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Muscle as an Endocrine Organ: Focus on Muscle-Derived Interleukin-6

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Pedersen BK, Febbraio MA. Muscle as an Endocrine Organ: Focus on Muscle-Derived Interleukin-6. *Physiol Rev* 88: 1379–1406, 2008; doi:10.1152/physrev.90100.2007.—Skeletal muscle has recently been identified as an endocrine organ. It has, therefore, been suggested that cytokines and other peptides that are produced, expressed, and released by muscle fibers and exert paracrine, autocrine, or endocrine effects should be classified as "myokines." Recent research demonstrates that skeletal muscles can produce and express cytokines belonging to distinctly different families. However, the first identified and most studied myokine is the gp130 receptor cytokine interleukin-6 (IL-6). IL-6 was discovered as a myokine because of the observation that it increases up to 100-fold in the circulation during physical exercise. Identification of IL-6 production by skeletal muscle during physical activity generated renewed interest in the metabolic role of IL-6 because it created a paradox. On one hand, IL-6 is markedly produced and released in the postexercise period when insulin action is enhanced but, on the other hand, IL-6 has been associated with obesity and reduced insulin action. This review focuses on the myokine IL-6, its regulation by exercise, its signaling pathways in skeletal muscle, and its role in metabolism in both health and disease.

I. INTRODUCTION AND HISTORICAL PERSPECTIVE

Skeletal muscle has recently been identified as an organ that produces and releases cytokines, which we have named "myokines." Given that skeletal muscle is the largest organ in the human body, our discovery that contracting skeletal muscle secretes proteins sets a novel paradigm: skeletal muscle is an endocrine organ producing and releasing myokines in response to contraction,

which can influence metabolism in other tissues and organs. With the discovery that exercise provokes an increase in a number of cytokines, a possible link between skeletal muscle contractile activity and immune changes was established.

For most of the last century, researchers sought a link between muscle contraction and humoral changes in the form of an "exercise factor," which could be released from skeletal muscle during contraction and mediate some of the exercise-induced metabolic changes in other organs such as the liver and the adipose tissue. We have suggested that cytokines or other peptides that are produced, expressed, and released by muscle fibers and exert either paracrine or endocrine effects should be classified as "myokines" (259). The nervous, endocrine, and immune systems all contribute to the maintenance of homeostasis. Interestingly, although these individual systems operate independently to a certain degree, each with their own collection of highly specific cells and regulatory factors, they also depend on each other for normal development and function.

Research, which dates back to 1930, demonstrated that if the pituitary gland was removed in rats, the thymus would undergo atrophy (320). Later in 1976, Pelletier et al. (273) showed that in the dwarf mouse, in which the pituitary function is abnormal, circulating thymic peptide levels undergo a premature decline. These pioneering studies led to the hypothesis that normal development of the immune system is dependent on factors produced by the hypothalamic-pituitary axis. It was shown that a number of pituitary hormones, e.g., prolactin, growth hormone, and adrenocorticotropin (ACTH), can serve as immunomodulatory factors (116, 157).

The discovery of cytokines (glycoproteins with molecular weights of 15,000–30,000) (79) and their immunoregulatory roles was followed by studies demonstrating that these were involved in a complex network of communication between the neuroendocrine and the immune system. In fact, it appeared that cytokines may also modulate the secretion from the hypopituitary-hypothalamus axis and that an important neuroendocrine-immune loop exists (69, 323).

Research through the past 20 years has demonstrated that exercise induces considerable changes in the immune system. The interactions between exercise and the immune system provided a unique opportunity to evaluate the role of underlying endocrine and cytokine mechanisms (263). In an attempt to understand the mechanisms underlying exercise-induced changes in the distribution and concentrations of lymphocyte subpopulations, we and others focused on cytokines and their possible roles as a link between muscle contractions and cellular immune changes (263). This research led to the discovery that exercise provokes an increase in a number of cytokines (91, 92, 257, 262, 266, 270).

In the year 2000, it became clear that contracting human skeletal muscle releases significant amounts of interleukin (IL)-6 into the circulation during prolonged single-limb exercise (340). An accompanying editorial to this publication pointed to the possibility that muscle-derived IL-6 could have metabolic roles: "It is an intriguing possibility that the IL-6 response may be a signal indicating that muscle glycogen stores are reaching critically low levels and that the active muscles' reliance on blood glucose as a source of energy is on the increase" (121). The latter statement was soon supported by experimental studies (166, 334), and a number of studies highlighted the fact that muscle-derived IL-6 is an important player in metabolism (52, 88, 92, 257, 258, 262, 266, 268, 277, 333).

Our research was originally driven by a curiosity as to whether exercise-induced cytokines would provide a mechanistic explanation to exercise-induced immune changes. However, the identification of skeletal muscle as a cytokine-producing organ soon led to the discovery that muscle-derived cytokines could account not only for exercise-associated immune changes, but that these muscle-derived cytokines played a role in mediating the exercise-associated metabolic changes, as well as the metabolic changes following training adaptation.

It appears that skeletal muscle has the capacity to express several myokines. To date the list includes IL-6, IL-8, and IL-15 (259). Contractile activity plays a role in regulating the expression of many of these cytokines in skeletal muscle (259). The discovery that IL-6 is released from contracting skeletal muscle has generated much interest among the scientific community because this finding is somewhat paradoxical. On one hand, IL-6 is markedly produced and released in the postexercise period when insulin action is enhanced, but on the other hand, IL-6 has been associated with obesity and reduced insulin action. Given the controversy, this review focuses on the metabolic roles of IL-6.

II. EXERCISE AND CYTOKINES WITH FOCUS ON INTERLEUKIN-6

A. Systemic Levels

It has been consistently demonstrated that the plasma concentration of IL-6 increases during muscular exercise (91, 92, 100, 227, 265–269).

This increase is followed by the appearance of IL-1 receptor antagonist (IL-1ra) and the anti-inflammatory cytokine IL-10. Concentrations of the chemokines, IL-8, macrophage inflammatory protein α (MIP-1α), and MIP-1β are elevated after strenuous exercise (252). In most exercise studies, tumor necrosis factor (TNF)-α does not change. Only highly strenuous, prolonged exer-

cise such as marathon running results in a small increase in the plasma concentration of TNF-α (42, 330, 346, 359). In general, the cytokine response to exercise and sepsis differs with regard to TNF-α. Thus the cytokine response to exercise is not preceded by an increase in plasma TNF-α (Fig. 1).

Even though there is a moderate increase in the systemic concentration of these cytokines, the underlying fact is that the appearance of IL-6 in the circulation is by far the most marked and that its appearance precedes that of the other cytokines.

Following exercise, the basal plasma IL-6 concentration may increase up to 100-fold, but less dramatic increases are more frequent (100, 261) (Table 1, Fig. 2). Thus the 8,000-fold increase of plasma IL-6 following a 246 km "Spartathlon" race (207) represents an atypical and extreme response. Of note, the exercise-induced increase of plasma IL-6 is not linear over time; repeated measurements during exercise show an accelerating increase of the IL-6 in plasma in an almost exponential manner (103, 251, 340). Furthermore, the peak IL-6 level is reached at the end of the exercise or shortly thereafter (103, 251), followed by a rapid decrease towards preexercise levels. Overall, the combination of mode, intensity, and duration of the exercise determines the magnitude of the exercise-induced increase of plasma IL-6. Since IL-6 is a classical inflammatory cytokine, it was first thought that the IL-6 response was related to muscle damage (41). However, it has become evident that eccentric exercise is not associated with a larger increase in plasma IL-6 than exercise involving concentric "nondamaging" muscle contractions (Fig. 2), clearly demonstrating that muscle damage is not required to increase plasma IL-6 during exercise. Rather, eccentric exercise may result in a delayed peak and a slower decrease of plasma IL-6 during recovery (135, 203, 396).

In contrast, the IL-6 response is sensitive to the exercise intensity (250), which again indirectly represents the muscle mass involved in the contractile activity. Since contracting skeletal muscle per se is an important source of IL-6 found in the plasma (103, 340), it is not surprising that exercise involving a limited muscle mass, e.g., the muscles of the upper extremities, may be insufficient to increase plasma IL-6 above preexercise level (24, 138, 246). In contrast, running, which involves several large muscle groups, is the mode of exercise where the most dramatic plasma IL-6 increases have been observed (Table 1, Fig. 2). Fischer (100) has shown that exercise duration is the single most important factor determining the postexercise plasma IL-6 amplitude (Table 1, Fig. 3). In fact, more than 50% of the variation in plasma IL-6 following exercise can be explained by exercise duration alone ($P < 10^{-12}$) (100).

Since exercise at high intensity is often associated with shorter duration of the exercise, and vice versa, the relationship between the plasma IL-6 increase and the duration may be even more pronounced if adjusted for the exercise intensity. Accordingly, 6 min of maximal rowing ergometer exercise may increase plasma IL-6 2-fold (231), but more than 10-fold increases of plasma IL-6 have not been observed in response to exercise lasting less than 1 h. Based on the log-log linear relationship between time and increase of plasma IL-6, a 10-fold increase of plasma IL-6 requires exercise for 1.9 h (CI 1.6–2.9 h, $P < 0.0001$), whilst a 100-fold increase of plasma IL-6 requires exercise lasting 6.0 h (CI 4.5–8.1 h, $P < 0.0001$). This relationship is remarkably insensitive to the mode of exercise, although generally the highest increases of plasma IL-6 are found in response to running.

The fact that IL-6 is synthesized and released from contracting muscles alone and not from resting muscles exposed to the same hormonal changes (159, 340) demonstrates that circulating systemic factors cannot explain why contracting muscles synthesize and release IL-6. It is more likely that local factors are involved, although systemic factors may modulate the IL-6 release from contracting muscle.

B. Sources of Contraction-Induced IL-6

Until the beginning of this millennium it was commonly thought that the exercise-induced increase in IL-6

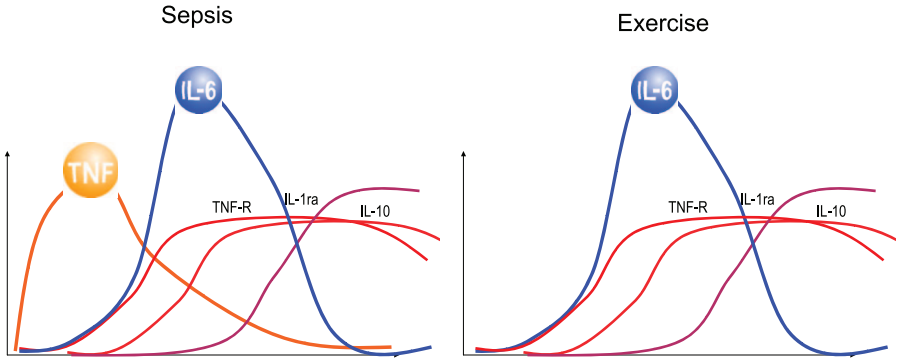

FIG. 1. Comparison of sepsis-induced verses exercise-induced increases in circulating cytokines. During sepsis, there is a marked and rapid increase in circulating tumor necrosis factor (TNF)-α, which is followed by an increase in interleukin (IL)-6. In contrast, during exercise, the marked increase in IL-6 is not preceded by elevated TNF-α.

