X/XO, xanthine/xanthine oxidase; hyper IL-6, IL-6 covalently linked to soluble IL-6 receptor; MG-132, proteasome inhibitor; AP-1, activator protein-1; HSF-1, heat shock factor 1;

the capacity of skeletal muscle cells to produce cytokines in vitro by culturing skeletal muscle cells with various agents, and by subjecting skeletal muscle cells to cyclic strain and electromagnetic pulse stimulation (Table 2).

Evidence from cell culture studies

C2C12 myoblasts, L6 muscle cells and human myoblasts constitutively express IL-8 (47, 133), IL-12 (72), IL-15 (180) and TGF-β (72). Some, but not all studies report that myoblasts

also constitutively express IL-1β, IL-1ra, IL-6, TNF-α and MCP-1 (17, 47, 70-73, 106, 133, 144). Myoblasts do not express IL-10 or interferon (IFN)-γ (144). The constitutive expression of cytokines is generally stronger in differentiated myotubes compared with myoblasts (83, 85, 86, 102, 107, 134, 144, 235) (Table 2).

Myoblasts and myotubes express and secrete cytokines *in vitro* in response to a wide range of stimuli (Table 2). ATP, H_2O_2, xanthine/xanthine oxidase, nitric oxide and epinephrine are produced during exercise through redox reactions and autonomic nervous activity. These agents directly regulate the synthesis of cytokines by skeletal muscle cells by activating various signaling pathways (6, 70-72, 96, 107, 128, 235). The regulatory influence of TNF-α, IL-1β, IL-6, IFN-γ, TGF-β and HSP60 is probably less direct, and depends on their relative concentration within the local microenvironment of skeletal muscle. Many of the agents listed above induce a concentration-dependent increase in the secretion of IL-6, IL-8, TNF-α and MCP-1 (70, 72, 73, 85, 107, 134, 144). LPS, TNF-α, IL-1β, IL-6, IFN-γ and epinephrine also induce a time-dependent increase in the secretion of IL-6, TNF-α, TGF-β and MCP-1 for up to 48 hours (70-73, 133, 144). Human myotubes that undergo cyclic mechanical strain release IL-6, IL-8, MCP-1 and G-CSF (172). Mouse (62, 146, 235), rat (31) and human (25, 182, 195) myotubes that contract in response to electromagnetic pulse stimulation release a wide array of cytokines (Table 2). In addition to well characterized cytokines, the list of 'contraction-responsive' cytokines continues to grow (182, 195).

The findings from cell culture studies provide important information on skeletal muscle cell secretion of cytokines in the context of trauma, sepsis or chronic inflammatory conditions. However, these findings are not necessarily applicable to understanding how skeletal muscle cells generate cytokines during exercise, for several reasons. The concentrations of most of the agents are most likely lower in skeletal muscle during exercise compared with the concentrations used in cell culture studies. The period for which skeletal muscle is exposed to these agents during exercise is also typically shorter than the incubation periods used in cell culture studies. Although epinephrine stimulates IL-6 mRNA expression and secretion (70), epinephrine appears to play a relatively minor role in regulating systemic changes in IL-6 during exercise (214). Last, cyclic strain and electromagnetic pulse stimulation of myotubes do not fully reflect the dynamic conditions in skeletal muscle during exercise, where both stimulatory and inhibitory agents are present.

Evidence from in vivo muscle analysis

Human biopsy studies reveal that skeletal muscle expresses mRNA for numerous cytokines (Table 1) (25, 29, 83, 91, 94, 109, 149, 152, 154, 212). Mature myofibers make up most of the cellular mass within skeletal muscle, and as described in the previous section, myotubes express mRNA for various cytokines. Nevertheless, muscle homogenates represent a mixture of different types of cells; other inflammatory and stromal cells in skeletal muscle also secrete cytokines. Some research has used immunohistochemistry and immunofluorescence staining to examine the cellular sources of cytokines in healthy human muscle at rest (68, 89, 149, 175). Malm et al. (129) found that IL-6 and IL-1β are localized to both muscle and non-muscle cells. The same group subsequently reported that IL-6 expression is low within skeletal muscle cells themselves, whereas it is expressed in the epimysium (130). In muscle of patients with inflammatory myopathies, cytokines are highly abundant, but are mainly localized to other cell types such as inflammatory T cells and macrophages, and in proximity to blood vessels in the endomysium and perimysium (46, 194). Collectively, these findings demonstrate that cytokines are likely secreted by various cell types present in skeletal muscle, and not exclusively by skeletal muscle cells themselves.

