Invited Review

Exercise-induced myokines and their role in chronic diseases

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ABSTRACT

Physical inactivity has recently been identified as a major and independent risk factor for the development of dementia and cognitive decline. In addition to the effect of exercise with regard to protection against neurodegenerative diseases, it is well-established that physical inactivity increases the risk of type 2 diabetes, cardiovascular diseases (CVD), colon cancer and postmenopausal breast cancer. These diseases constitute a network of related diseases, also called "the diseasome of physical inactivity". In this review, physical inactivity is given the central role as an independent and strong risk factor for accumulation of visceral fat and consequently the activation of a network of systemic inflammatory pathways, which promote development of neurodegeneration as well as insulin resistance, atherosclerosis, and tumour growth. The recent finding that muscles produce and release myokines provides a conceptual basis for understanding some of the molecular mechanisms underlying organ cross talk, including muscle-fat cross talk. Accumulating data suggest that contracting skeletal muscles release myokines, which may work in a hormone-like fashion, exerting specific endocrine effects on visceral fat or mediating direct anti-inflammatory effects. Other myokines work locally within the muscle via paracrine mechanisms, exerting their effects on signalling pathways involved in fat oxidation.

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1. Introduction

Recent evidence suggests that physical inactivity is an independent player in the development of dementia (Aarsland et al., 2010). Physical exercise appears to be a factor that strongly affects brain plasticity. In rodents, physical exercise improves memory function and structural parameters such as synapse density, neuronal complexity, and hippocampal neurogenesis (Wu et al., 2008). It has also been established that exercise induces neuroprotection in animal models of stroke (Hayes et al., 2008), traumatic brain injury (Griesbach et al., 2007), and Parkinson disease (Yoon et al., 2007) and that voluntary running significantly restores hippocampal neurogenesis after irradiation (Naylor et al., 2008). These experimental studies suggest that physical exercise has an impact on cognitive performance.

In humans, it has been shown that higher levels of cardiovascular fitness are associated with increased hippocampal volume as well as better memory function (Erickson et al., 2009). Moreover, a recent study measured hippocampus size in response to 12 weeks of aerobic training in patients with schizophrenia and healthy controls. Following exercise training, relative hippocampal volume increased significantly in patients (12%) and healthy subjects (16%), with no change in the non exercise group of patients (−1%) (Pajonk et al., 2010).

A couple of meta-analyses demonstrate a positive association between cardiovascular (or "aerobic") fitness and cognitive performance in elderly subjects (Angevaren et al., 2008; Colcombe and Kramer, 2003; Etnier et al., 2006; Heyn et al., 2004). Physical activity during midlife appears to protect against dementia or cognitive decline and to improve cognitive performance in older adults with memory impairment (Rovio et al., 2005; Sun et al., 2010; Etgen et al., 2010; Liu-Ambrose et al., 2010; Andel et al., 2008; Lautenschlager et al., 2008) and recently, a strong statistical association was found between fitness and intelligence in the youngsters (Aberg et al., 2009).

Thus, there appears to be accumulating evidence suggesting that regular exercise protects against dementia and cognitive decline. Moreover, exercise may also offer some protection to the occurrence of depression (Sui et al., 2009). In addition to the effect of exercise with regard to protection against neurodegenerative diseases, it is well-established that physical inactivity increases the risk of type 2 diabetes (Tuomilehto et al., 2001), cardiovascular diseases (CVD) (Nocon et al., 2008), colon cancer (Wolin et al., 2009), and postmenopausal breast cancer (Monninkhof et al., 2007).