TABLE 1. *Effect of acute exercise on plasma IL-6 in humans*

Knee Extensor				Bicycling				Running			
n	Duration, h	IL-6, fold change	Reference Nos.	*n*	Duration, h	IL-6, fold change	Reference Nos.	*n*	Duration, h	IL-6, fold change	Reference Nos.
7	3.0	3	105	9	0.4	1	94	12	0.2	1	401
7	0.8	3	134	9	0.3	1	371	19	6.0	4	81
7	3.0	6	272	16	0.7	1	211	7	1.0	4	240
6	3.0	11	166	7	1.0	2	35	8	1.5	4	352
7	3.0	12	103	17	1.0	2	366	6	9.1	6	276
6	3.0	15	338	6	2.0	2	140	8	1.5	8	353
6	5.0	19	340	9	0.5	2	41	30	2.5	8	224
7	5.0	36	334	8	1.0	2	198	7	1.0	9	328
				9	1.5	2	194	12	0.9	9	241
				7	0.3	2	117	10	1.6	10	319
				7	0.3	2	117	16	3.0	10	234
				8	0.4	2	94	10	1.5	20	279
				8	1.5	2	345	10	2.5	25	251
				6	2.0	3	140	13	9.8	28	236
				11	1.5	3	356	7	9.9	29	239
				6	0.8	3	374	7	2.5	29	332
				8	2.0	4	36	9	2.5	30	339
				8	1.0	5	201	50	4.5	42	237
				7	1.0	5	328	18	3.7	43	55
				9	1.0	5	303	6	3.0	50	186
				7	1.5	6	329	10	2.5	52	238
				6	2.0	8	90	16	3.3	63	254
				18	3.0	8	274	10	2.6	80	344
				8	1.0	9	248	18	3.5	88	48
				8	2.0	11	141	10	3.5	92	360
				8	3.0	13	164	16	2.5	109	346
				15	2.5	16	233	60	26.3	126	235
				6	2.0	20	327	10	3.5	128	252
				10	2.5	24	238				
				6	3.0	26	247				
				8	2.0	38	130				

Shown is the relation between exercise mode (dynamic knee-extensor, bicycling, and running), exercise duration, and plasma interleukin (IL)-6 increase (fold change from preexercise level). In studies investigating the effect of an intervention on the IL-6 response to exercise, e.g., carbohydrate supplementation, only the result from the control group (exercise without intervention) is presented. Hence, the *n* value presented in Table 1 may be lower than the *n* value presented in the original study. [Modified from Fischer (100).]

was a consequence of an immune response due to local damage in the working muscles (238), and it was hypothesized that the immune cells were responsible for this increase (224). An early study by our group (366) and a recent study by others (218) demonstrated, however, that IL-6 mRNA in monocytes, the blood mononuclear cells responsible for the increase in plasma IL-6 during sepsis, did not increase as a result of exercise. More recent work from our group has clearly demonstrated that monocytes are not the source of the exercise-induced increase in plasma IL-6. Using flow cytometric techniques, we have demonstrated that the number, percentage, and mean fluorescence intensity of monocytes staining positive for IL-6 either do not change during cycling exercise (327) or do in fact decrease during prolonged running (330). Therefore, the previously held assumption that the IL-6 response to exercise may involve immune cells does not appear to be correct. Today, it is very clear that the contracting skeletal muscle per se is the main source of the IL-6 in the circulation in response to exercise (Fig. 4). In resting human skeletal muscle, the IL-6 mRNA content is very low, while small amounts of IL-6 protein predominantly in type I fibers may be detected using sensitive immunohistochemical methods (287). In response to exercise, an increase of the IL-6 mRNA content in the contracting skeletal muscle is detectable after 30 min of exercise, and up to 100-fold increases of the IL-6 mRNA content may be present at the end of the exercise bout (166, 338).

Although the earlier studies demonstrated that IL-6 mRNA is increased in skeletal muscle biopsy samples, they did not prove that skeletal muscle is the source of the increase in the contraction-induced increase in IL-6. However, we demonstrated that the net IL-6 release from the contracting limb contributes to the exercise-induced increase in arterial plasma concentrations (340). By obtaining arterial-femoral venous differences over an exercising leg, we found that exercising limbs released IL-6. During the last 2 h of exercise, the release per unit time was ~17-fold higher than the amount accumulating in the plasma.

Although IL-6 appeared to be produced in the contracting skeletal muscle, it was not fully clear which cell type within the muscle is responsible for the production.

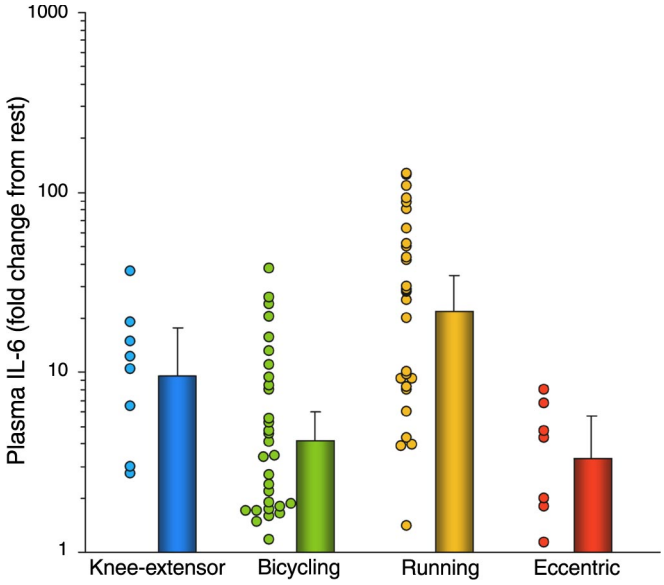

FIG. 2. Different modes of exercise and the corresponding increase in plasma IL-6 levels. Graph is based on 73 exercise trials and represents ~800 subjects. Each dot indicates one exercise trial; the corresponding bars represent geometric means with 95% confidence intervals. Although different modes of exercise are associated with different levels of muscle damage, the increase in plasma IL-6 levels postexercise is a consistent finding. [Modified from Fischer (100) and Pedersen and Fischer (261).]

Whereas myoblasts had been shown to be capable of producing IL-6 (19, 72), endothelial cells (402), fibroblasts (72), and smooth muscle cells (171) had been shown to produce IL-6 under certain circumstances. Langberg et al. (185) demonstrated that IL-6 is produced by the peritendinous tissue of active muscle during exercise. In an attempt to determine which cells produce the IL-6, Keller et al. (166) isolated nuclei from muscle biopsies obtained before, during, and after exercise. With the use of RT-PCR, it was demonstrated that the nuclear transcription rate for IL-6 increases rapidly and markedly after the onset of exercise (166). This suggested that a factor associated with contraction increases IL-6 transcriptional rate, probably in the nuclei from myocytes, given the observation that IL-6 protein is expressed within muscle fibers (205). Further evidence that contracting muscle fibers themselves are a source of IL-6 mRNA and protein has been achieved by analysis of biopsies from the human vastus lateralis using in situ hybridization and immunohistochemistry (139, 274). In addition, assessment of the interstitial IL-6 concentration using microdialysis indicates that the concentration of IL-6 within the contracting skeletal muscle may be 5- to 100-fold higher than the levels found in the circulation (186, 305). Accordingly, IL-6 appears to accumulate within the contracting muscle fibers as well as in the interstitium during exercise. However, it has been the simultaneous measurement of arteriovenous IL-6 concentrations and blood flow across the leg that has demonstrated that large amounts of IL-6 are released from the exercising leg (340). In the same study, we also estimated that the net release from the exercising leg could account for the systemic increase of plasma IL-6, assuming that IL-6 is distributed in the extracellular compartment and that IL-6 content in blood is the same in plasma and in the cellular fraction. Since IL-6 appears to be transported solely in the noncellular fraction of the blood (54), the net release of IL-6 from the exercising leg was probably overestimated. Another approach was based on the close log-log linear relationship between recombinant human IL-6 (rhIL-6) dose and resulting steady-state plasma IL-6 concentration, supporting the concept that IL-6 released from the exercising limb may account for the systemic plasma IL-6 increase following exercise. At the end of the exercise, the average release of IL-6 from the contracting leg was 15 ng/min, while the systemic plasma IL-6 concentration was 14 pg/ml (340). On the basis of the dose-response relationship, the expected systemic plasma IL-6 concentration corresponding to an IL-6 dose of 15 ng/min is 16 pg/ml ($\text{antilog}_{10}[1.05 \times \log_{10}[15\ \text{ng/ml}] + 0.07]$), which corresponds well to the observed value (100). Although IL-6 released from the contracting muscles may account for most of the IL-6 found in the circulation, other studies have demonstrated that skeletal muscle is not the sole source of exercise-induced IL-6. With the use of oral supplementation with vitamins C and E for 4 wk, the IL-6 net release from the exercising legs was almost blocked completely, yet the systemic increase of plasma IL-6 was only reduced by 50% (103).

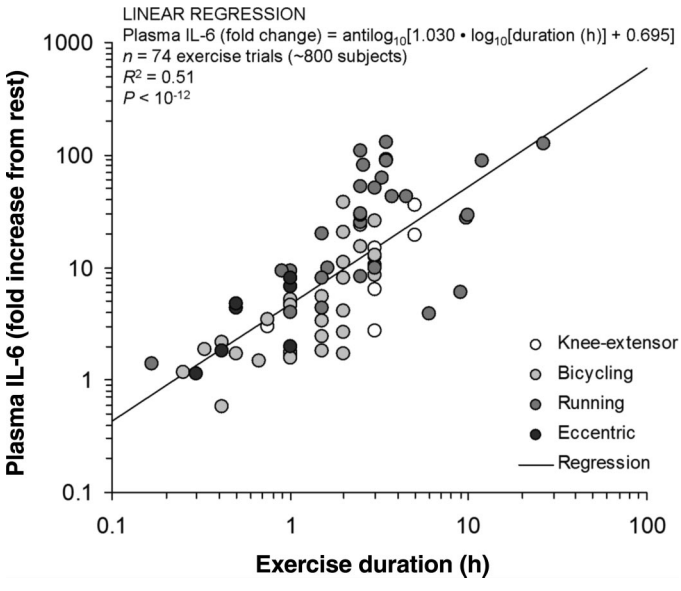

FIG. 3. The overall $\log_{10}$-$\log_{10}$ linear relation (straight solid line) between exercise duration and increase in plasma IL-6 (fold change from preexercise level) indicates that 51% of the variation in plasma IL-6 increase can be explained by the duration of exercise. [Modified from Fischer (100).]