Surprisingly little research has used RNA *in situ* hybridization, immunohistochemistry or immunofluorescence staining to identify which fibers and resident cell types (e.g., endothelial cells, infiltrating leucocytes, satellite cells) in skeletal muscle produce cytokines in response to exercise. Table 3 summarizes the results of studies that have attempted to identify where cytokines are expressed in skeletal muscle after exercise or muscle contractions. Hiscock et al. (89) report that following endurance exercise, both IL-6 mRNA and protein are expressed mainly in type II fibers with high muscle glycogen content. They propose that the greater IL-6 expression in type II fibers may result from greater release of Ca^{2+} from the sarcoplasmic reticulum into the cytosol of the type II fibers (89). Following eccentric exercise, Hubal et al. (94) observed that MCP-1 is mainly expressed within the interstitial space between myofibers, and localizes with macrophages and Pax7+ satellite cells. Two studies have demonstrated that IL-6 also localizes with Pax7+ satellite cells in the basal lamina of muscle fibers after eccentric exercise (138) and compensated hypertrophy (197). Following downhill running, Malm et al. (130) reported that IL-1β is mainly localized to non-muscle cells, whereas Fielding et al. (66) found that IL-1β is localized to the pericellular space. Using immunofluorescence staining for MCP-1 and IL-8, we recently reported that these chemokines are not present within mature myofibers after exercise. Rather, they are localized within the endomysium between muscle fibers and in close proximity to a number of cell types including macrophages, satellite cells and blood vessels (50). Hoier et al (90) investigated the subcellular localization of VEGF in muscle 2 h after cycling. They discovered that VEGF was located in the subsarcolemmal regions, between the contractile elements within the muscle fibers, and in pericytes positioned on the skeletal muscle capillaries. Lauritzen et al (116) conducted an elegant study in which they incorporated an enhanced green fluorescent protein tagged for IL-6 into muscle fibers isolated from the quadriceps muscles of mice. At rest, the fluorescent tag was localized in vesicular structures at the surface and in the interior of the transfected muscle fiber. Following *in situ* contractions of the fibers, the number of vesicles expressing the fluorescent tag decreased in both locations, indicating vesicular transport of IL-6 out of the fiber. These diverse findings highlight the need for more research to gain a better understanding of the local regulation and secretion of cytokines in muscle during exercise.

Table 3. Cytokine localization in skeletal muscle after exercise.

Cytokine	Species	Exercise mode	Muscle	Located within muscle fibers	Located outside muscle fibers	Ref.
IL-6	Humans	Endurance	Vastus lateralis	✓ (type II fibers)		(89)
IL-6*	Rats	Endurance	Plantaris	✓ (type I and IIa fibers)		
IL-6	Humans	Eccentric	Vastus lateralis		✓ (satellite cells)	(138)
IL-6	Humans	Eccentric	Vastus lateralis	low	✓ (fibroblasts)	(130)
IL-6	Humans	Eccentric	Vastus lateralis	low	low	(129)
IL-6	Mice	Eccentric	Gastroc.	✓	✓ (inflammatory and satellite cells)	(226)
LIF	Humans	Eccentric	Vastus lateralis		✓ (endothelial cells)	(130)
IL-1α	Humans	Eccentric	Vastus lateralis	✓	✓ (endothelial cells)	(129)
IL-1β	Humans	Eccentric	Vastus lateralis	✓	✓	(129)
IL-1β	Humans	Eccentric	Vastus lateralis		✓ (pericellular space)	(66)
MCP-1	Humans	Eccentric	Vastus lateralis		✓ (macrophages and satellite cells)	(94)
MCP-1	Humans	Resistance	Vastus lateralis		✓ (macrophages, satellite cells, blood vessels)	(50)
IL-8	Humans	Resistance	Vastus lateralis		✓ (macrophages, blood vessels)	(50)
VEGF	Humans	Endurance	Vastus lateralis	✓ (subsarcolemmal sarcoplasm)	✓ (pericytes)	(90)
VEGF*	Rats	Endurance	Plantaris	✓ (type IIb fibers)		(22)
VEGF*	Rats	Endurance	Gastroc.	✓ (type I and IIa fibers)		(28)
TGF-β_1	Rats	Eccentric	Gastroc.	✓ (injured myofibers)		(201)

* mRNA. Gastroc, gastrocnemius.