Type 2 diabetes is associated with impaired cognitive function as well as with both Alzheimer's disease and vascular dementia, and individuals with type 2 diabetes also have a high prevalence
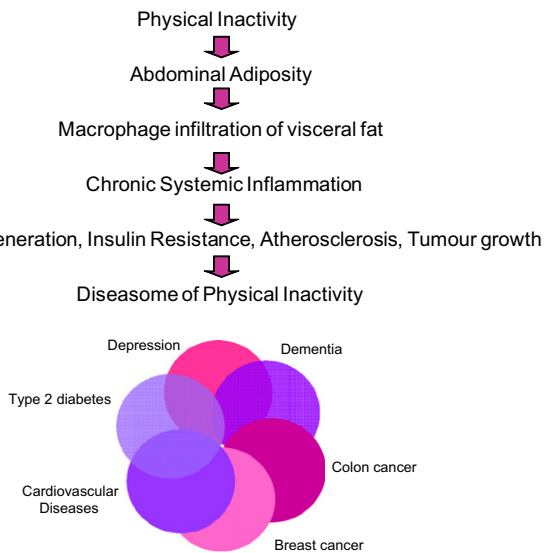
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Fig. 1. Hypothesis: Physical inactivity leads to accumulation of visceral fat and consequently to invasion of macrophages and the activation of a network of systemic inflammatory pathways, which promotes the development of neurodegeneration, insulin resistance, atherosclerosis, and tumour growth, leading to the formation of "the diseasome of physical inactivity". Modified from (Pedersen, 2009).

of affective illness, including major depression, reviewed in Komulainen et al. (2008). Other studies report that type 2 diabetes is associated with an elevated risk of CVD (Diamant and Tushuizen, 2006), colon and breast cancer, as well as pancreatic, liver, and endometrial cancer (Richardson and Pollack, 2005).

Thereby, dementia and depression together with type 2 diabetes, cardiovascular diseases, colon cancer and postmenopausal breast cancer constitute a network or a cluster of diseases, which we have previously identified as "the diseasome of physical inactivity" (Pedersen, 2009). The diseasome of physical inactivity represents diseases with highly different phenotypical presentation. However, these diseases appear to share important pathogenetic mechanisms. It is well-established that independently of body mass index (BMI), physical inactivity is a risk factor for all-cause mortality (Pedersen, 2007). Moreover, chronic systemic inflammation is associated with physical inactivity independent of obesity (Fischer et al., 2007). Based on the prevailing literature, it is suggested that physical inactivity leads to accumulation of visceral fat and consequently the activation of a network of inflammatory pathways, which promote development of neurodegeneration as well as insulin resistance, atherosclerosis, and tumour growth and thereby the development of the diseases belonging to the "diseasome of physical inactivity", Fig. 1.

2. Physical activity and abdominal adiposity

A substantial amount of subcutaneous adipose tissue has little or no damaging effect and may even offer protection against chronic diseases, whereas strong evidence exists for the detrimental effects of visceral fat and fat in the liver and in muscle (Pischon et al., 2008). In this context, fat is not just fat and ectopic fat accumulation may be regarded as fat in "the wrong places". Abdominal adiposity is associated with both dementia (Whitmer et al., 2008), cardiovascular disease (CVD) (Haffner, 2007), type 2 diabetes (Bays, 2009), colon cancer (Giovannucci, 2007), and breast cancer (Xue and Michels, 2007) as well as all-cause mortality independently of BMI, even in people with a normal body weight (Pischon et al., 2008). Thus, the health consequences of abdominal adiposity

and physical inactivity are similar. Moreover, both physical inactivity (Pedersen and Febbraio, 2008) and abdominal adiposity (Yudkin, 2007) are associated with persistent systemic low-grade inflammation (Festa et al., 2002; Handschin and Spiegelman, 2008).

A number of studies point to an independent effect of exercise on abdominal adiposity. A recent review highlighted the notion that repeated bouts of exercise have a major impact on abdominal adiposity (Ross and Bradshaw, 2009). Thus, most studies show that increased physical activity is associated with significant reductions in waist circumference and/or visceral fat, despite either no change in body weight or a change of <3%, regardless of sex or age (Ross and Bradshaw, 2009).

In a couple of studies (Ross et al., 2000; Ross et al., 2004) men and women with abdominal obesity exercised under supervision and were required to consume additional food calories to prevent exercise-induced weight loss. The objective was to determine whether chronic exercise (40–60 min of daily exercise for 12–16 weeks) without weight loss was associated with reductions in obesity. The results from these studies illustrate that considerable reductions in total fat, abdominal fat (particularly visceral fat, which decreased by 12–18%), and waist circumference can be achieved in the absence of weight loss. In addition to marked reductions in these measures of obesity, increases were also observed in skeletal muscle mass and cardiorespiratory fitness.