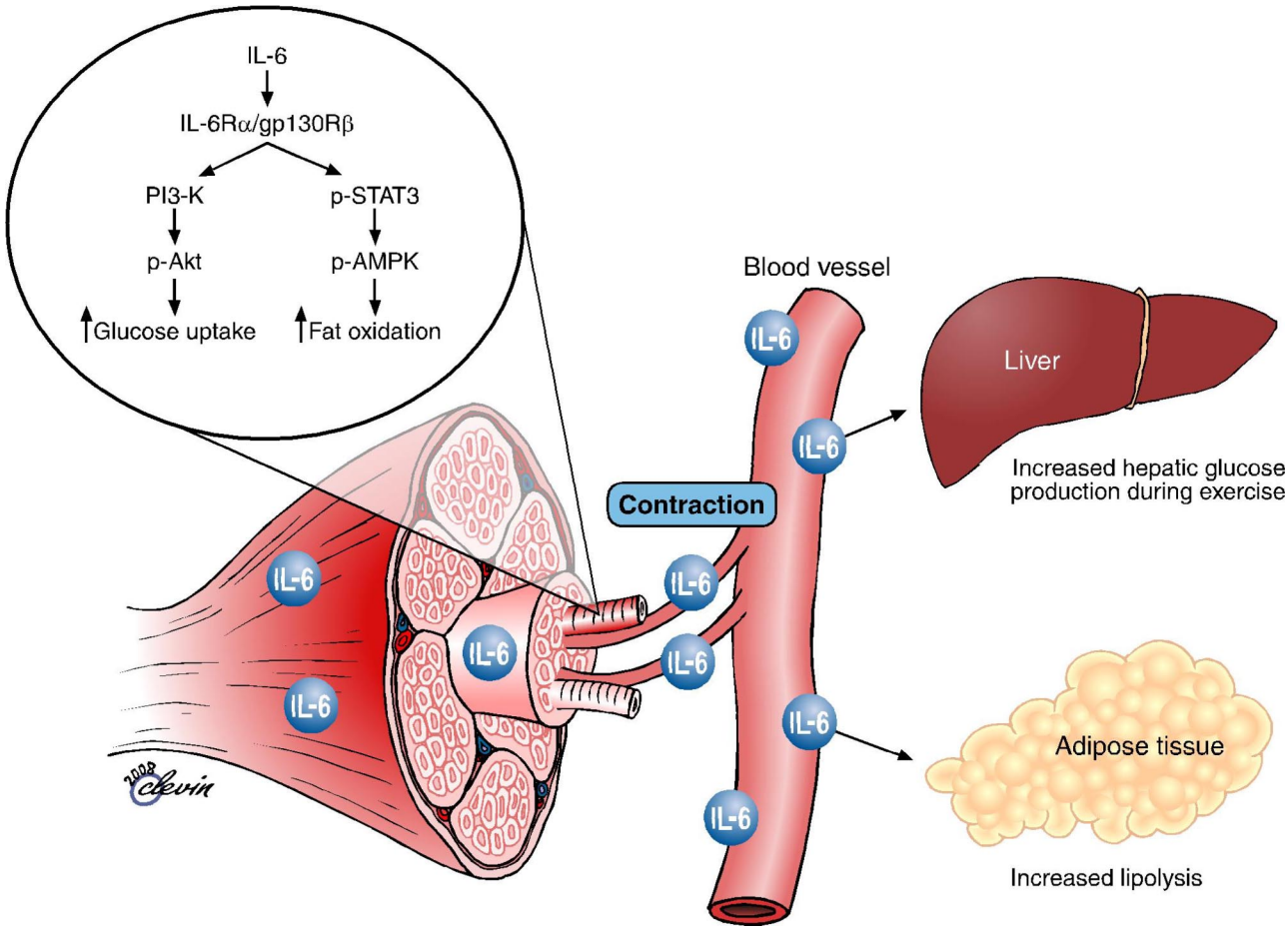

FIG. 4. Biological role of contraction-induced IL-6. Skeletal muscle expresses and releases myokines into the circulation. In response to muscle contractions, both type I and type II muscle fibers express the myokine IL-6, which subsequently exerts its effects both locally within the muscle (e.g., through activation of AMP-kinase) and, when released into the circulation, peripherally in several organs in a hormonelike fashion. Specifically, in skeletal muscle, IL-6 acts in an autocrine or paracrine manner to signal through a gp130Rβ/IL-6Rα homodimer to result in activation of AMP-kinase and/or phosphatidylinositol 3-kinase to increase glucose uptake and fat oxidation. IL-6 is also known to increase hepatic glucose production during exercise or lipolysis in adipose tissue. [Modified from Pedersen and Fischer (261).]

As mentioned above, very high concentrations of IL-6 have been detected along the Achilles' tendon using microdialysis in response to prolonged running (186), but since the muscle mass involved in exercise is much higher than the mass comprised by tendons, the mutual contribution of peritendinous versus muscle-derived IL-6 to the systemic IL-6 is unclear. In addition, a small net release of IL-6 from the internal jugular vein has been reported, suggesting that the central nervous system may contribute to the IL-6 found in the circulation (248). The findings are contrasted by the consistent findings that peripheral blood mononuclear cells do not contribute to the IL-6 found in the circulation of healthy subjects, neither at rest nor in response to exercise (254, 327, 366, 374). The adipose tissue may contribute markedly to IL-6 in the circulation at rest (217, 322). However, although IL-6 mRNA levels increase in adipose tissue during exercise (164), measurement of arteriovenous plasma IL-6 differences across the abdominal subcutaneous adipose tissue bed shows that this compartment does not contribute to the exercise-induced IL-6 in the circulation until the recovery phase (200). Since almost any cell type may synthesize IL-6 upon adequate stimulation (7), further studies may discover other sites contributing to the IL-6 in the circulation in response to exercise.

C. Role of Muscle Glycogen and Glucose Ingestion

Skeletal muscle cells are capable of producing IL-6 in response to various stimuli such as incubation with lipopolysaccharide, reactive oxygen species, and inflammatory cytokines. In these circumstances, the upstream signaling events that lead to the induction of IL-6 have been well categorized, and the signaling events that lead to IL-6 production in cultured skeletal muscle cells are consistent with experiments conducted in cardiac myocytes and monocytes. However, human skeletal muscle appears

unique, in that it can produce IL-6 during contraction in the absence of observable markers of inflammation (91) and in a TNF-independent fashion (162), linking IL-6 to metabolism rather than inflammation. The factors that lead to IL-6 gene transcription during contraction rather than inflammation are not fully elucidated. However, both intramuscular IL-6 mRNA expression (166) and protein release (334) are exacerbated when intramuscular glycogen is compromised, suggesting that IL-6 is somehow related to glycogen content.

A number of studies have demonstrated that glucose ingestion during exercise attenuates the exercise-induced increase in plasma-IL-6 (137, 184, 193–195, 224, 232–234, 238). However, whereas supplementation with carbohydrates during exercise inhibits the exercise-induced increase of IL-6 in plasma, IL-6 mRNA expression within the contracting muscle is unaffected (93, 224, 238, 328). As carbohydrate availability is reduced, the sympathoadrenal response to exercise is exacerbated, and it has been suggested that epinephrine may stimulate IL-6 gene transcription via β-adrenergic stimulation of protein kinase A. There are studies within the literature that show a link between epinephrine concentration and exercise-induced increases in plasma IL-6. However, we recently tested the hypothesis that epinephrine mediates IL-6 production by skeletal muscle. We incubated rat skeletal muscle ex vivo in various concentrations of epinephrine and measured IL-6 mRNA expression and protein release into the incubation media. Although pharmacological doses (1,000 nmol) of epinephrine increased IL-6 mRNA expression, more physiological doses (100 and 10 nmol) had no such effect, whereas epinephrine did not result in an IL-6 protein release irrespective of dose. We have previously hypothesized that contraction may lead to IL-6 gene transcription via calcium (Ca^{2+}) being released from the lateral sacs of the sarcoplasmic reticulum to activate IL-6 through activation of nuclear factor of activated T cells (144). When muscle strips were incubated with ionomycin, an increase in IL-6 mRNA expression and protein release was observed (144). Moreover, in human skeletal muscle cell cultures, IL-6 mRNA increases time- and dose-dependently with ionomycin stimulation, an effect that is blunted by ~75% in the presence of the calcineurin inhibitor cyclosporin A. In contrast, TNF-α gene expression is decreased by ~70% in response to ionomycin treatment but increases in response to addition of CSA. These data demonstrate that IL-6 and TNF-α are regulated differentially in skeletal muscle cells in response to a Ca^{2+} stimulus (162). In a recent study, Banzet et al. (18) used cyclosporin A and FK506, which are both specific inhibitors of calcineurin, and concluded that contraction-induced IL-6 transcription in rat slow-type muscle is partly dependent on calcineurin activation (18).

D. Role of Training Adaptation

Exercise training involves multiple adaptations including increased preexercise skeletal muscle glycogen content, enhanced activity of key enzymes involved in the β-oxidation (312), increased sensitivity of adipose tissue to epinephrine-stimulated lipolysis (68), and increased oxidation of intramuscular triglycerides (281), whereby the capacity to oxidize fat is increased (143, 311). As a consequence, the trained skeletal muscle is less dependent on plasma glucose and muscle glycogen as substrate during exercise (281).

Several epidemiological studies have reported a negative association between the amount of regular physical activity and the basal plasma IL-6 levels: the more physically active, the lower basal plasma IL-6 (57, 64, 255). Basal plasma IL-6 is more closely associated with physical inactivity than other cytokines associated with the metabolic syndrome (101). The epidemiological data are supported by findings from intervention studies, although these produce less consistent results. Basal levels of IL-6 are reduced after training in patients with coronary artery disease (123). Aerobic training for 10 mo of adults aged 64 yr or more also decreases basal plasma IL-6 (175). In severely obese subjects, the combination of a hypocaloric diet and regular physical activity for 15 wk reduces not only plasma IL-6, but also the IL-6 mRNA content in subcutaneous adipose tissue and in skeletal muscle (38). In addition, elite competition skiers have lower basal plasma IL-6 during the training season than off-season (302); still, the fact that others have not observed any changes in basal IL-6 levels in response to training should be acknowledged (40, 187, 226).

At present, evidence is limited as to whether the exercise-induced increase of plasma IL-6 is affected by training. With the use of knee-extensor exercise, seven healthy men trained for 1 h, 5 times per week for 10 wk (105). Before and after the training, the participants performed knee-extensor exercise for 3 h at 50% of their maximal work load. Due to the adaptive nature of habitual exercise, the absolute work load compared with that pretraining was 44% higher following training. Despite this fact, the increase in IL-6 mRNA content by acute exercise was 76-fold before training but only 8-fold after training. In addition, the exercise-induced increase of plasma IL-6 was similar before and after training. Accordingly, it could be speculated that differences in training status, and in particular in muscle glycogen content, may explain why elderly subjects release the same amount of IL-6 from the leg as young subjects during knee-extensor exercise at the exact same relative, but half the same absolute, work load (272) (Fig. 5).