DISSOCIATION BETWEEN LOCAL AND SYSTEMIC CYTOKINE RESPONSES TO EXERCISE

Curiously, although many cytokines are expressed in skeletal muscle following exercise, with the exception of IL-6, they are not released into the circulation—at least in large amounts (65, 68, 211, 212). In explanation of these observations, it has been suggested that some cytokines are produced locally by interstitial cells, and may not enter the circulation (130, 191). Catoire et al (37) recently conducted a systematic comparison of cytokine gene expression in muscle and plasma cytokine concentrations after one-legged 1 h cycling at 60% heart rate reserve. They discovered that mRNA expression of IL-6, MCP-1, CXCL2 (macrophage inflammatory protein-2α) and CX3CL1 (fractalkine) was significantly upregulated. By contrast, mRNA expression of other cytokines including IL-7, IL-8, IL-15 and BDNF did not change significantly after exercise. Within plasma, MCP-1 and fractalkine increased after exercise, whereas IL-6 remained unchanged. This is the only study to report simultaneous changes in MCP-1 and fractalkine within muscle and plasma following exercise. The finding that plasma IL-6 concentration did not change despite local expression in muscle may reflect the relatively small muscle mass and low intensity of exercise (37). An alternative explanation for the dissociation between local and systemic cytokine responses is that skeletal muscle may not secrete sufficient quantities of cytokines to increase their concentration in the systemic circulation.

Although distinct from exercise, Borge et al. (23) conducted an elegant study to investigate whether cytokines are released systemically from skeletal muscle in response to lipopolysaccharide (LPS). Plasma and interstitial fluid were collected from mice 0.5, 1.5 and 3 h after intravenous administration of 3.5 mg/kg LPS. The concentrations and kinetics of changes in cytokines were markedly different between interstitial fluid and plasma. The findings from this study by Borge et al. (23) provide important information about skeletal muscle as a source of circulating cytokines. The higher concentration of IL-1β in interstitial fluid compared with plasma suggests that although skeletal muscle cells produce IL-1β, the systemic release of IL-1β from skeletal muscle is probably tightly regulated. The higher concentrations of TNF-α, IL-10, MCP-1 in plasma compared with interstitial fluid 1.5 h after LPS infusion suggests that skeletal muscle is not a major source of these cytokines in the circulation. The smaller difference in the concentrations of IL-6 in plasma and interstitial fluid is consistent with other evidence that skeletal muscle releases IL-6 into the circulation during exercise (68, 211, 212). The time course of changes in the secretion of cytokines in this study is similar to that reported in plasma following exercise (160). The early secretion of TNF-α and IL-1β probably stimulated the sustained production of IL-6 (44, 71, 72, 125, 162). Constitutive expression of IL-10 in skeletal muscle cells is low (144), but IL-10 production may have increased in response to the early rise in TNF-α and IL-1β secretion (67).

OTHER SOURCES OF LOCAL AND SYSTEMIC CYTOKINES DURING EXERCISE

Cells within the microvasculature, namely endothelial cells and pericytes, are important regulators of angiogenesis and myogenesis, making them key players in both muscle and vascular generation following injury (2). Endothelial cells (78, 100, 111, 217, 238) and pericytes secrete various cytokines (41, 108). Fibroblasts contribute to production of the extracellular matrix of muscle connective tissue by secreting fibronectin, laminin, specific tenascins and neural cell adhesion molecules (141). In response to muscle injury, fibroblasts proliferate and begin to produce collagen-rich extracellular matrix to restore the muscle's framework (121). Fibroblasts also secrete assorted cytokines (47, 78, 118, 136, 163). Neutrophils play an important role in breaking down damaged muscle tissue in the acute phase of muscle injury (148, 174), whereas monocytes/macrophages regulate subsequent tissue regeneration (12, 218). Neutrophils (36, 58, 132, 187, 223) and monocytes/macrophages (8, 48, 54, 78, 93, 123, 131, 179) both secrete a variety of cytokines. As cytokine-producing cells, endothelial cells, pericytes, fibroblasts, neutrophils and monocytes/macrophages may all contribute to global cytokine expression in skeletal muscle.

