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Exercise and health — emerging roles of IL-6

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Skeletal muscle works as a secretory organ with the capacity to produce hundreds of myokines. This finding provides a conceptual basis for understanding how muscles communicate with other organs such as adipose tissue, liver, pancreas, bones, and brain. The myokine IL-6 is released into the blood during exercise and it has been shown that IL-6 has multiple immunologic and metabolic effects. Here, we discuss recent advances regarding the physiology of IL-6. Human studies show that IL-6 infusion delays gastric emptying, reduces postprandial glucose concentrations and reduces insulin secretion, whereas experimental studies suggest a role for IL-6 in appetite regulation. Evidence is also accumulating for a central role of IL-6 in training-induced loss of visceral adipose tissue mass in humans. Moreover, recent experimental studies in mice show that voluntary exercise suppresses tumor growth through epinephrine-dependent and IL-6-dependent mobilization and redistribution of cytotoxic NK cells. It has been known for a while that IL-6 is a pleiotropic molecule; however, recent advances suggest that the physiological roles of IL-6 involve multiple aspects of metabolism as well as a role in tumor defense.

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Introduction

The positive clinical effects of regular exercise are well documented [1,2•], and evidence exists that exercise may be prescribed as medicine for several chronic diseases [3]. The identification of skeletal muscle as a secretory organ provides a conceptual basis for understanding how muscles communicate with other organs. Skeletal muscle produces several hundred myokines, some of which are induced by muscle contraction and differentially regulated in healthy and metabolically diseased individuals [4].

As with many paradigm shifting findings, the identification of muscle-derived IL-6 was somewhat serendipitous. Twenty years ago, in our search for a mechanism explaining exercise effects on the immune system, we came across the finding that plasma levels of IL-6 increased in an exponential fashion in response to a single bout of exercise [5].

The magnitude of the increase in plasma IL-6 is related to the amount of muscle mass involved in the exercise and to the duration of the exercise [2•]. Training intensity also plays a major role, especially if the performed exercise leads to depletion of intramuscular glycogen stores. Accordingly, studies have shown that muscular glycogen depletion markedly augments IL-6 release from the working muscles [2•]. Blood lactate is lower at a given power output in trained athletes [6]. The same is true for IL-6, which is likely to reflect that trained people have higher muscle glycogen concentrations compared untrained people [7].

In line with this intrinsic energy dependency, IL-6 release has been suggested to correlate with lactate production in the working muscles [8]. This has led to the proposal of a model that links exercise intensity, lactate production and IL-6 release during strenuous exercise. In a most recent study, high intensity exercise in humans and intramuscular lactate injections in mice were tightly correlated with systemic IL-6 release [9]. Moreover, it was suggested that lactate production during exercise initiates a protease-dependent release of IL-6 from the muscle as blockade with the matrix metalloprotease inhibitor, marimastat, attenuated the exercise and lactate-induced release of IL-6. With such a link between lactate production and IL-6 release, this model may also explain why IL-6 secretion is augmented during high intensity exercise and glycogen depletion [9].

Knowledge gathered from several studies demonstrates that physiological concentrations of IL-6 have multiple effects: IL-6 regulates glucose and lipid metabolism, it induces anti-inflammatory effects, it has anabolic properties and it is involved in controlling tumor growth [10,11,12,13•,14•]. Here, we briefly summarize new exciting results regarding the biological roles of IL-6.

Exercise-induced changes in visceral adipose tissue mass are regulated by IL-6 signaling

Recent large-scale epidemiological studies show that abdominal adiposity is associated with low fitness and low-grade inflammation independent of body mass index [15,16]. These data are in line with studies showing that

physical inactivity, without weight gain, leads to accumulation of visceral adipose tissue, whereas exercise training reduces visceral adipose tissue mass [4].

We have previously suggested that a physically inactive lifestyle provokes a vicious cycle of inflammation. According to this hypothesis, physical inactivity leads to accumulation of visceral fat and consequently to the activation of a network of inflammatory pathways that promote the development of conditions such as insulin resistance, atherosclerosis, neurodegeneration, tumor growth, and muscle waste.