It is worth noting that while plasma-IL-6 appears to be downregulated by training, the muscular expression of the IL-6 receptor appears to be upregulated. In response

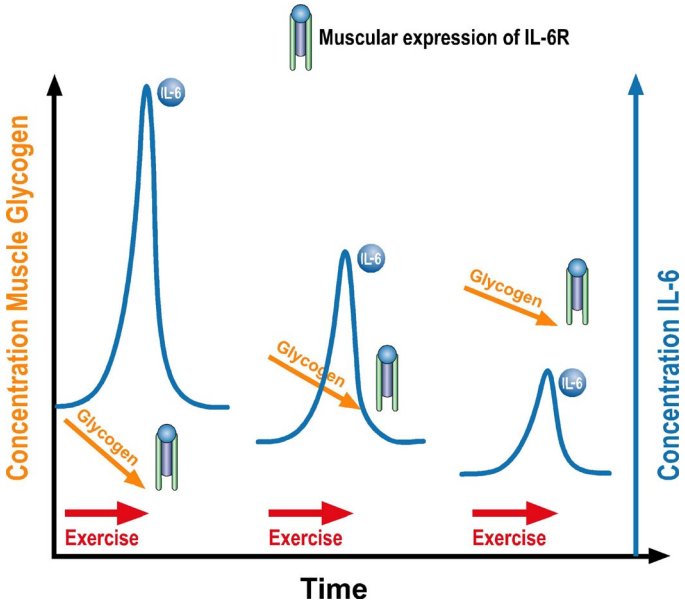

FIG. 5. The figure presents a model on how IL-6 is regulated in response to training adaptation. Regular exercise leads to an enhancement of glycogen synthase, and a trainined muscle will consequently store more muscle glycogen. During acute exercise, the untrained muscle is highly dependent on glycogen as substrate, whereas training leads to an enhancement of β-oxidating enzymes and an enhanced capability to oxidize fat and hence to use fat as substrate during exercise. This means that the trained muscle uses less glycogen during work. The activation of muscle-IL-6 is glycogen dependent. At conditions with low muscle-glycogen, the transcription rate of IL-6 is faster, and relatively more IL-6 is produced at the same relative work compared with conditions with a high muscle glycogen. Thus the acute plasma IL-6 response is lower in a trained versus an untrained subject. The mechanisms whereby basal plasma IL-6 is decreased by training and whereby the muscular expression of IL-6 receptors (IL-6R) is enhanced are not fully understood. However, it appears that a trained muscle may be more sensitive to IL-6.

to exercise training, the basal IL-6R mRNA content in trained skeletal muscle is increased by ~100% (165). Accordingly, it is possible that the downregulation of IL-6 is partially counteracted by an enhanced expression of IL-6R, whereby the sensitivity to IL-6 is increased. It remains to be determined if the increased IL-6R mRNA content corresponds to an increased expression of the IL-6R protein. Furthermore, it is not known if the enhanced IL-6R expression following training occurs in several tissues or only locally within the trained skeletal muscle. In the circulation, the IL-6R concentration is affected neither by training nor acute exercise (165).

Thus sound evidence exists that low physical activity results in elevated basal IL-6 levels, while a high level of physical activity results in low basal IL-6 levels. Yet, there is limited evidence indicating that the exercise-induced increase of IL-6 in the contracting muscle as well as in the circulation is attenuated by training. Since training adaptation includes changes known to counteract potential stimuli for IL-6, it is very likely that further studies will demonstrate alterations in the exercise-induced IL-6 response by training.

III. MOLECULAR MECHANISMS LEADING TO CONTRACTION-INDUCED INTERLEUKIN-6 PRODUCTION IN MYOCYTES

Despite the fact that nondamaging muscular contraction rapidly induces transcription of the IL-6 gene in skeletal myocytes, the intracellular signaling events that mediate this process remain poorly understood. The intracellular signaling pathway for IL-6 was originally characterized in endotoxin-stimulated monocytes and macrophages (73, 178, 295). In these cells, binding of the bacterial endotoxin, namely, lipopolysaccharide (LPS) to the Toll-like receptor (TLR)-4 recruits myeloid differentiation primary-response protein 88 (MyD88) to its cytoplasmic domain. By acting as an adaptor molecule, MyD88 triggers a cascade of intracellular signaling consisting of IL-1 receptor-associated kinase (IRAK)-1 and TNF-α receptor-associated factor (TRAF)-6, leading to the activation of the IkappaB kinase (IKK)-nuclear factor of κB (NFκB) pathway. NFκB is a transcription factor that usually resides in the cytosol during resting conditions, where its activity is highly restricted by the association with IkappaB (IκB), the inhibitory subunit of NFκB. Activation of IKK phosphorylates this inhibitory subunit, targeting it for ubiquitination and hence subsequent proteasomal degradation resulting in activation of NFκB. NFκB is then able to translocate into the nucleus and to exert its transcriptional effects on the immunologically relevant genes such as IL-6, TNF-α, and IL-1β that mediate the classic inflammatory response (5, 8, 27, 127, 178, 192, 196).

A. Nitric Oxide

Skeletal muscle cells are capable of producing IL-6 in response to various stimuli such as lipopolysaccharide (LPS) (111, 112), reactive oxygen species (ROS) (177), inflammatory cytokines (112, 199) and, as discussed in detail previously, during contraction. LPS, ROS, and inflammatory cytokines like TNF-α and IL-1β can elicit the production of IL-6 via signaling pathways that involve the mitogen-activated protein kinases (MAPKs), namely, c-jun NH_2-terminal kinase (JNK) (112) and p38 (199), and the transcription factors NFκB and activator protein-1 (AP1) (177). These signaling events that lead to IL-6 production in cultured skeletal muscle cells are consistent with experiments conducted in cardiac myocytes (67) and monocytes (364). However, the upstream signaling events in skeletal muscle during contraction that lead to gene activation are much less understood, although recent advances suggest a role for nitric oxide (NO) pro-

duction within skeletal muscle (337). In vitro studies have provided evidence that NO may be involved in transcriptional control through several potential mechanisms (31). Thus NO may directly alter signaling networks by redox-sensitive modification or by nitrosation of proteins within the cytoplasm or nucleus (136). The NO-induced increase in cGMP may also exert effects on transcription (282). The neuronal NO synthase isoform (nNOS) is abundantly expressed in human skeletal muscle (108), and a number of observations provide evidence that NO production is significantly increased within contracting skeletal muscle (16, 126, 188, 189, 301, 318).

A recent exercise study in humans demonstrated that NO production within contracting skeletal muscles is a key regulator of pretranslational signaling events leading to muscle-IL-6 production. Pharmacological inhibition of NO production during exercise attenuated the increase in IL-6 mRNA levels in human skeletal muscle. In addition, it was shown that prolonged intra-arterial infusion of an NO donor was accompanied by increases in IL-6 mRNA content in resting skeletal muscle. Moreover, the drug-induced changes of IL-6 mRNA expression were accompanied by similar alterations in IL-6 protein release, supporting the functional significance of the IL-6 mRNA change (337).

B. NFκB

It is tempting to hypothesize that NFκB is implicated in upstream signaling processes, since it is the major pathway by which IL-6 is transcribed in macrophages and lymphocytes. However, although the NFκB signaling pathway is activated by contraction in rodent skeletal muscle (142, 156), no such effect is observed in humans (60, 337).

NFκB is a redox-sensitive transcription factor (314) that may be activated by ROS. Increased ROS formation in skeletal muscle following exercise has been demonstrated directly in animals (70, 153) and indirectly in humans (15). In vitro, murine skeletal myotubes release IL-6 when exposed to oxidative stress in a NFκB-dependent way (177). In addition, supplementation with different antioxidants attenuates the systemic increase of IL-6 in response to exercise (353, 374). Using arteriovenous differences of IL-6 across the leg, we observed that the reduced systemic increase of IL-6 during exercise was due to an almost complete inhibition of the net leg release of IL-6 in the group pretreated with vitamins C and E for 4 wk (103). The observation that indomethacin, a member of the nonsteroid anti-inflammatory drugs (NSAID), which are known to inhibit NFκB activity, reduces the exercise-induced increase of IL-6 further supports the notion that NFκB is likely to serve as a link between contractile activity and IL-6 synthesis (176, 299). On the other hand, increased oxidative stress, as well as low glucose availability, low glycogen content, catecholamines, increased intracellular calcium levels, hyperthermia, and ischemia-reperfusion are all features of exercise capable of inducing heat shock proteins (HSPs) (25, 56, 95, 256, 378, 391), which may in turn activate IL-6 synthesis via HSF1 and HSF2 (289).

In favor of the before-mentioned studies, demonstrating that the NFκB signaling pathway is not activated by contraction in human skeletal muscle (60, 337), it was shown that the IκB kinase beta (IκKβ) does not increase the transcription of IL-6 (46), suggesting that IL-6 gene transcription in skeletal muscle is unlikely to be dependent on activation of the IKK/ NFκB signaling pathway.

C. Calcineurin-NFAT

As discussed, it is generally understood that the contraction-induced IL-6 gene expression is related to the intensity and duration of the exercise, the mass of muscle recruited, and one's endurance capacity. It is of note that the mechanical load during contraction is a potent stimulus for Ca^{2+} release from the sarcoplasmic reticulum (111), and a low sustained intracellular concentration of Ca^{2+} has been shown to activate nuclear factor of activated T-cell (NFAT) through the action of calcineurin (80, 111, 151) and IL-6 gene expression in cultured human muscle cells (162). Moreover, the abundance of NFAT in neuronal and muscles cells is 10-fold higher when compared with other cell types (249). Taken together with the fact that prolonged skeletal muscle contractile activity is also characterized by a low sustained intracellular concentration of Ca^{2+}, it is possible that contraction could activate IL-6 gene transcription via NFAT signaling. However, in human muscle biopsies obtained after 60 min of concentric exercise, the nuclear abundance of the NFAT protein does not measurably increase (60). Since NFAT is a transcription factor, its overall activity depends on the balance between dephosphorylation by calcineurin, a serine/threonine phosphatase that is sensitive to elevated intracellular Ca^{2+}, and rephosphorylation by NFAT kinases like glycogen synthase kinase (GSK)-3 (98). Therefore, it is possible that the lack of nuclear abundance was due to a rapid rephosphorylation of NFAT which resulted in a subtle nuclear localization, seeing that a more recent study has observed nuclear localization of NFAT following a 20-min stimulation with ionomycin, a potent calcium ionophore (243).