3. Physical inactivity and abdominal adiposity

We recently conducted a model of physical inactivity that certainly also points to a direct link between physical inactivity and accumulation of visceral fat. A group of young healthy men decreased their daily stepping for 2 weeks to 1500 steps from the range recommended for adults of around 10000. During this time, they developed a markedly impaired glucose tolerance as well as attenuation of postprandial lipid metabolism. The intervention was associated with a 7% increase in intra-abdominal fat mass, measured by MR-scanning, without a change in total fat mass while total fat-free mass and body mass index decreased (Olsen et al., 2008). A follow-up study revealed that the volunteers developed a marked decline in peripheral insulin sensitivity without an effect on hepatic endogenous glucose production. The insulin-stimulated ratio of $pAkt^{thr308}$/total Akt decreased after step reduction. In addition, the two-week period induced a 7% decline in VO_2 max (ml/min; cardiovascular fitness). Lean mass of legs, but not of arms and trunk, decreased concurrently (Krogh-Madsen et al., 2010). However, circulating levels of plasma cytokines and muscular expression of TNF were not influenced by a fortnight of physical inactivity.

4. Visceral fat; a cause of low-grade systemic inflammation

Models of lipodystrophy suggest that if the subcutaneous fat becomes inflamed and adipocytes undergo apoptosis/necrosis, the fat storing capacity is impaired; hence, fat is deposited as ectopic fat. Given the anti-inflammatory effects of regular exercise (Petersen and Pedersen, 2005), physical inactivity may lead to inflammation of subcutaneous adipose tissue and impaired ability to store fat, also in people who do not fulfil the criteria for lipodystrophy.

Evidence exists that visceral fat is more inflamed than subcutaneous fat and constitutes an important source of systemic inflammation (Yudkin, 2007). Although speculative, one explanation to the differential outcome of accumulating fat subcutaneously or as ectopic fat could be that when fat is stored in "the wrong places", it will stimulate an inflammatory response. An alternative

explanation is that obesity is linked to an increased sympathetic activity in adipose tissue. Since neurotransmitters of the sympathetic nervous system are chemoattractive for monocytes, this may lead to accumulation of monocyte-derived macrophages in adipose tissue (Straub et al., 2010).

Thus, although two weeks of inactivity did not provoke an increase in circulating levels of cytokines, evidence exists of an association between physical inactivity and low-grade systemic inflammation in healthy, young individuals (Petersen and Pedersen, 2005). These findings would be compatible with the notion that accumulation of visceral fat precedes chronic systemic inflammation.

5. Inflammation – a cause of chronic diseases

Chronic inflammation promotes development of insulin resistance, atherosclerosis, neurodegeneration, and tumour growth (Handschin and Spiegelman, 2008) and thereby the development of the diseases belonging to the "diseasome of physical inactivity".

Mounting evidence suggests that TNF-α plays a direct role in the metabolic syndrome, whereas the role of IL-6 in insulin resistance is highly controversial, as reviewed in Pedersen and Febbraio (2008). A number of studies indicate that IL-6 enhances lipolysis, as well as fat oxidation, via an activation of AMPK (Pedersen and Febbraio, 2008). Consistent with this idea, Wallenius et al. (2002) demonstrated that IL-6 deficient mice developed mature-onset obesity and insulin resistance. To determine whether physiological concentrations of IL-6 affected lipid metabolism, our group administered physiological concentrations of rhIL-6 to healthy young and elderly humans as well as to patients with type 2 diabetes (Petersen et al., 2005; van Hall et al., 2003). The latter studies identified IL-6 as a potent modulator of fat metabolism in humans, increasing lipolysis as well as fat oxidation without causing hypertriacylglycerolaemia.

Whereas it is known that both TNF-α and IL-6 induce lipolysis, only IL-6 appears to induce fat oxidation (Plomgaard et al., 2007; van Hall et al., 2003). Given the different biological profiles of TNF-α and IL-6 and given that TNF-α may trigger an IL-6 release, one theory holds that it is TNF-α derived from adipose tissue that is actually the major "driver" behind inflammation-induced insulin resistance and atherosclerosis. Importantly, also tumour initiation, promotion, and progression is stimulated by systemic elevation of pro-inflammatory cytokines (Handschin and Spiegelman, 2008).