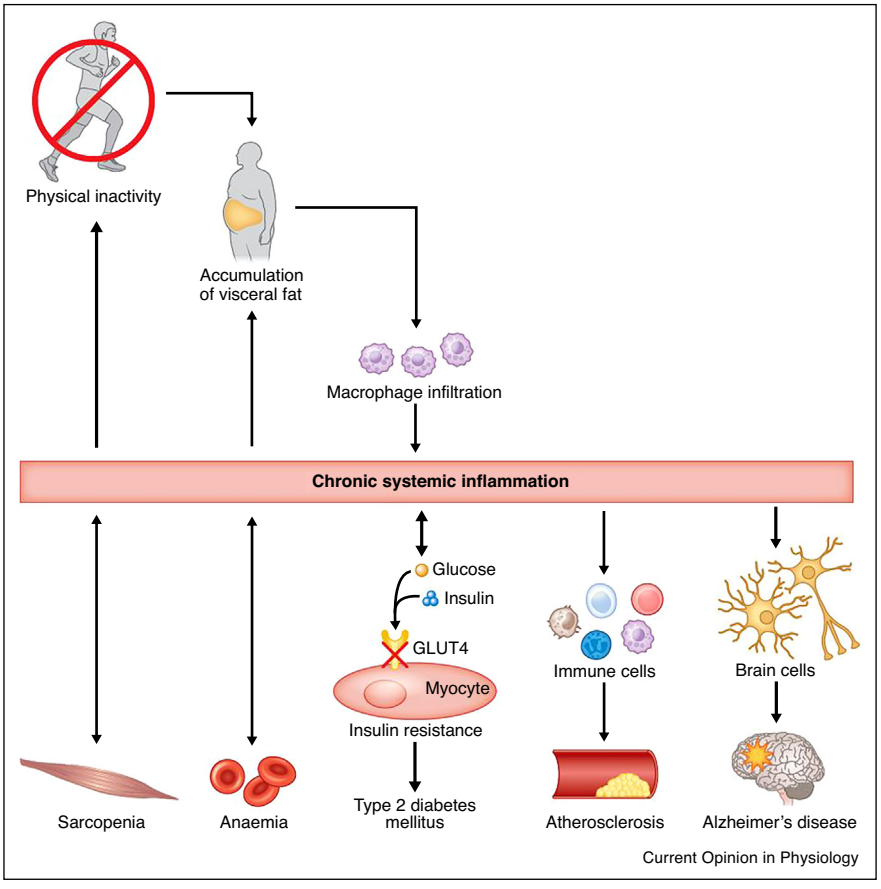
Figure 1 shows how lack of exercise may provoke inflammation and thereby a network of diseases. While there is a lot of research supporting the associations between inactivity, abdominal adiposity, systemic inflammation and disease, it was not until very recently that the mechanistic link between exercise and abdominal fat was discovered. Recently, we reported a central role for IL-6 in training-induced loss of visceral adipose tissue mass [17]. In a randomized placebo-controlled trial, abdominally obese adults were randomized to tocilizumab (IL-6 receptor antibody) or placebo during a 12-week intervention with either bicycle exercise or no exercise [18]. While exercise reduced visceral adipose tissue mass in line with previous observations, this effect of exercise was abolished in the presence of IL-6 receptor blockade, as appears from Figure 2.

Also, IL-6 receptor blockade increased cholesterol levels and worsened the lipid profile. Thus, this study points to a physiological role of IL-6 as a lipolytic factor in humans with abdominal obesity. It further highlights a potentially important metabolic consequence of IL-6 receptor blockade as used in for example patients with rheumatoid arthritis [19].

Interleukin-6 delays gastric emptying in humans

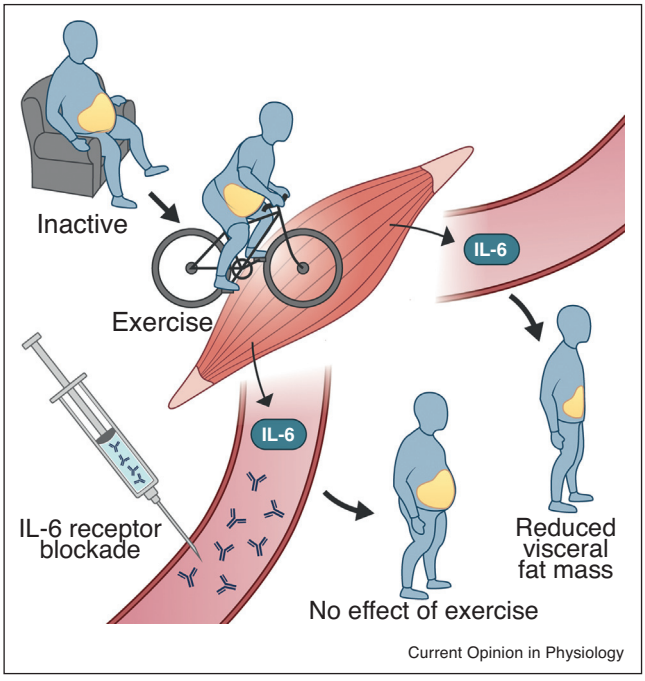
Gastric emptying is the most important regulator of postprandial glucose [20]. In a series of human physiological studies, we recently showed that elevated levels of IL-6 delays the rate of gastric emptying leading to improved postprandial glycemia [21], Figure 3.