As previously discussed, while the Ca^{2+}/NFAT pathway represents one arm of the IL-6 gene regulation, intramuscular glycogen content has also been shown to play an influential role in this process. Since depletion of intramuscular glycogen content not only limits the energy

availability for the working muscles, it could also have a profound effect on a variety of cellular processes including gene transcription (131). Of note, p38 MAPK is a stress-activated protein kinase (23), which is often seen activated in skeletal muscle during contraction (6, 124, 395). Accordingly, we recently tested the hypothesis that reduced glycogen content during prolonged exercise activates p38 MAPK to potentiate the transcription of IL-6 in the working muscles (60). Indeed, a reduced intramuscular glycogen content has been found to increase the phosphorylation of p38 MAPK in the nucleus (60). The mechanism of p38 MAPK activation is regulated by phosphorylation of a threonine and a tyrosine residue located in subdomain VIII through a combination action of MAPK kinase (MKK)-3 and -6 (294). Once activated, p38 MAPK can either remain cytosolic (23) or translocate into the nucleus (294) to carry out its functions. A causal relationship is likely to exist between p38 MAPK phosphorylation in the nucleus and the transcription of IL-6 in skeletal muscle, since inhibition of p38 MAPK phosphorylation within the nucleus results in ablation of the IL-6 mRNA response in stimulated myotubes (60). It is known that p38 MAPK phosphorylates a wide range of nuclear proteins such as the MAPK-activated protein kinase-2 (MAPKAP kinase-2) that participate in transcriptional control (110, 310), activating transcription factor (ATF)-2 (294) and Elk1 (393). Taken together, these findings suggested that phosphorylation of p38 MAPK may be the upstream event that leads to activation of downstream nuclear coactivators and their binding to the transcription regulatory region of the IL-6 gene in the contracting muscle. However, using chromatin immunoprecipitation analyses, we have, to date, been unable to determine the precise transcription factor that binds to the IL-6 promoter when muscle cells are either contracted in culture or treated with Ca^{2+} ionophores.

D. IL-6 Promoter

The transcription regulatory region, also known as the promoter region, of IL-6 is located at the 5′-flanking region immediately upstream of the first coding exon. This promoter region contains *cis*-acting response elements that are important in dictating gene expression upon binding with transcription factors resulting from signaling pathway activation. The importance of this region was highlighted when the first 300-bp sequence of the human promoter was found to share more than 80% homology with that of the mouse (349), suggesting that its role in this region is of evolutionary importance. Using a site-directed mutagenesis approach, Dendorfer et al. (74) reported the mapping of potential *cis*-acting elements (transcription factor docking sites) within the IL-6 promoter; these included response elements for glucocorticoid receptor (GRE), AP-1, Ets family of transcription factors, GATA proteins, NFκB, and a multiple response element (MRE), which comprised of elements for nuclear factor IL-6 (NF-IL-6) and cAMP response element binding protein (CREB). Of interest, both AP-1 and GATA proteins are known transcription partners of NFAT, and their synergistic dimerization has been shown to enhance the transcriptional activity of NFAT on a variety of target genes (151, 202).

Moreover, it is possible that the downstream targets of p38 MAPK, ATF-2, and Elk1 may also play a role in regulating the expression of IL-6, due to the fact that ATF-2 is a subunit of the AP-1 heterodimer (Jun:ATF) (369), while Elk1 is a member of the Ets superfamily of transcription factors (405). It appears, therefore, that unlike IL-6 signaling in macrophages, which seems dependent on activation of the NFκB signaling pathway, intramuscular IL-6 expression is regulated by a network of signaling cascades that among other pathways are likely to involve cross-talk between the Ca^{2+}/NFAT and glycogen/p38 MAPK pathways (see Fig. 6).

IV. INTERLEUKIN-6 AND ITS SIGNALING PATHWAYS

IL-6 was first discovered and named interferon (IFN)-β2 in 1980 by Weissenbach et al. (390) during an effort to clone and characterize the IFN-β gene in human fibroblast. The cytokine was subsequently named B-cell stimulatory factor-2 (8), B cell differentiation factor, T cell-replacing factor, 26-kDa protein (66, 128), hybridoma growth factor (34, 368), interleukin hybridoma plasmacytoma factor 1, plasmacytoma growth factor (244), hepatocyte-stimulating factor (118), macrophage granulocyte-inducing factor 2, cytotoxic T cell differentiation factor (348), and thrombopoietein due to its biological functions. In 1989, when these variously named proteins were found to be identical on the basis of their amino acid and/or nucleotide sequences, the name IL-6 was adopted (7, 321).

A. The gp130 Receptor Family Cytokines and Their Signaling Processes

IL-6 is a member of a family of cytokines known as "the IL-6 family," "long type I," or "gp130 cytokine." Apart from IL-6, the family consists of ciliary neurotrophic factor (CNTF), IL-11, leukemia inhibitory factor (LIF), oncostatin M (OsM), cardiotrophin 1 (CT-1), and cardiotrophin-like cytokine (CLC) (304). Although there is some cross-talk among the IL-6 family cytokines (315), the complex signal transduction cascade is not common to all family members. IL-6 and IL-11 are the only members of the family that signal via the

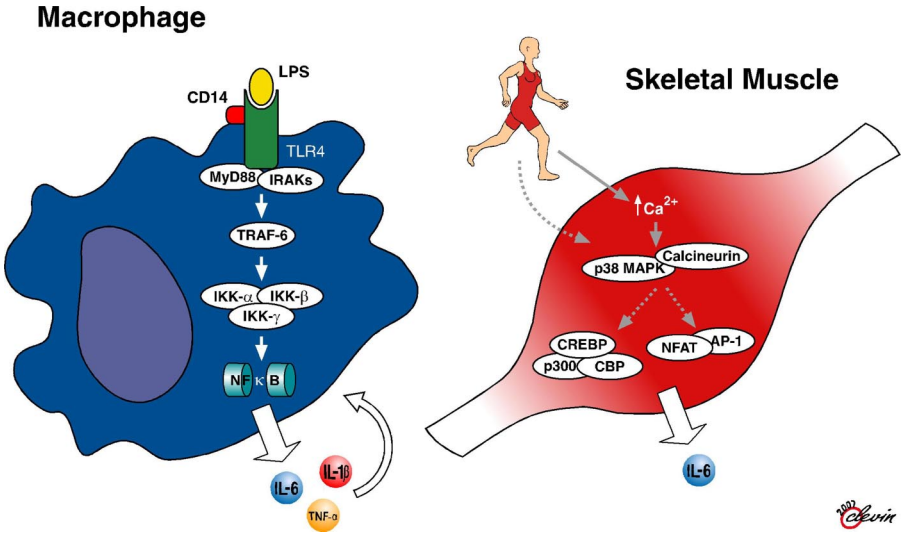

FIG. 6. The proposed cytokine signaling pathways for macrophages and contracting skeletal muscle. While it is well known that transcription of IL-6 and other proinflammatory cytokines such as TNF-α and IL-β is principally regulated by the TLR receptor signaling cascade that results in nuclear translocation and activation of NFκB, evidence in contracting skeletal muscle suggests that contraction leads to increased cytosolic Ca^{2+} and activation of p38 MAPK and/or calcineurin which leads to activation of transcription factors depending on these upstream events.

induction of a gp130 homodimer after binding their specific α-receptors, IL-6Rα and IL-11Rα. In contrast, CNTF, CT-1, and CLC first bind to their specific α-receptors, which are not involved in signal transduction per se, but binding of the ligand to the specific receptor induces formation of a heterodimer of the signal transducing β-receptors gp130Rβ [and LIF receptor (LIFRβ)] to allow signal transduction. LIF and OsM directly induce formation of a gp130β/LIFRβ or gp130β/OsM receptor heterodimer, respectively (83). The gp130Rβ in isolation cannot transduce signals without other specific α-receptor subunits and, therefore, although gp130 is ubiquitously expressed across all mammalian cell types, cell specific responses to gp130 cytokines are dependent on the relative expression of the α-receptor within a cell type in most, but not all cell types. The caveat to this complex is the capacity for so-called "*trans*-signaling" of IL-6. The IL-6Rα protein has been found to be expressed not only on the plasma membrane of cells but also in soluble form (sIL-6Rα) (222). Cells that do not express the IL-6Rα protein and, therefore, cannot undergo classical gp130 receptor signaling can be stimulated by a ligand/receptor soluble complex of IL-6 and the sIL-6Rα (204, 347). This complex binds the ubiquitously expressed gp130Rβ in IL-6Rα-deficient cells. Through a so-called *trans*-signaling mechanism, IL-6 is able to stimulate cells that lack an endogenous IL-6R (304). The mechanisms for the appearance of IL-6Rα have recently been uncovered. It is now known that the membrane-bound IL-6Rα can be shed by the metalloproteinases ADAM10 (208) and ADAM17 (11). In addition, sIL-6Rα can be generated via translation of alternatively spliced mRNA (158). The biological significance of classical versus *trans*-signaling processes will be discussed subsequently.

B. The Genes Encoding IL-6 and the IL-6 Receptor

The human IL-6 gene maps to chromosome 7p21, and IL-6 has a high degree of sequence homology with the murine IL-6, in particular in regulatory proximal promoter sequences (180). There are several polymorphisms in and close to IL-6 (107, 180, 350). Studies investigating the genetic association between IL-6 polymorphisms and disease, including type 2 diabetes, insulin resistance, and other features of the metabolic syndrome, have mainly focused on the three common single nucleotide polymorphisms (SNPs) in the IL-6 promoter: IL-6–174G>C, IL-6–572A>G, and IL-6–597A>G. The IL-6–174G>C promoter SNP, which has been suggested to functionally affect IL-6 promoter activity (107) (an issue discussed in further detail later), is a suitable haplotype marker for the common IL-6 promoter polymorphisms (350).

The human IL-6 receptor gene (IL-6R; online Mendelian inheritance in human no. 147880) maps to chromosome 1q21 in a region of replicated linkage to type 2 diabetes (11, 12). The common genetic variants in IL-6R have been identified recently, and a more general pattern of linkage disequilibrium of these variant needs to be established (380).