A chronic inflammatory environment will lead to a state of insulin resistance with hyperinsulinaemia. The so-called hyperinsulinaemia-hypothesis goes hand in hand with the inflammation-hypothesis. The hyperinsulinaemia-hypothesis suggests that elevated levels of insulin and free IGF-1 promote proliferation of colon cells and lead to a survival benefit of transformed cells, ultimately resulting in colorectal cancer (Berster and Goke, 2008). In addition, a number of neurodegenerative diseases are linked to a local inflammatory response in the brain (neuroinflammation) (Zipp and Aktas, 2006). Moreover, in addition to the neuroinflammation found in many neurodegenerative disorders, systemic inflammation may further exacerbate the progression of neurodegeneration (Perry et al., 2007).

6. The myokine concept

Regular exercise protects against a number of chronic diseases associated with chronic inflammation. This might be due to an anti-inflammatory effect of regular exercise, which could be mediated via several mechanisms. It is suggested that the long-term anti-inflammatory effects of exercise may be mediated via effects of exercise leading to a reduction in visceral fat mass.

In line with the acceptance of adipose tissue as an endocrine organ, we came up with the idea that also skeletal muscle should be viewed as an endocrine organ. In continuation, we have suggested that cytokines and other peptides that are produced, expressed, and released by muscle fibres and exert paracrine or endocrine effects should be classified as "myokines". Given that skeletal muscle is the largest organ in the human body, our discovery of contracting muscle as a cytokine producing organ opens for a new paradigm: through evolution muscle has had a central role in orchestrating metabolism of other organs. This paradigm provides a conceptual basis explaining the multiple consequences of a physically inactive life style. If the endocrine function of the muscle is not stimulated through contractions, this will cause malfunction of several organs and tissues of the body as well as an increased risk of cardiovascular disease, cancer, and dementia.

Today, it appears that skeletal muscle has the capacity to express several myokines. The list includes interleukin IL-6, IL-8, IL-15, BDNF, LIF, FGF21 and Follistatin-like-1 (Broholm et al., 2008; Izumiya et al., 2008; Ouchi et al., 2008; Hojman et al., 2009).Thus, although the idea of an "exercise factor" can be traced back many years, our recent identification of muscle as a myokine-producing organ opens for a whole new field of research. In this review, a brief highlight of some myokines with a specific effect on fat oxidation will be given.

6.1. IL-6: the myokine prototype

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 exercise. The identification of an 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 post exercise period when insulin action is enhanced but, on the other hand, IL-6 has also been associated with obesity and reduced insulin action. However, a number of studies during the past decade have revealed that in response to muscle contractions, both type I and type II muscle fibres express the myokine IL-6, which subsequently exerts its effects both locally within the muscle (e.g. through activation of AMPK) and – when released into the circulation – peripherally in several organs in a hormone-like fashion. Within skeletal muscle, IL-6 acts locally to signal through gp130Rβ/IL-6Rα, resulting in the activation of AMP-kinase and/or PI3-kinase to increase glucose uptake and fat oxidation. IL-6 may also work in an endocrine fashion to increase hepatic glucose production during exercise or lipolysis in adipose tissue, reviewed in Pedersen and Febbraio (2008).

It appears, that unlike IL-6 signalling in macrophages, which seems dependent on activation of the NFκB signalling pathway, intramuscular IL-6 expression is regulated by a network of signalling cascades that amongst other pathways are likely to involve cross-talk between the Ca^{2+}/NFAT and glycogen/p38 MAPK pathways. The finding that muscular IL-6 does not activate NFκB signalling supports the idea that the exercise-induced IL-6 response is not mediating strong pro-inflammatory activities. In fact, NfκB is not activated human contracting skeletal muscle, and the IκB kinase beta (IκKβ) does not increase the transcription of IL-6, further suggesting that IL-6 gene transcription in skeletal muscle is unlikely to be dependent on activation of the IKK/NFκB signalling pathway.