In addition to skeletal muscle, IL-6 is also released from the brain (158) and peritendinous tissue (114) after exercise. Whereas IL-6 mRNA is expressed in adipose tissue following exercise (45, 103), IL-6 is not released from adipose tissue during exercise (126). Evidence indicates that macrophages secrete IL-1β in the brain following downhill running (35), but it is unknown whether IL-1β is released from the brain into the circulation during exercise. Exercise also increases gene expression of IL-1ra and IL-15 receptorα in the liver in fasting rats (30), but it remains unknown if the liver is a source of circulating cytokines after exercise.

Leucocytes are probably only a minor source of circulating cytokines following exercise (Table 4). Studies on cytokine production by leucocytes can be divided into those that have measured cytokine gene expression in leucocytes, intracellular cytokine production, and extracellular cytokine secretion. Leucocyte mRNA expression of IL-1β, IL-1ra, IL-8 and IL-10 increases, whereas IL-6 mRNA expression remains unchanged after exercise (1, 20, 154, 161). Monocyte intracellular cytokine production of IL-1β, IL-6, TNF-α, BDNF increases, decreases or remains unchanged following exercise (27, 185, 207, 209, 210). Extracellular cytokine secretion by mononuclear cells or in whole blood stimulated with LPS is also variable (1, 18, 19, 56, 57, 81, 87, 112, 173, 189, 202, 231). Fewer studies have investigated changes in cytokine expression or secretion by T lymphocytes following exercise. Two studies have reported that the number of IFN-γ^+ T cells decreases after exercise, while the number of IL-4^+ T cells remains unchanged (113, 213). In contrast with these findings, Zaldivar et al (239) found that the percentage of T cells that expressed IL-4, IL-6 and TNF-α increased following exercise. Kakanis et al (99) also observed that the secretion of both Th1 cytokines (IL-2 and TNF-α) and Th2 cytokines (IL-6, IL-10) by T cells stimulated with phytohemagglutinin increased after exercise. Work by La Voy et al (117) demonstrated that cytokine production during exercise may depend on changes in the numbers certain subsets of T cells.

Skeletal muscle has been proposed as the dominant source of circulating IL-6 based on the increase in the arterial-femoral venous differences in the concentration of IL-6 (215). However, this does not provide *prima facie* evidence that skeletal muscle cells are the main cell type that secretes cytokines such as IL-6 into the circulation during exercise. Skeletal muscle is composed of many other cell types such as fibroblasts, myeloid cells, pericytes which also secrete cytokines. The organs and cells that secrete other cytokines (not produced in abundance by skeletal muscle cells) into the circulation during exercise remain to be determined. The results from many of these studies on cytokine secretion by leucocytes *in vitro* highlight the importance of how we interpret such data. It is important to consider differences in stimulated versus spontaneous cytokine secretion, intracellular cytokine production versus extracellular secretion, and changes in the absolute amount of cytokines that are secreted versus cytokine secretion per cell.

REGULATION OF CYTOKINE SYNTHESIS AND SECRETION

Cytokine secretion by skeletal muscle cells involves various intracellular factors, including mitogen-activated protein

Table 4. Leucocyte cytokine mRNA expression and secretion in response to exercise.

	mRNA expression	Unstimulated production		Stimulated production			Production per cell			Change in plasma	
IL-1β	↑	↓		↑	↓		↓			↑	↔
IL-1ra	↑	↑		↑		↔				↑↑↑	
IL-6	↓	↓	↔	↑	↓	↔	↑	↓	↔	↑↑↑↑	
IL-8	↑									↑↑	↔
IL-10	↑	↓		↓				↓		↑↑↑	
TNF-α		↓		↓		↔	↑	↓	↔	↑	↔