C. Janus-Activated Kinase/Signal Transducers and Activator of Transcription Signaling

In many ways IL-6 signaling resembles that of leptin. The leptin receptor (LRb) and gp130Rβ share a large degree of sequence homology and both activate the Janus-activated kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathways (83). It must be noted, however, that the LRb and gp130Rβ cannot bind each other's specific ligand, since the actions of the IL-6

family cytokine CNTF are not compromised in the leptin receptor deficient (*db/db*) mice (383). When IL-6 binds to the homodimerized IL-6Rα/gp130Rβ, it results in a signaling cascade that is initiated by the autophoshorylation and activation of JAK. This, in turn, results in the phosphorylation of a single membrane proximal tyrosine residue at Tyr^{757} in the murine gp130Rβ or Tyr^{759} in the human gp130Rβ. Phosphorylation of this residue results in recruitment of the SH2-domain, containing cytoplasmic protein tyrosine phosphatase SHP2, which, in turn, is tyrosine phosphorylated. This leads to an activation of the RAS-ERK1/2 signaling cascade (325). Unlike signaling through the LRb, gp130Rβ has an addition of four ($Tyr^{767, 814, 905, 915}$) rather than the one (Tyr^{1136}) tyrosine phosphorylation sites distal to the SHP-2 domain at $Tyr^{759/757}$. This may be functionally important because activation of STAT3 transcribes the gene encoding the suppressor of cytokine signaling (SOCS) proteins. In immune and neural cells, it is known that SOCS3 binds to the phosphorylated LRb through its SH2 domain. Such a process inhibits JAK tyrosine kinase activity via its NH_2-terminal kinase inhibitory motif, which functions as a pseudo-substrate (30, 87, 403). In addition, in immune cells, the COOH-terminal SOCS box is known to recruit ubiquitin-transferases to lead to degradation of JAK/STAT signaling proteins (10), and it has recently been shown that deletion of the SOCS box abrogates proteosomal degradation (225). In muscle cells that overexpress SOCS3, leptin can no longer phosphorylate STAT3 (383). It is clear, therefore, that in these systems SOCS proteins transpire to negate the effects of leptin resulting in leptin resistance. While the negative actions of SOCS1/3 also affect autophoshorylation and activation of JAK and phosphorylation of a $Tyr^{757/759}$, STAT3 phosphorylation of the IL-6 family cytokine CNTF is maintained in muscle cells that overexpress SOCS3 (383). Of note, gp130Rβ signaling module mutation (SIMM) mice ($gp130^{STAT}$) harbor a truncation of the COOH-terminal domain that eliminates the tyrosine residues Tyr^{767} to Tyr^{915}, which, in their phosphorylated states, provide the docking sites for STAT1/3 (83). When these mice are treated with CNTF, STAT3 phosphorylation is eliminated (383). This highlights the functional importance of these tyrosine residues.

D. IL-6 and AMP-Activated Protein Kinase Signaling

The AMP-activated protein kinase (AMPK) is an $\alpha\beta\gamma$ heterotrimeric enzyme that is activated by phosphorylation of Thr^{172} within the α-subunit activation loop by the constitutively active upstream AMPK kinase (AMPKK) LKB1 (399) and allosteric activation by increasing cellular AMP (342). AMPK is described as a cellular "energy sensor" because its activity is increased when AMP levels increase, resulting in increased catabolism and ATP regeneration. AMPK exerts an acute regulatory role on numerous metabolic processes, including fatty acid oxidation (213). It does so because activation of AMPK phosphorylates acetyl CoA carboxylase β (ACCβ), resulting in inhibition of ACC activity, which in turn leads to a decrease in malonyl CoA content, relieving inhibition of carnitine palmitoyl transferase 1 (CPT-1) and increasing fatty acid oxidation (160). In recent years, work from several groups (215, 343, 383) has demonstrated that leptin, signaling through the LRb, can activate AMPK in peripheral tissues such as skeletal muscle. Given the similarities between LRb and gp130Rβ signaling, it is not surprising that we (53, 167, 383) and others (9, 122) have shown that IL-6 and other family members are also capable of activating AMPK. The precise signal transduction pathways for this effect are unclear and, at least for IL-6, unstudied. It must be noted, however, that work from our laboratories has attempted to unravel the signal transduction cascade by which the IL-6 family cytokine CNTF activates AMPK (383). We examined the signaling responses of CNTF in BAF/3 cells which lack the gp130Rβ complex, stably transfected with various combinations of the receptor complex. CNTF did not increase STAT3 phosphorylation or stimulate AMPK activity in native BAF/3 cells. Stable transfection of the gp130Rβ/LIFRβ/CNTFRα or gp13R0β/LIFRβ/IL-6Rα led to STAT3 phosphorylation and AMPK signaling. In the absence of either the CNTFRα or IL-6Rα, STAT3 phosphorylation by CNTF was maintained, but AMPK and ACCβ phosphorylation was not, indicating that gp130Rβ in the presence of either CNTFRα or IL-6Rα is sufficient for AMPK activation; however, this is not dependent on STAT3 phosphorylation. To test this further, we infected skeletal muscle cells with a dn-STAT3 construct and treated the cells with CNTF. The CNTF-mediated increases in AMPK activity and ACCβ phosphorylation were similar when comparing dn-STAT3 with mock infected cells, demonstrating that STAT3 phosphorylation is not required for AMPK signaling. However, treating the previously mentioned SIMM $gp130^{STAT}$ mice with CNTF did not activate AMPK, suggesting that an intact gp130Rβ is mandatory. It is noteworthy that treating cells with CNTF results in increased ATP turnover (383). Therefore, the likely mechanism by which IL-6 or IL-6 family cytokines activate AMPK involves allosteric activation by increasing cellular AMP.

V. BIOLOGICAL ROLE OF INTERLEUKIN-6 AND ITS RELATIONSHIP TO OBESITY AND INSULIN RESISTANCE

Almost 15 years ago, Hotamisligil et al. (148) observed that adipose tissue from obese mice was producing TNF-α, a proinflammatory molecule known for its role

in autoimmunity and inflammation, but not previously linked to adiposity or metabolic disease. Since this observation, it has become apparent that obesity is linked to a state of chronic inflammation (145, 392), which occurs in tissues such as the liver, adipose tissue, and skeletal muscle. It is now recognized that obesity results in the secretion of not only TNF-α, but many cytokines including resistin, IL-1β, and IL-6 and that these cytokines are secreted not only from adipocytes, but from macrophages within the adipose tissue bed (389). Given this proinflammatory response and the observation that systemic IL-6 concentrations are elevated in obesity and in patients with type 2 diabetes (21, 51, 377), it is generally thought that elevations in the plasma and/or tissue concentrations of IL-6 have a negative effect on metabolism (190).

Unlike the very careful analysis of TNF-α-induced insulin resistance undertaken by Hotamisligil and coworkers (146, 148, 367), which employed loss and gain of function in experimental protocols in vivo, the role of IL-6 in the etiology of obesity-induced insulin resistance is not resolved. Indeed, whether IL-6 has positive or negative effects on metabolism is the subject of continuing controversy (51, 179, 219, 260). The "dogma" that IL-6 induces insulin resistance has been challenged by the previously discussed findings that IL-6 is both produced (139, 371) and subsequently released (334, 340) from contracting skeletal muscle cells because regular physical exercise is known to increase insulin sensitivity (170), while, in the immediate postexercise period, insulin action is enhanced (397).

A. Signaling Through the gp130 Receptor: Activation of AMPK and Phosphatidylinositol 3-Kinase

Recent studies support the notion that IL-6, acting through the gp130 receptor, can activate pathways that have both antiobesogenic and insulin-sensitizing effects. While this may appear contrary to the view that IL-6 may induce insulin resistance, it must be noted that the gp130 receptor and LRb share a deal of sequence homology and signaling events (for review, see Ref. 89). Like leptin, IL-6 has been shown to activate AMPK in both skeletal muscle and adipose tissue (9, 53, 122, 167). Activation of AMPK may increase glucose uptake (106) via mechanisms thought to involve enhanced insulin signal transduction (154). In a recent study, acute treatment of muscle cells with IL-6 increased both basal glucose uptake and translocation of the glucose transporter GLUT4 from intracellular compartments to the plasma membrane (53). Moreover, IL-6 increased insulin-stimulated glucose uptake in vitro, while infusion of recombinant human IL-6 into healthy humans during a hyperinsulinemic, euglycemic clamp increased glucose infusion rate without affecting the total suppression of endogenous glucose production (53). The effects of IL-6 on glucose uptake in vitro appeared to be mediated by activation of AMPK, since the results were abolished in cells infected with an AMPK dominant negative adenovirus (53). Apart from the effects of IL-6 on glucose metabolism, several studies have reported that IL-6 can increase intramyocellular (37, 53, 278) or whole body (372) fatty acid oxidation. This effect is also likely to be mediated by AMPK, because this enzyme plays a central role in the regulation of fuel metabolism in skeletal muscle because its activation stimulates fatty acid oxidation (160). Indeed, when cells infected with a dominant negative AMPK construct are treated with IL-6, the marked increase in fatty acid oxidation is completely blunted (53). It should be noted that apart from activating AMPK, signaling through the gp130 receptor results in activation of phosphatidylinositol 3-kinase (PI3-K) (89). Recent studies in vitro have demonstrated that IL-6 may activate PI3-K and its downstream target Akt (9, 385–387), but it must be noted that this is not observed in all studies (53). It appears, therefore, that IL-6 acutely signaling through the gp130 receptor exhibits many "leptinlike" actions such as activating AMPK and insulin signaling.

B. Chronic IL-6 Treatment and Hepatic Insulin Resistance

Despite the fact that acute IL-6 treatment may enhance glucose uptake and fat oxidation in skeletal muscle, there are, nonetheless, a number of studies both in vitro (182, 307, 316, 317) and in rodents in vivo (168, 172, 173) that demonstrate that IL-6 is capable of inducing insulin resistance. It appears that most, if not all, in vivo studies seem to suggest that IL-6 induces insulin resistance via adverse effects on the liver. Subjecting lean mice to chronically elevated IL-6 for 5 days causes hepatic insulin resistance (317), while treating either *ob/ob* (leptin-deficient) mice (172) or liver-inducible kappa kinase (LIKK) transgenic mice that display hepatic insulin resistance (47), with IL-6 neutralizing antibodies improves hepatic insulin resistance. The IL-6-induced insulin resistance appears due to increased SOCS-3 expression (317), since it is thought that SOCS3 may directly inhibit the insulin receptor (365). However, even the negative effect of SOCS3 on insulin action has recently been brought into question. Liver specific STAT3 knockout mice that express low levels of hepatic SOCS3 protein, paradoxically are unable to suppress hepatic glucose production after intracerebral ventricular insulin infusion (152). Moreover, the prevention of IL-6 signaling either by neutralizing antibodies or by genetic deletion of IL-6 markedly reduces insulin-induced phosphorylation of hepatic STAT3 (152). These results suggest that the local production of IL-6 is

important for the phosphorylation of hepatic STAT3 induced by the brain insulin action. In a separate study, liver specific SOCS3 knockout mice exhibited obesity and systemic insulin resistance with age (362). Furthermore, in this recent study, insulin signaling was reduced in skeletal muscle (362), suggesting that deletion of the SOCS3 gene in the liver modulates insulin sensitivity in other organs. Possibly, the most convincing data to suggest that IL-6 may be antiobesogenic is the observation that IL-6 knockout mice develop mature onset obesity and glucose intolerance (379); however, even this observation is unclear (76). Whether IL-6 has positive effects on obesity and insulin action is clearly unresolved and requires further work. However, IL-6 unquestionably has a poor prognosis for certain inflammatory diseases (223), and due to the immunoreactive nature of IL-6, it is clear that rhIL-6 treatment may not be a wise therapeutic treatment strategy in human disease. This is most likely due to the previously described *trans*-signaling of IL-6. The soluble IL-6 receptor controls the transition from the acute to the chronic phase in many proinflammatory diseases such as peritonitis (150), a transition that can be inhibited by treatment with a soluble gp130 receptor fragment that neutralizes the *trans*-signaling process (150). Therefore, other cytokines that signal through the gp130 receptor, but which do not activate *trans*-signaling of IL-6, such as CNTF, show some therapeutic promise as an antiobesity therapy (for review, see Ref. 89).