We have suggested that muscular derived IL-6 mediates anti-inflammatory effects. These findings are supported by studies in humans in which we have demonstrated that IL-6 infusion inhibits endotoxin-induced TNF production and stimulate the occurrence of anti-inflammatory cytokines, such as IL-1 receptor antagonist (IL-1ra) and IL-10 (Pedersen and Febbraio, 2008). The anti-inflammatory effects of IL-6 may be mediated via a direct inhibitory effect

of IL-6 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 (Schindler et al., 1990) and levels of TNF-α are markedly elevated in anti-IL-6-treated mice and in IL-6 deficient knock-out mice (Mizuhara et al., 1994), 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 human (Starkie et al., 2003). Following exercise, the high circulating levels of IL-6 are followed by an increase in IL-1ra and IL-10. The latter two anti-inflammatory cytokines can be induced by IL-6 (Steensberg et al., 2003). Whereas IL-10 influences multiple cytokines, the biological role of IL-1ra is to inhibit signalling transduction through the IL-1 receptor complex. The IL-1ra is a member of the IL-1 family that binds to IL-1 receptors but does not induce any intracellular response (Pedersen and Febbraio, 2008). In relation to exercise, IL-6 may therefore be involved in mediating the anti-inflammatory effects of exercise. However, a number of other mechanisms have been identified. Exercise increases the release of adrenaline, cortisol, growth hormone, prolactin and other factors that have immunomodulatory effects (Handschin and Spiegelman, 2008).

6.2. IL-15 – a role in muscle-fat cross talk?

IL-15 is expressed in human skeletal muscle and has been identified as an anabolic factor in muscle growth. In addition to its anabolic effects on skeletal muscle *in vitro* and *in vivo*, IL-15 appears to play a role in lipid metabolism (Nielsen and Pedersen, 2007). Therefore, IL-15 was suggested to be involved in muscle-fat cross talk.

IL-15 mRNA levels were upregulated in human skeletal muscle following a bout of strength training (Nielsen et al., 2007) suggesting that IL-15 may accumulate within the muscle as a consequence of regular training. Interestingly, we further demonstrated a negative association between plasma IL-15 concentration and trunk fat mass, but not limb fat mass, in humans. In support of the human data, we demonstrated a decrease in visceral fat mass, but not subcutaneous fat mass, when IL-15 was overexpressed in murine muscle (Nielsen et al., 2008). Quinn et al. found that elevated circulating levels of IL-15 resulted in significant reductions in body fat and increased bone mineral content, without appreciably affecting lean body mass or levels of other cytokines (Quinn et al., 2009). Although the latter model represented an artificial system, the findings lend some support to the idea that IL-15 secretion from muscle tissue may modulate visceral fat mass in particular via an endocrine mechanism.

6.3. BDNF – a role in peripheral metabolism

BDNF is recognised as playing a key role in regulating survival, growth, and maintenance of neurons, and BDNF plays a role in learning and memory (Tyler et al., 2002). Hippocampal samples from Alzheimer's disease donors show a decreased BDNF expression (Connor et al., 1997) and individuals with Alzheimer's disease have low plasma levels of BDNF (Laske et al., 2005). Also, patients with major depression have lower levels of serum BDNF than normal control subjects (Karege et al., 2002). Other studies suggest that plasma BDNF is a biomarker of impaired memory and general cognitive function in ageing women (Komulainen et al., 2008) and a low circulating BDNF level was recently shown to be an independent and robust biomarker of mortality risk in old women (Krabbe et al., 2009). In addition, it has previously been described that patients with acute coronary syndromes have reduced levels of BDNF in plasma (Manni et al., 2005). Interestingly, we found low levels of circulating BDNF also in individuals with both obesity and type 2 diabetes (Krabbe et al., 2007). Thus, BNDF is low in people with

Alzheimer's disease, major depression, impaired cognitive function, CVD, type 2 diabetes, and obesity.