↑ or ↓ indicate an increase/decrease in plasma cytokine concentrations (more arrows denotes a greater increase). ↔ indicates no increase in plasma cytokine concentrations. (Inclusion of two symbols indicates conflicting data.). Unstimulated production refers to assays in which whole blood or cells were incubated with no external agent. Stimulated production refers to assays in which whole blood or cells were incubated with an external agent such as lipopolysaccharide.

kinases, heat shock factor 1, histone deacetylases and transcription factors such as nuclear factor of activated T cells (NFAT), activating protein (AP)-1 and NFκB (6, 70-72, 107,128, 233, 212, 235). In addition, cellular processes such as $Ca2^{+}$ signaling and protein unfolding also stimulate muscle cells to express cytokine genes and/or secrete cytokines (92, 233). Activating transcription factor 3 is an important regulator of cytokine secretion by macrophages (76), and may also play a role in skeletal muscle cells. In comparison with our knowledge of the factors that induce cytokine synthesis, much less is known about the factors that restrict and/or inhibit cytokine expression and secretion (145). In the context of exercise, this information is important because it could account for why IL-1β and TNF-α mRNA expression in skeletal muscle increases, yet the circulating concentrations of these cytokines remains comparatively low following exercise (150-152, 212). Below, we propose some potential negative regulatory mechanisms that may govern cytokine expression and secretion by skeletal muscle cells.

RNA-binding proteins

Intracellular utilization of mRNA depends on several processes including mRNA maturation, shuttling and stability. In turn, these post-transcriptional processes are under the control of RNA-binding proteins and microRNAs. RNA-binding proteins regulate mRNA utilization by binding to adenine/uracyl-rich elements downstream of the 3' untranslated regions of transcripts (205). A small subset of RNA-binding proteins are active in skeletal muscle, including human antigen R, KH-type splicing regulatory protein, CUG binding protein 1, poly(A) binding protein, Lin-28 and tristetraprolin (9). These RNA-binding proteins are known to regulate myogenesis (9), but they may also control cytokine translation in skeletal muscle cells. Human antigen R enhances the stability of TNF-α mRNA (49, 140). However, together with CUG binding protein 1 and tristetraprolin, human antigen R may also silence TNF-α translation (33, 98, 101, 240). Tristetraprolin expression increases (221), whereas the expression of human antigen R decreases (181) in response to the anti-inflammatory cytokines IL-4 and IL-10.

Relatively little research has examined changes in the expression of RNA-binding proteins in skeletal muscle following exercise. Hubal et al. (94) reported that mRNA expression of zinc finger protein 36 (a member of the tristetraprolin family) increases in skeletal muscle following exercise. This response is greater following eccentric exercise compared with concentric exercise, and is augmented following repeated bouts of eccentric exercise (94) which suggests a role for zinc finger protein 36 in regulating skeletal muscle adaptation following injury. Another study observed that tristetraprolin mRNA expression precedes that of LPS-inducible CXC chemokine mRNA expression in C2C12 myoblasts and in skeletal muscle following freeze injury (193). Geyer et al (75) performed an elegant study in which they induced the expression of the RNA-binding protein tristetraprolin in C2C12 myotubes. This treatment suppressed mRNA expression of MCP-1, KC (IL-8) and IL-6, while it also reduced MCP-1 secretion following LPS stimulation. These findings highlight the need for further research to gain greater insights into the role of RNA-binding proteins in regulating cytokine secretion by skeletal muscle cells.

MicroRNAs

MicroRNAs also bind to the 3' untranslated regions of transcripts (222) and interact with RNA-binding proteins to regulate the fate of mRNA (59, 98, 127). MicroRNAs such as Let-7, miR-146, miR-221, miR-155 and miR-106 regulate the expression of IL-1, IL-6, IL-8, TNF-α and IL-10 by immune cells (21, 38, 59, 98, 170, 198, 224, 229). Skeletal muscle cells express a number of microRNAs, including miR-133, miR-1, miR-367, miR-135a, miR-222, miR-29a, b and c, miR-221, miR-223 and miR-206 (34, 42, 105). MicroRNA Let-7 inhibits the secretion of IL-13 in human myotubes (97). Other microRNAs such as miR-367, miR-222, and miR-29 may control cytokine secretion by skeletal muscle cells indirectly by altering the activity of endothelial nitric oxide synthase (188) and signal transducer and activator of transcription (STAT) proteins (53). As more microRNAs are identified in skeletal muscle, this may improve our knowledge of whether they regulate cytokine expression and secretion by skeletal muscle cells.