VI. ANTI-INFLAMMATORY EFFECTS OF INTERLEUKIN-6

Systemic low-level inflammation is defined as two- to fourfold elevations in circulating levels of proinflammatory and anti-inflammatory cytokines, naturally occurring cytokine antagonists, and acute-phase proteins, as well as minor increases in counts of neutrophils and natural killer cells (45). Although these increases are far from the levels observed during acute, severe infections, systemic low-level inflammation is strongly associated with increasing age, life-style factors such as smoking, obesity, and dietary patterns, together with increased risk of cardiovascular disease, type 2 diabetes cognitive decline, and wasting/cachexia (loss of skeletal muscle cells) (26, 39, 75, 86, 97, 271, 288, 309, 357, 394, 400). Moreover, systemic low-level inflammation is a strong, consistent, and independent predictor of all-cause mortality and CVD-cause mortality in elderly populations (43, 44, 49, 132, 220, 297, 306, 308, 376, 388, 404). Recent findings demonstrate that physical activity induces an increase in the systemic levels of a number of cytokines with anti-inflammatory properties (277). The "protective" effects of regular exercise against diseases such as cardiovascular disease, type 2 diabetes, colon cancer, and breast cancer are well-established (183, 191, 264, 354), and the possibility exists that the anti-inflammatory activity induced by regular exercise may exert some of the beneficial health effects of exercise in patients with chronic diseases.

The initial cytokines as they appear in the circulation in relation to an acute infection consist of the following (named in order): TNF-α, IL-1β, IL-6, IL-1 receptor antagonist (IL-1ra), soluble TNF-α-receptors (sTNF-R), and IL-10. IL-1ra inhibits IL-1 signal transduction, and sTNF-R represents the naturally occurring inhibitors of TNF-α. Chronic low-grade systemic inflammation has been introduced as a term for conditions in which a two- to threefold increase in the systemic concentrations of TNF-α, IL-1, IL-6, IL-1ra, sTNF-R, and CRP is reflected. In the latter case, the stimuli for the cytokine production are not known, but the likely origin of TNF in chronic low-grade systemic inflammation is mainly the adipose tissue. Mounting evidence suggests that TNF-α plays a direct role in the metabolic syndrome (284). Patients with type 2 diabetes demonstrate a high protein expression of TNF-α in skeletal muscle and increased TNF-α levels in plasma (286, 363).

As discussed, direct effects of TNF-α on insulin action in skeletal muscle have been demonstrated in vitro (147) and in vivo both in animals (214) and humans (284). TNF-α inhibits the insulin signaling cascade at several pivotal regulatory proteins, such as the insulin receptor substrate (IRS) and Akt substrate 160 in human skeletal muscle in vitro (33) and in vivo (281). The latter two studies indicate that elevated TNF-α is not secondary to the pathological conditions associated with insulin resistance, but that TNF-α plays a direct pathogenic role in glucose metabolism. It appears that TNF provides a direct molecular link between low-grade systemic inflammation and insulin resistance (284).

In relation to exercise, IL-6 is typically the first cytokine present in the circulation during exercise, and the appearance of IL-6 in the circulation is by far the most marked and its appearance precedes that of the other cytokines. The fact that the classical proinflammatory cytokines, TNF-α and IL-1β, in general do not increase with exercise indicates that the cytokine cascade induced by exercise markedly differs from the cytokine cascade induced by infections. Another finding in relation to exercise is increased circulating levels of well-known anti-inflammatory cytokines, cytokine inhibitors such as IL-1ra, IL-10, and sTNF-R (250, 252). Taken together, exercise provokes an increase primarily in IL-6, followed by an increase in IL-1ra and IL-10. sTNF-R represents the naturally occurring inhibitors of TNF-α (6, 7, 77).

Data suggest that IL-6 exerts inhibitory effects on TNF-α and IL-1 production. IL-6 inhibits LPS-induced TNF-α production both in cultured human monocytes and in the human monocytic line U937 (313), and levels of TNF-α are markedly elevated in anti-IL-6-treated mice and

in IL-6 deficient knock-out mice (209, 216), indicating that circulating IL-6 is involved in the regulation of TNF-α levels. In addition, rhIL-6 infusion as well as exercise inhibit the endotoxin-induced increase in circulating levels of TNF-α in healthy humans (326). The anti-inflammatory effects of IL-6 are also demonstrated by IL-6 stimulating the production of IL-1ra and IL-10 (336). Whereas IL-10 influences multiple cytokines (32, 381, 382), the biological role of IL-1ra is to inhibit signaling transduction through the IL-1 receptor complex (78). The IL-1ra is a member of the IL-1 family that binds to IL-1 receptors but does not induce any intracellular response. Studies have demonstrated that IL-1ra is also an acute phase protein (115) as both cultured human hepatocytes and the human hepatoma cell line HepG2 produce sIL-1ra in response to stimulation with IL-6. A small increase of the CRP levels is seen the day after acute exercise of a longer duration (263).

IL-6 infusion also induces a delayed increase of CRP from the liver via activation of the STAT3 pathway (336, 407). CRP was originally characterized as an acute phase protein involved in precipitation of the somatic C-polysaccharide of *Streptococcus pneumoniae* (355). Whether CRP has proinflammatory effects or not is being debated (275). When purified adequately, even high doses of recombinant CRP do not induce a proinflammatory response (275); rather, CRP may contribute to the increase of plasma IL-1ra during late recovery from exercise by enhancing the release of IL-1ra from monocytes (290). In addition, in a recent study (227), human CRP overexpression mice were crossed with atherosclerosis-prone mice. The results from this study demonstrated that rather than being proinflammatory and proatherogenic, CRP slowed these processes.

A recent number of papers have documented that self-reported physical activity or physical performance is correlated inversely with systemic low-level inflammation (43, 57, 64, 82, 101, 155, 169, 206, 255, 283, 298, 331, 361), although the lack of an association has also been reported (109, 296, 375). These correlation data do, however, not provide any information with regard to a possible causal relationship. However, several studies have reported that exercise intervention programs reduce systemic low-level inflammation in patients with coronary heart disease (123), in claudicants (2, 65, 119, 187, 358), and in healthy, young adults (210).

Following exercise, the high circulating levels of IL-6 are followed by an increase in IL-1ra and IL-10, and the latter two anti-inflammatory cytokines can be induced by IL-6 (336). Therefore, IL-6 induces an anti-inflammatory environment by inducing the production of IL-1ra and IL-10, but it also inhibits TNF-α production as suggested by in vitro (99) and animal studies (209, 216). In addition, rhIL-6 infusion, which causes an increase in plasma IL-6 mimicking the exercise-induced IL-6 response, inhibits an endotoxin-induced increase in plasma TNF-α in humans (326). However, exercise is likely to suppress TNF-α also via IL-6 independent pathways as demonstrated by the finding of a modest decrease of TNF-α following exercise in IL-6 knock-out mice (163). High levels of epinephrine are provoked by exercise, and epinephrine infusion has been shown to blunt the appearance of TNF-α in response to endotoxin in vivo (370). As epinephrine infusion induces only a small increase in IL-6 (332), the mechanism whereby epinephrine inhibits TNF-α production is not clear. However, it appears that epinephrine and IL-6 inhibit an endotoxin-induced appearance of TNF-α via independent mechanisms.

We suggest that with regular exercise, the anti-inflammatory effects of an acute bout of exercise will protect against chronic systemic low-grade inflammation, but such a link between the acute effects of exercise and the long-term benefits has not yet been proven. Given that the atherosclerotic process is characterized by inflammation, one alternative explanation would be that regular exercise, which offers protection against atherosclerosis, indirectly offers protection against vascular inflammation and hence systemic low-grade inflammation.

VII. INTERLEUKIN-6:A MARKER OR A CAUSE OF DISEASE?

There is strong evidence that IL-6 serum concentration increases with age (43, 63, 85, 96, 129, 132, 161, 212, 384), and in 1993, William Ershler, in his article "IL-6: A Cytokine for Gerontologists," indicated IL-6 as one of the main signaling pathways implicated in aging and chronic morbidity (84).

Many studies report that IL-6 plasma levels are increased in patients with unstable angina compared with those with stable angina or healthy subjects and that it could be useful as a prognostic marker of CVD outcome (28, 29, 197). In addition, elevated levels of IL-6 were shown to predict future risk of type 2 diabetes development (149, 288, 324). In a recent paper, Karin and colleagues (223) also found that administration of the carcinogen diethylnitrosamine elevated circulating IL-6 in mice, which ultimately promoted liver cancer in male but not female mice. They argued that the estrogen-mediated inhibition of IL-6 production by Kupffer cells reduced liver cancer risk in females. As discussed earlier, *trans*-signaling of IL-6 results in inflammation and is therefore linked to high-grade inflammatory disorders and possibly liver cancer. However, the situation regarding metabolic disease is not as clear. High circulating levels of IL-6 may or may not be found in patients with type 2 diabetes, but in general, IL-6 is not elevated in lean subjects with insulin resistance (51, 280) or associated with insulin resistance after adjustment for obesity (104). High levels of IL-6 are associ-

ated with obesity (406) and further associated with physical inactivity, independently of obesity (101), and it is possible that correlational relationships between IL-6 and insulin resistance may be ascribed to that IL-6 is a marker of obesity and physical inactivity. Due to the observation that plasma IL-6 is often elevated in patients with metabolic disease, the common believe is that IL-6 is a cause of chronic disease and that IL-6 is a proinflammatory cytokine that promotes insulin resistance and hyperlipidemia. However, it is now well known that IL-6 is rapidly released into the circulation following exercise and, from a simplistic physiological point of view, it seems paradoxical that working muscle would release a factor that inhibits insulin signaling when insulin action is enhanced in the immediate postexercise period (398).

In the present review, we have challenged the generally held view that IL-6 is a "bad guy" with regard to metabolism. There is strong evidence that an acute increase in circulating levels of IL-6 enhances fat oxidation, improves insulin-stimulated glucose uptake, and has anti-inflammatory effects. However, highly elevated chronic levels of IL-6, as seen in patients with rheumatoid arthritis, play a pathogenetic role in this disease as demonstrated by the fact that blocking IL-6 has beneficial effects on arthritis (1, 62, 242). With regard to patients with low-grade chronic inflammation, as seen, e.g., in patients with CVD or type 2 diabetes, there are no published data that allow us to evaluate the direct metabolic effects of modest, but chronic, elevated levels of IL-6 corresponding to the levels seen in these patients. However, blocking IL-6 in clinical trials with patients with rheumatoid arthritis leads to enhanced cholesterol and plasma glucose levels, indicating that functional lack of IL-6 may lead to insulin resistance and an atherogenic lipid profile (1, 62, 242). These clinical findings are in accordance with the finding that IL-6 knockout mice develop late-onset obesity and impaired glucose tolerance (379). Subjects with risk genotypes for both TNF-α (AA; A shows increased TNF transcription) and IL-6 (CC; C shows decreased transcription) have the highest incidence of diabetes (181), favoring the theory that high levels of TNF-α and low production of IL-6 are determining factors in the metabolic syndrome (51, 280).