The finding of low BDNF plasma levels in patients with type 2 diabetes stimulated us to study if the brain could potentially contribute to the systemic levels of BDNF. In a human *in vivo* model, we demonstrated that there is a cerebral output of BDNF at basal condition, and that cerebral output of BDNF is inhibited during hyperglycaemic clamp conditions in humans. The latter finding may explain the concomitant finding of low circulating levels of BDNF in individuals with type 2 diabetes, and the association between low plasma BDNF and the severity of insulin resistance (Krabbe et al., 2007). We further studied whether skeletal muscle would produce BDNF in response to exercise (Matthews et al., 2009). We found a modest increase in BDNF mRNA and protein expression in human skeletal muscle after exercise. However muscle-derived BDNF appeared not to be released into the circulation. BDNF mRNA and protein expression were increased in muscle cells that were electrically stimulated. Interestingly, BDNF increased phosphorylation of AMPK and ACC and enhanced fat oxidation both *in vitro* and *ex vivo*. Thus, we have been able to identify BDNF as a novel contraction-induced muscle cell-derived protein that may increase fat oxidation in skeletal muscle in an AMPK-dependent fashion. The possibility exists that BDNF may be classified as a myokine that works in an autocrine or paracrine fashion with strong effects on peripheral metabolism, including fat oxidation with a subsequent effect on the size of adipose tissue.

7. The anti-inflammatory effects of exercise

In the context of specific myokines, it is suggested that physical inactivity is an *independent* cause of fat accumulation in "the wrong places". Accordingly, contracting skeletal muscles release myokines, which work in a hormone-like fashion, exerting specific endocrine effects on visceral fat and other ectopic fat deposits and mediating anti-inflammatory effects. Other myokines will work locally within the muscle via paracrine mechanisms, exerting their effects on signalling pathways involved in fat oxidation.

Regular exercise has anti-inflammatory effects, suggesting that physical activity *per se* may suppress systemic low-grade inflammation. And several studies show that markers of inflammation are reduced following longer-term behavioural changes involving both reduced energy intake and increased physical activity, reviewed in Petersen and Pedersen (2005). However, the mediators of this effect are unresolved. A number of mechanisms have been identified. Exercise increases the release of epinephrine, cortisol, growth hormone, prolactin, and other factors that have immunomodulatory effects (Nieman, 2003; Handschin and Spiegelman, 2008).

To study whether acute exercise induces a true anti-inflammatory response, a model of "low-grade inflammation" was established in which a low dose of *Escherichia coli* endotoxin was administered to healthy volunteers, who had been randomised to either rest or exercise prior to endotoxin administration. In resting subjects, endotoxin induced a 2–3-fold increase in circulating levels of TNF-α. In contrast, when the subjects performed 3 h of ergometer cycling or received a 3 h infusion of recombinant human IL-6 prior to a bolus of endotoxin1 bolus, the TNF-α response was totally blunted (Starkie et al., 2003). This study provides some evidence that acute exercise and IL-6 may inhibit TNF production.

The cytokine response to exercise differs from that elicited by severe infections. The fact that the classical pro-inflammatory 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, reviewed in Pedersen and Febbraio (2008).

Typically, IL-6 is the first cytokine released into the circulation during exercise. The level of circulating IL-6 increases in an exponential fashion (up to 100-fold) in response to exercise and declines in the post exercise period. The circulating levels of well-known anti-inflammatory cytokines such as IL-1ra and IL-10 also increase after exercise. Taken together, exercise provokes an increase primarily in IL-6, followed by an increase in IL-1ra and IL-10. It appears that muscle-derived IL-6 may account for most of the systemic IL-6 response to exercise.

The possibility exists 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 direct link between the acute effects of exercise and the long-term benefits has yet to be established.

8. Conclusion

Lifestyle, e.g. regular exercise, offers protection against dementia and cognitive decline. Dementia as well as depression, type 2 diabetes, CVD and some cancers constitute a network of related diseases, the so-called "diseasome of physical inactivity". In this review, physical inactivity has been given the central role as an independent and strong risk factor for accumulation of visceral fat and consequently the activation of a network of inflammatory pathways, which promotes the development of neurodegeneration as well as insulin resistance, atherosclerosis, and tumour growth. Our finding that muscles produce and release myokines provides a conceptual basis for understanding some of the molecular mechanisms underlying organ cross talk, including muscle-fat cross talk. Accumulating data suggest that contracting skeletal muscles release myokines, which may work in a hormone-like fashion, exerting specific endocrine effects on visceral fat or mediating direct anti-inflammatory effects. Other myokines work locally within the muscle via paracrine mechanisms, exerting their effects on signalling pathways involved in fat oxidation.

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