Figure 1



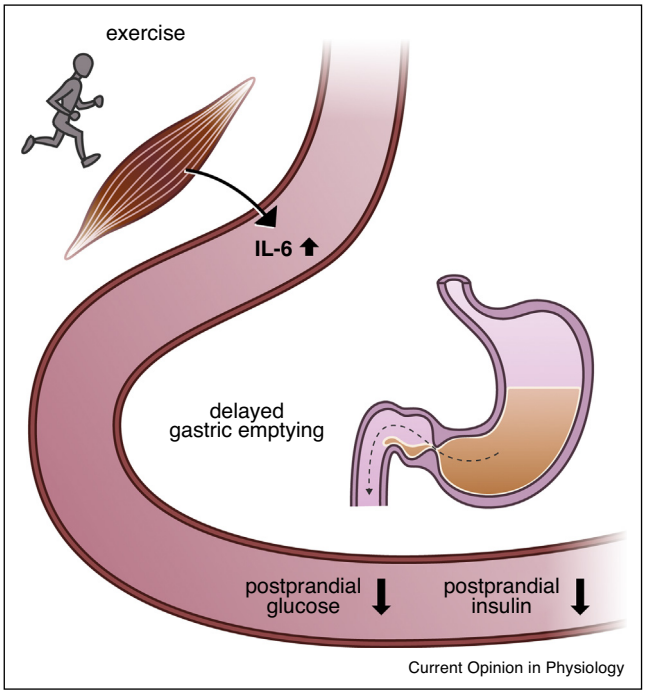
The links between physical inactivity, abdominal adiposity, inflammation, and disease.
Adapted with permission from Ref. [2•].

Figure 2



Exercise training reduces visceral adipose tissue mass and this effect of exercise is abolished in the presence of IL-6 blockade. Adapted with permission from Ref. [17].

Figure 3



Gastric emptying is a critical regulator of postprandial glucose. IL-6 and exercise delay the rate of gastric emptying in humans and reduce postprandial glycemia and insulin secretion in humans. Adapted with permission from Ref. [21].

To investigate if acutely increased plasma concentrations of IL-6, as seen with for example a bout of exercise, impacts on postprandial glycemia and insulin secretion in humans, recombinant human (rh) IL-6 was infused into healthy volunteers to obtain physiological concentrations of IL-6. Infusion of IL-6 before a mixed meal tolerance test (MMTT) delayed gastric emptying rate, improved postprandial glucose concentrations and reduced insulin secretion.

To clarify whether IL-6-induced changes in postprandial glucose were causally linked to changes in gastric emptying, we bypassed the stomach with a nasoduodenal tube. Bypassing the stomach abolished the effect of IL-6 on postprandial glycemia, showing that IL-6-induced improvements in postprandial glycemia are dependent upon delayed gastric emptying. To investigate whether the IL-6-induced delay in gastric emptying involved GLP-1, the GLP-1 receptor antagonist exendin 9–39 (ex-9–39) was used to block GLP-1 actions. IL-6 regulation of gastric emptying was, however, found to be independent of GLP-1. IL-6 receptor blockade increased gastric emptying during a post exercise meal, suggesting that IL-6 also regulates gastric emptying under physiological conditions. Moreover, IL-6 delayed gastric emptying and reduced insulin secretion in individuals with type 2 diabetes. The effects of IL-6 on gastric emptying are physiological and compatible with what might be expected to be necessary during an exercise bout: reduction of gastric motility while promoting substrate availability via a reduced insulin/glucagon ratio.