Suppressor of cytokine signaling (SOCS)

Surprisingly little research has investigated the role of SOCS proteins in regulating cytokine synthesis and signaling by skeletal muscle cells. Paradoxically, the limited evidence available indicates that overexpression of SOCS3 increases IL-6 transcription in myotubes (204). Under some conditions, the interaction between SOCS proteins and cytokines may be reciprocal. IL-6 and TNF-α induce SOCS3 mRNA expression in C2 myoblasts (5) and cardiac myoblasts (230). TNF-α infusion *in vivo* also stimulates SOCS3 mRNA in murine muscle (60). Further research is warranted to examine in greater detail the function of SOCS proteins as regulators of cytokine synthesis and signaling by skeletal muscle cells.

Soluble receptors

Soluble receptors can also restrict cytokine signaling through two main mechanisms. First, soluble receptors can act as a 'non-signaling sink' that directly competes with membrane-bound receptors for ligand binding. If the ligand-binding affinity of soluble receptors and membrane-bound receptors is similar, the capacity of soluble receptors to inhibit signaling depends on the balance between the two types of receptors (84). Soluble receptors for IL-1 and TNF-α appear to operate in this manner (3, 10). Second, soluble receptors can arise through the proteolytic cleavage of membrane-bound receptors. This process results in fewer membrane-bound receptors to bind ligands and initiate cell signaling (84). TNF-α and IL-6 can also induce shedding and/or endocytosis of their own receptors (55, 79, 88, 177). These actions may represent an autocrine negative feedback loop to prevent excess ligand stimulation. Currently, there is insufficient evidence to determine whether soluble receptors regulate cytokine signaling in skeletal muscle following exercise. Gene expression of soluble IL-6 receptor (but not gp130) is elevated in skeletal muscle between 4.5 and 9 h after exercise (104), whereas the plasma concentration of soluble IL-6 receptor does not change (104) or only increases slightly (120). The presence of circulating soluble IL-6 receptors after exercise may depend on proteolytic cleavage of IL-6 receptors (120). Gene expression of TNF-α and IL-1β in skeletal muscle is elevated for up to 24 h after exercise (124, 150-152). Although the plasma concen-

trations of soluble TNF-α receptors and IL-1ra are also elevated for several hours after exercise (152, 160, 225), it is unknown whether these receptors are derived from, and are active in skeletal muscle.

Other factors

Other factors such as IL-6 and HSP72 produced locally in skeletal muscle during exercise may also regulate cytokine synthesis. IL-6 inhibits LPS-induced synthesis of TNF-α by monocytes (196). In response to LPS treatment *in vivo*, TNF-α concentration is lower in serum and broncho-alveolar lavage fluid from IL-$6^{+/+}$ mice compared with IL-$6^{-/-}$ mice (236). An increase in plasma IL-6 concentration following IL-6 infusion or exercise inhibits the systemic release of TNF-α in response to LPS (206). Local production of IL-6 may therefore regulate the synthesis and systemic release of TNF-α during exercise.

In addition to cytokines, endurance exercise induces HSP72 mRNA expression in skeletal muscle (16). Heat exposure increases HSP72 mRNA expression and IL-6 mRNA expression and protein synthesis in C2C12 myotubes in a temperature-dependent manner (234). As further evidence for this regulatory role of HSP72, the heat shock inhibitor Knk437 attenuates HSP72 mRNA expression, and completely blocks IL-6 mRNA expression in myotubes incubated at 42°C (234). The interaction between HSP72 and IL-6 appears to be reciprocal, because IL-6 infusion induces HSP72 mRNA expression in skeletal muscle (63). Huey and Meador (95) demonstrated that IL-6 regulates the expression of HSPs in skeletal muscle in response to LPS, but not exercise. In direct contrast with IL-6, heat exposure inhibits TNF-α mRNA expression in myotubes (234) and TNF-α protein synthesis in other cell types (61, 142). These findings implicate HSP72 as a negative regulator of TNF-α mRNA expression and synthesis, but further research is required to confirm this notion. The upstream regulator of HSPs, heat shock factor -1 may play a more central role than HSPs in regulating cytokine secretion by skeletal muscle cells (233). Ohno et al (159) have also demonstrated that acute heat stress suppresses NFκB activity in C2C12 muscle cells. This response was accompanied by increased expression of HSP72 (159), but it remains to be determined if HSP72 can block NFκB activity in muscle cells.