Given the different biological profiles of TNF-α and IL-6 and given that TNF-α may trigger IL-6 release, one current theory is that adipose tissue-derived TNF-α is actually the "driver" behind the metabolic syndrome and that increased systemic levels of IL-6 reflect locally produced TNF-α (277). Accordingly, elevated levels of IL-6 might represent a "defense" mechanism against proinflammatory actions caused by TNF. An alternative hypothesis is that increased IL-6 production represents a compensatory mechanism, whereby insulin-resistant individuals or individuals at risk of developing insulin resistance stimulate an alternative mechanism with regard to maintaining glucose homeostasis. Finally, chronically elevated IL-6 levels may simply reflect a feedback mechanism due to impaired IL-6 signaling. It is, however, not known if "IL-6 resistance" exists as a phenomenon in line with the fact that a chronically elevated level of insulin or leptin most often reflects insulin resistance or leptin resistance, respectively.

VIII. OTHER MYOKINES

While most of this review focuses on muscle-derived IL-6, it should be mentioned that skeletal muscle has the capacity to produce and express cytokines belonging to distinctly different families. To date, the list includes IL-6, IL-8, and IL-15, and contractile activity plays a role in regulating the expression of these cytokines in skeletal muscle.

A. IL-8

IL-8 belongs to the CXC family of chemokines. The CXC nomenclature relates to the presence of two conserved cysteine residues at the NH_2 terminus separated by one amino acid. IL-8 belongs to a subdivision of CXC-chemokines, which has an amino acid sequence Glu-Leu-Arg (ELR) preceding the first conserved cysteine amino acid residue in the primary structure of these proteins (14). IL-8 is a known chemokine that attracts primarily neutrophils. In addition to its chemokine properties, IL-8 acts as an angiogenic factor.

IL-8, like IL-6, is influenced by physical activity. The plasma concentration of IL-8 increases in response to exhaustive exercise such as running, which involves eccentric muscle contractions (234, 236, 237, 253, 344). In contrast, concentric exercise such as bicycle ergometry (59) or rowing (137) of moderate intensity does not increase plasma IL-8 concentration. However, intense cycle ergometry has been reported to increase IL-8 plasma concentration to a small degree (221).

The possibility of contracting skeletal muscle expressing IL-8 has received some attention. In a pioneering study by Nieman et al. (234), a severalfold increase in IL-8 mRNA was found in skeletal muscle biopsies from subjects having completed a 3-h treadmill run concomitantly with increased plasma levels of IL-8 (234). Similarly, IL-8 mRNA increased in response to 1 h of cycle ergometry exercise, but with no change in the plasma concentration of IL-8 (59). In a recent study, we found that IL-8 protein was clearly expressed in human skeletal muscle as a response to concentric exercise (4). The finding of a marked increase of IL-8 mRNA in muscle biopsies during and following exercise, and IL-8 protein expression within skeletal muscle fibers in the recovery from exercise, strongly indicates that exercise per se stimulates muscle

cells to produce IL-8. This is in accordance with the finding that muscle cells in vitro have the capacity to express IL-8 both at the mRNA and protein levels (72).

The physiological function of IL-8 within the muscle is still unknown. The main part of the systemic increase in IL-8 as seen during exercise with an eccentric component is most likely due to an inflammatory response. In accordance with this, we and others observe no increase in the systemic IL-8 plasma concentration during or after concentric exercise (4, 59, 137, 234). However, when measuring the arteriovenous concentration difference across a concentrically exercising limb, we detected a small and transient net release of IL-8, which did not result in an increase in the systemic IL-8 plasma concentration (4). The fact that a high local IL-8 expression takes place in contracting muscle with only a small and transient net release may indicate that muscle-derived IL-8 acts locally and exerts its effect in an autocrine or paracrine fashion. A plausible function of the muscle-derived IL-8 would be chemo-attraction of neutrophils and macrophages when, in fact, in concentric exercise there is little or no accumulation of neutrophils or macrophages in skeletal muscle.

A more likely function of muscle-derived IL-8 is to stimulate angiogenesis. IL-8 associates with the CXC receptor 1 and 2 (CXCR1 and CXCR2). It induces its chemotactic effects via CXCR1, whereas CXCR2, which is expressed by human microvascular endothelial cells, is the receptor responsible for IL-8-induced angiogenesis (22, 174, 245). Recently, we examined the expression of the IL-8 receptor CXCR2 in human skeletal muscle biopsies after concentric exercise. Skeletal muscle CXCR2 mRNA increased significantly in response to bicycle exercise. The increase in CXCR2 protein was seen not only in the muscle fibers but to a greater extent in the vascular endothelium, suggesting that it may play a role in angiogenesis (113).

In summary, the finding that a high local IL-8 expression takes place in contracting muscle with only a small and transient release indicates that muscle-derived IL-8 exerts its effect locally. The IL-8 produced by the exercising limb might elicit its response by interacting with the CXCR2 receptor present in the endothelia of capillaries (3, 133). The recent finding that concentric exercise induces CXCR2 mRNA and protein expression in the vascular endothelial cells of the muscle fibers suggests that muscle-derived IL-8 acts locally to stimulate angiogenesis through CXCR2 receptor signaling (113). We suggest that muscle-derived IL-8 should be classified as a myokine.

B. IL-15

IL-15 (14–15 kDa) is a four-α-helix cytokine with structural similarities to IL-2 (17, 125). Two isoforms of IL-15 with altered glycosylation have been shown to exist: a long signaling peptide form (48 amino acids) that is secreted from the cell, and a short signaling peptide (21 amino acids) form that remains intracellular, localized to nonendoplasmic regions in both cytoplasmic and nuclear compartments. Cell membrane expression might be crucial in mediating an extracellular function rather than secretion and, in part, explains the difficulty in detecting soluble IL-15 in biological systems. IL-15 functions via a widely distributed heterotrimeric receptor (IL-15R), which consists of a β-chain (shared with IL-2) and common γ-chain, together with a unique α-chain (IL-15α) that in turn exists in eight isoforms. Like IL-2, the IL-15R$\alpha\beta\gamma$ complex signals through Janus kinases 1 and 3 and STAT-3 and -5 (20, 120).

The regulatory role of muscle contraction with regard to IL-15 is unclear. Nieman et al. (234) found that muscle IL-15 mRNA levels were unchanged immediately after a 3-h run, and Ostrowski et al. (251) found that plasma IL-15 (measured up to 6 h into recovery) did not change in response to 2.5 h of treadmill running. Skeletal muscle IL-15 mRNA levels, measured immediately after a 2-h weight training bout, did not differ from baseline (232), whereas plasma IL-15 protein was increased immediately after acute resistance exercise in one study (300). We have recently demonstrated that IL-15 mRNA levels are upregulated in human skeletal muscle following a bout of strength training (227). IL-15 has been identified as an anabolic factor, which is highly expressed in skeletal muscle (125). Furthermore, IL-15 has been suggested to play a role in muscle-adipose tissue interaction (13). In human skeletal myogenic cultures, IL-15 induces an increase in accumulation of the protein myosin heavy chain (MHC) in differentiated muscle cells, suggesting IL-15 as an anabolic factor in muscle growth (114), and IL-15 stimulates myogenic differentiation independently of insulin-like growth factors (IGFs) (292). Moreover, in opposition to the growth factor IGF-I, IL-15 has effects on fully differentiated myoblasts (291). The potential therapeutic effect of IL-15 was demonstrated in an in vivo model, which demonstrated that IL-15 was able to antagonize the enhanced muscle protein breakdown in a cancer cachexia model. Interestingly, while IL-15 has been reliably demonstrated to have anabolic effects on skeletal muscle in vitro and in vivo, IL-15 seems to play a role in reducing adipose tissue mass. When IL-15 was administered to adult rats for 7 days, it resulted in a 33% decrease in white adipose tissue mass (50). The tissue response to IL-15 was related to the amount of IL-15/IL-15 receptor complex expression, suggesting a direct action of IL-15 on adipose tissue (12). IL-15 mRNA expression has been examined in both 3T3-L1 adipogenic cells and C_2C_{12} murine skeletal myogenic cells. Quantitative real-time PCR indicated that IL-15 mRNA was expressed by C_2C_{12} skeletal myogenic cells and was upregulated more than 10-fold in differen-

tiated skeletal myotubes compared with undifferentiated myoblasts. In contrast, 3T3-L1 cells expressed little or no IL-15 mRNA on either the undifferentiated preadipocyte or differentiated adipocyte stages (293). These findings provide support for the hypothesis that IL-15 functions in a muscle-to-fat endocrine axis that modulates fat:lean body composition and insulin sensitivity.

In summary, IL-15 is a recently discovered anabolic factor that is constitutively expressed by skeletal muscle and regulated by strength training. While IL-15 has solid anabolic effects, it also seems to play a role in reducing adipose tissue mass, and it is therefore suggested that IL-15 may play a role in muscle-fat cross-talk. We suggest that muscle-derived IL-15 should be classified as a potential myokine.

IX. CONCLUSION AND PERSPECTIVES

The recent identification of skeletal muscle as an endocrine organ that produces and releases myokines expands our knowledge on how the nervous, endocrine, and immune systems contribute to the maintenance of homeostasis, especially when energy demands are increased. Current techniques do not allow us to adopt a "plasma proteomic" approach to identify new myokines that are released in response to the physiological stress of muscle contraction. However, given the fact that during contraction skeletal muscle cells undergo a major disruption to cellular quiescence, we hypothesize that muscle cells release a number of biologically active substances that we term myokines, which participate in cell-to-cell and organ-to-organ cross-talk. It is our vision that the myokine field will dominate the coming decade, just as the discovery of adipose tissue as a secretory organ in the mid 1990s has been a dominating research area in the past decade, giving rise to the identification of new regulatory peptides and their receptors. Visceral and subcutaneous adipose tissues have been regarded as the major sources of cytokines (adipokines); however, the finding that muscles produce and release cytokines (myokines) suggests that in addition to adipose tissue working skeletal muscle may be a major source of secreted molecules.

Myokines may be involved in mediating the health beneficial effects of exercise and play important roles in the protection against diseases associated with low-grade inflammation, insulin resistance, hyperlipidemia such as cardiovascular diseases, type 2 diabetes, and cancer. It is obvious that knowledge about the mechanisms whereby regular exercise offers protection against chronic diseases in combination with clinical research serves as a foundation for the development of public health guidelines with regard to exercise. Moreover, more specific knowledge about the mechanisms whereby exercise alters the function and metabolism in other organs, such as adipose tissue, liver, and brain, is required to prescribe exercise as therapy in the form of endurance training, metabolic training, or strength conditioning (264).

Finally, it is obvious that the identification of new myokines and their receptors will potentially serve as pharmacological targets for the treatment of metabolic disorders and other diseases.

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GRANTS

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