Interleukin-6 is involved in the regulation of appetite

Whereas systemic IL-6 KO mice develop mature-onset obesity [22,23], adeno-associated viral delivery of IL-6 in rat hypothalamus [24] and central overexpression of IL-6 [25,26] reduces fat mass accumulation and body weight gain in response to high fat diet. These results suggest that IL-6 is involved in the control of body weight. It is possible that IL-6 may cause these effects through regulation of hypothalamic neuropeptides involved in energy homeostasis [27].

In fact, absence of muscular IL-6 in male mice results in decreased body weight and food consumption in response to leptin and saline injections, suggesting that muscle IL-6 has an impact on CNS and plays a role in mouse metabolism, not only during exercise but also in the basal state and in situations where energy balance is altered [27].

Recently, the Brüning group [28••] applied IL-6 centrally in mice and found that it suppressed food intake. When the same IL-6 dose was injected intraperitoneally there was no effect on food intake, clearly demonstrating that the observed effect was mediated via the CNS. However,

when mice were injected with a fourfold higher IL-6 dose, than the centrally injected dose, peripheral injection of IL-6 at the high dose significantly reduced food intake. One conclusion from this study is that peripherally derived IL-6, when present at high concentrations, can pass the blood brain barrier and reach the CNS to reduce feeding. This finding leaves open the possibility that in relation to exercise of high intensity and long duration, muscle-derived IL-6 may inhibit appetite. In fact, an exercise study found some support for the idea that IL-6 as well as lactate could mediate the negative effect of high-intensity exercise on appetite [29].

Exercise and cancer — a role for IL-6

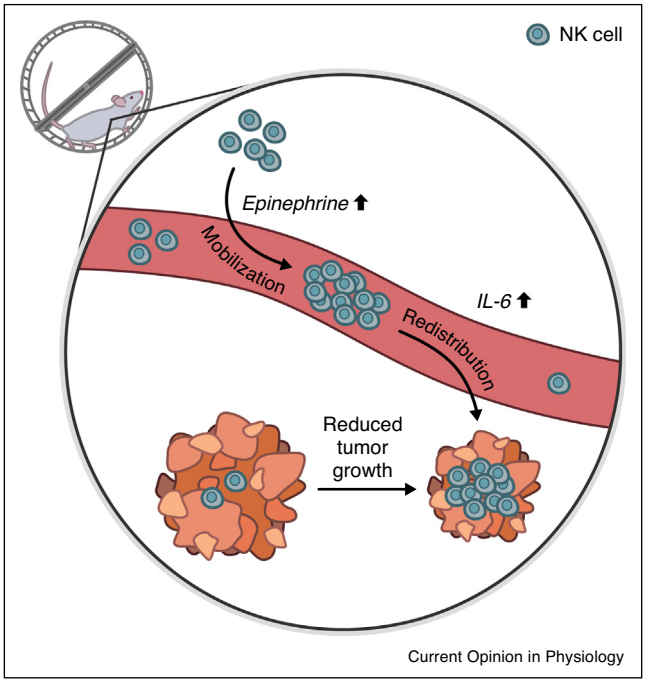
According to epidemiological studies, leisure-time physical activity appears to reduce the risk of at least 13 different cancer types [13•,30,31••,32••]. Observational studies show that people who are physically active after being diagnosed with breast cancer, colorectal cancer, and prostate cancer have a statistically higher chance of survival compared to those who are physically inactive, reviewed in Ref. [2•].

Several cancers are associated with systemic low-grade chronic inflammation and the anti-inflammatory effects of physical training, which can lower systemic low-grade inflammation, may contribute to mediating some of the protective effects on cancer development [13•]. In contrast, locally in the tumor inflammation and high infiltration of cytotoxic immune cells are associated with better prognosis [33].

To explore the effect of exercise on tumor growth in a preclinical study [30,31••], a B16F10 melanoma model was established. Tumor-bearing mice were randomized to voluntary wheel running or control. Mice with access to a running wheel demonstrated a reduction in tumor volume and incidence of at least 60% across several different tumor models. The effects of exercise on tumor growth were mediated via a direct regulation of natural killer (NK) cell trafficking, involving an epinephrine-dependent mobilization of NK cells to the circulation and an IL-6-dependent redistribution to tumors. When exercise-induced IL-6 was blocked by anti-IL-6 antibodies, the exercise-induced inhibition of tumor growth as well as the infiltration of NK cells into tumors were inhibited, suggesting that IL-6 is involved in enhancement of the intratumoral infiltration of cytotoxic immune cells, Figure 4.