Skeletal muscle expresses the gene for tumor necrosis factor receptor-associated factor (TRAF)-6-inhibitory zinc finger protein (TIZ) (77). By inhibiting the activation of NFκB, c-Jun N-terminal kinase and AP-1 (199), zinc finger proteins such as TIZ may restrict cytokine secretion by skeletal muscle cells. Similar to other factors described above, future research could investigate the regulatory roles of zinc finger proteins in skeletal muscle.

In another interesting study, Lee (119) demonstrated that treatment of C2C12 myotubes with IGF-1 inhibited mRNA expression of IL-6 and TNF-α. This effect was due to suppression of TLR4 signaling, which was in turn mediated by inhibition of the PI3K/Akt signaling pathway (119). These findings provide further evidence of potential autocrine loops and cross-talk between cytokines and growth factors within skeletal muscle.

Cytokine trafficking and secretion

In contrast with cells of the immune system, regulation of cytokine trafficking and secretion in muscle cells remains largely unknown. Hoier et al (90) made the first attempt to characterize the subcellular localization of VEGF in skeletal muscle. However, they did not investigate dynamic changes in trafficking of VEGF within muscle cells. Lauritzen et al (116) have provided the most detailed insights to date on the mechanisms of cytokine secretion by skeletal muscle fibers. Stow and Murray (216) have provided a comprehensive overview on the mechanisms of trafficking and secretion in immune cells, and this may be used as a guide to new research in muscle cells.

REGULATION OF CYTOKINE EXPRESSION AND SECRETION IN MYOBLASTS VERSUS MYOTUBES

As noted previously, and summarized in Table 2, the constitutive expression of cytokines varies between myoblasts and myotubes. Below we discuss some of these differences, some of the mechanisms that may govern alterations in cytokine expression and secretion by skeletal muscle cells as they differentiate, and the possible biological significance of these differences.

Gene expression of numerous chemokines and their receptors increases markedly after 16−48 h of differentiation (80). Of note, MCP-1 mRNA expression peaks at 16 h, whereas TNF-α mRNA expression increases 10-fold between 16 and 24 h and declines thereafter (80). Several studies indicate that myoblasts and myotubes constitutively express similar levels of IL-6 mRNA. However, compared with myotubes, myoblasts produce substantially more IL-6 protein upon stimulation with IL-1β, TNF-α and LPS (71, 144, 178). In response to TNF-α and LPS, myoblast production of IL-6 increases in a linear manner, whereas myotube production of IL-6 increases in a more 'bell-shaped' manner (178). The greater sensitivity of myoblasts to pro-inflammatory stimuli such as TNF-α and LPS may reflect the requirement for myoblasts to secrete factors such as IL-6 to promote myoblast proliferation (13, 110), and therefore, muscle regeneration (178). Protein expression of MCP-1 (85), IL-6 (15) and LIF (25) also increases during the first 24−48 h of differentiation. Protein expression of IL-7 and IL-15 increases more steadily between 2−7 d of differentiation (83, 180). Protein expression of IL-1β and IL-1ra (14) and MCP-1 secretion (40) increase after 12−16 d of differentiation. Gene and protein expression BDNF expression decreases after 4 d (143).

The factors responsible for changes in cytokine expression by skeletal muscle cells as they differentiate are uncertain. Some of the factors that regulate cytokine expression in skeletal muscle cells (e.g., mitogen-activated protein kinases, histone deacetylases, NFAT and NFκB) also control muscle cell differentiation (11, 15, 139, 169), and may therefore account for alterations in cytokine expression and secretion in skeletal muscle cells as they differentiate. The expression of some toll-like receptors (e.g., TLR2, TLR5) increases during muscle cell differentiation (24), which may also influence signaling path-