A few mechanistic studies have also investigated the effect of the acute induction of IL-6 and other exercise factors on cancer cell growth. 'Serum obtained immediately before and after an acute bout of exercise, and thus conditioned with systemic exercise factors can reduce cancer cell growth with about 10% [34], but no direct role has been identified for IL-6. In contrast, the

Figure 4



Exercise reduces tumor incidence and growth in several mouse models. Voluntary running suppresses tumor growth through epinephrine-dependent and IL-6-dependent NK cell mobilization and redistribution.
Adapted with permission from Ref. [31••].

myokines Oncostatin M, irisin and SPARC has been shown to suppress breast and colon cancer [35,36], while the catecholamines, epinephrine and norepinephrine has been demonstrated to markedly suppress breast cancer cell growth and reduce tumor formation by 50% through regulation of the Hippo signaling pathway [37]. Thus, repetitive acute bouts of exercise and thereby the release of myokines and hormones may slow tumor progression.

Conclusion

The finding that contracting skeletal muscle produces and secretes IL-6 into the circulation suggests that IL-6 could be involved in mediating some of the health benefits of exercise. Recent advances in understanding the physiological and biological roles of IL-6 demonstrate that IL-6 contributes to the regulation of glucose homeostasis in humans by affecting gastric emptying.IL-6 also seems to play a central role in regulating visceral adipose tissue mass in humans. Finally, IL-6 plays a role in directing natural killer cells to the tumor site during exercise and thereby appears to be involved in mediating exercise-induced anti-cancer effects.

Taken together, these studies consolidate the pleiotropic nature of IL-6 and demonstrate a physiological role of IL-6 in regulating clinically relevant parameters related to

energy homeostasis and immune cell regulation in cancer. However, there are still many unanswered questions regarding the specific role of exercise-induced IL-6 in affecting metabolic disease and cancer in humans.

We need a better understanding of the metabolic consequences of IL-6 receptor blockade in patients receiving pharmacological treatment with drugs such as tocilizumab. We also need to understand if IL-6 receptor blockade regulates lipolysis and the ability to use fatty acids as energy source and hence whether this has impact on endurance. It also remains unanswered how IL-6 regulates gastric emptying and pancreatic hormone secretion. Giving that exercise reduces tumor volume across many tumor-models, it is of interest to determine to which extend, IL-6 is involved in mediating an anti-cancer effect. Mechanistic insight into these effects might reveal new pathways of importance for patients with diabetes and cancer.

Conflict of interest statement

Nothing declared.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Pedersen BK: **Which type of exercise keeps you young?** *Curr Opin Clin Nutr Metab Care* 2019, **22**:167-173.

2. • Pedersen BK: **The physiology of optimizing health with a focus on exercise as medicine**. *Ann Rev Physiol* 2018, **81**:607-627.
This article provides a translational perspective on exercise as medicine and could be of use for example teaching.

3. Pedersen BK, Saltin B: **Exercise as medicine - evidence for prescribing exercise as therapy in 26 different chronic diseases**. *Scand J Med Sci Sports* 2015, **25(Suppl. 3)**:1-72.

4. Benatti FB, Pedersen BK: **Exercise as an anti-inflammatory therapy for rheumatic diseases-myokine regulation**. *Nat Rev Rheumatol* 2015, **11**:86-97.

5. Pedersen BK: **Muscle as a secretory organ**. *Compr Physiol* 2013, **3**:1337-1362.

6. Brooks GA: **The science and translation of lactate shuttle theory**. *Cell Metab* 2018, **27**:757-785.

7. Steensberg A, Febbraio MA, Osada T, Schjerling P, van HG, Saltin B *et al.*: **Interleukin-6 production in contracting human skeletal muscle is influenced by pre-exercise muscle glycogen content**. *J Physiol* 2001, **537**:633-639.

8. Minetto MA, Rainoldi A, Gazzoni M, Ganzit GP, Saba L, Paccotti P: **Interleukin-6 response to isokinetic exercise in elite athletes: relationships to adrenocortical function and to mechanical and myoelectric fatigue**. *Eur J Appl Physiol* 2006, **98**:373-382.

9. Hojman P, Brolin C, Norgaard-Christensen N, Dethlefsen C, Lauenborg B, Olsen CK *et al.*: **IL-6 released from muscles during exercise is stimulated by lactate-dependent protease activity**. *Am J Physiol Endocrinol Metab* 2019, **316**:E940-E947.