ways linked to cytokine expression and secretion in skeletal muscle cells (69). Changes in cytokine expression during muscle cell differentiation appear to play an important functional role. For example, increased expression of IL-6 (15) and reduced expression of BDNF (143) in skeletal muscle cells is necessary for them to differentiate. Conversely, increased expression of TNF-α during muscle cell differentiation (80) may inhibit myoblast differentiation (115, 227), although this effect is not entirely consistent (43). Using an RNAi screen, Ge et al (74) identified more than 100 cytokines that act regulate myoblast differentiation. Based on their results, they were able to classify these cytokines according to their capacity to initiate differentiation, regulate myocyte fusion and inhibit differentiation. Increased chemokine expression during differentiation may also control the migration and/or positioning of myoblasts so that they can successfully fuse with nascent myotubes (80). Alternatively, increased cytokine expression during muscle cell differentiation may promote muscle cell proliferation (122, 237), and migration of monocytes (40) and mesenchymal stem cells (176) to support muscle growth. Last, autocrine cross-talk between cytokines may also control muscle cell differentiation (4, 7, 71, 125).

CONCLUSION

Our understanding of the importance of skeletal muscle and cytokines as mediators of metabolism has increased substantially over the last decade or so. Research to date has identified more than 600 different proteins that are secreted by skeletal muscle cells (168). In this rapidly advancing age of '-omics' technologies, the muscle cell secretome will continue to grow and provide new targets on which to focus. We now know that myokines exert various endocrine effects on various metabolically active organs, including adipose tissue, the liver, the pancreas and the brain. Nevertheless, perhaps with the exception of IL-6 and LIF, our knowledge of the factors and mechanisms that regulate cytokine production and release from skeletal muscle cells during exercise remains somewhat limited. Skeletal muscle cells produce numerous cytokines in response to various agents, but not all these agents are present at similar concentrations and/or are active in the muscle microenvironment during exercise. The capacity for these individual agents to stimulate skeletal muscle cells to produce cytokines is well characterized. However, the control of cytokine production in skeletal muscle during exercise is more complex than the *in vitro* setting, and depends on interactions between a variety of local and systemic factors. Future research should aim to treat skeletal muscle cells with combinations and concentrations of agents that are present in skeletal muscle during exercise.

Cyclic strain and electromagnetic stimulation of skeletal muscle myotubes *in vitro* has generated useful insights into the signaling pathways that govern cytokine production by skeletal muscle cells during exercise. Adding other factors—such as cytokines themselves—to this experimental system could simulate the muscle microenvironment during exercise. In doing so, this approach may assist in characterizing interactions between factors that stimulate or inhibit the ability of skeletal muscle cells to produce cytokines during exercise.

More research is warranted to identify the feedback mechanisms that govern cytokine synthesis by skeletal muscle cells; in particular, which mechanisms are most important, how they interact with each other, and how they are induced and regulated. These research endeavors are important for several reasons. First, this information may help to understand the factors governing the systemic release of cytokines. Second, this information may help to understand the processes that regulate acute inflammatory responses to tissue injury. Last, this information may help to determine why some pro-inflammatory cytokines are chronically elevated in skeletal muscle of patients with idiopathic myopathies, rheumatoid arthritis and muscular dystrophy.

Finally, much has been written about the anti-inflammatory effects of exercise. Petersen et al (171) first proposed the notion that exercise-induced increases in IL-6, IL-1ra and IL-10 exert beneficial anti-inflammatory effects to counteract obesity and insulin resistance. Although this theory is appealing from a mechanistic perspective (206), cytokines may play a relatively minor role in regulating the health benefits of exercise training. Evidence in support of this notion is that brisk walking does not stimulate any discernible increase in circulating cytokines (135), yet regular walking is associated with many health benefits. Furthermore, marathon running induces high physiological stress and a large cytokine response (155), but it is doubtful the cytokines are increased for the purposes of health. Instead, exercise-induced cytokine changes may represent a more generalized response to internal and/or external stress. Factors such as oxidative or nitrosative stress, damaged or unfolded proteins, hyperthermia or energy imbalance likely induce cytokine production during exercise through catecholamines, endotoxin, alarmins, ATP and pro-inflammatory cytokines themselves (232). These issues highlight the need for further research to enhance our understanding of the biological significance of exercise-induced cytokine responses.

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