10. Pedersen BK: **Anti-inflammatory effects of exercise: role in diabetes and cardiovascular disease**. *Eur J Clin Invest.* 2017, **47**:600-611.

11. Lee JH, Jun HS: **Role of myokines in regulating skeletal muscle mass and function**. *Front Physiol* 2019, **10**:42.

12. Kim S, Choi JY, Moon S, Park DH, Kwak HB, Kang JH: **Roles of myokines in exercise-induced improvement of neuropsychiatric function**. *Pflugers Arch* 2019, **471**:491-505.

13. • Hojman P, Gehl J, Christensen JF, Pedersen BK: **Molecular mechanisms linking exercise to cancer prevention and treatment**. *Cell Metab* 2018, **27**:10-21.
A comprehensive review of the molecular mechanisms underlying exercise effects on tumor growth.

14. • Pedersen BK: **Physical activity and muscle-brain crosstalk**. *Nat Rev Endocrinol* 2019. [Epub ahead of print].
A most recent update on the molecular mechanisms underlying exercise effects on cognitive function and learning.

15. Wedell-Neergaard AS, Krogh-Madsen R, Petersen GL, Hansen AM, Pedersen BK, Lund R *et al.*: **Cardiorespiratory fitness and the metabolic syndrome: Roles of inflammation and abdominal obesity**. *PLoS One* 2018, **13**:e0194991.

16. Wedell-Neergaard A, Eriksen L, Grønbæk M, Pedersen BK, Krogh-Madsen R, Tolstrup J: **Low fitness is associated with abdominal adiposity and low-grade inflammation independent of BMI**. *PLoS One* 2018, **13**:e0190645.

17. Wedell-Neergaard AS, Lang Lehrskov L, Christensen RH, Legaard GE, Dorph E, Larsen MK *et al.*: **Exercise-induced changes in visceral adipose tissue mass are regulated by IL-6 signaling: a randomized controlled trial**. *Cell Metab* 2019, **29** 844-855.e3.

18. Christensen RH, Wedell-Neergaard AS, Lehrskov LL, Legard GE, Dorph EB, Nymand S *et al.*: **The role of exercise combined with tocilizumab in visceral and epicardial adipose tissue and gastric emptying rate in abdominally obese participants: protocol for a randomised controlled trial**. *Trials* 2018, **19**:266.

19. Fleischmann R: **Interleukin-6 inhibition for rheumatoid arthritis**. *Lancet* 2017, **389**:1168-1170.

20. Woerle HJ, Albrecht M, Linke R, Zschau S, Neumann C, Nicolaus M *et al.*: **Importance of changes in gastric emptying for postprandial plasma glucose fluxes in healthy humans**. *Am J Physiol Endocrinol Metab* 2008, **294**:E103-E109.

21. Lang Lehrskov L, Lyngbaek MP, Soederlund L, Legaard GE, Ehses JA, Heywood SE *et al.*: **Interleukin-6 delays gastric emptying in humans with direct effects on glycemic control**. *Cell Metab* 2018, **27**:1201-1211.

22. Wallenius V, Wallenius K, Ahren B, Rudling M, Carlsten H, Dickson SL *et al.*: **Interleukin-6-deficient mice develop mature-onset obesity**. *Nat Med* 2002, **8**:75-79.

23. Matthews VB, Allen TL, Risis S, Chan MH, Henstridge DC, Watson N *et al.*: **Interleukin-6-deficient mice develop hepatic inflammation and systemic insulin resistance**. *Diabetologia* 2010, **53**:2431-2441.

24. Li G, Klein RL, Matheny M, King MA, Meyer EM, Scarpace PJ: **Induction of uncoupling protein 1 by central interleukin-6 gene delivery is dependent on sympathetic innervation of brown adipose tissue and underlies one mechanism of body weight reduction in rats**. *Neuroscience* 2002, **115**:879-889.

25. Hidalgo J, Florit S, Giralt M, Ferrer B, Keller C, Pilegaard H: **Transgenic mice with astrocyte-targeted production of interleukin-6 are resistant to high-fat diet-induced increases in body weight and body fat**. *Brain Behav Immun* 2010, **24**:119-126.

26. Senaris RM, Trujillo ML, Navia B, Comes G, Ferrer B, Giralt M *et al.*: **Interleukin-6 regulates the expression of hypothalamic neuropeptides involved in body weight in a gender-dependent way**. *J Neuroendocrinol* 2011, **23**:675-686.

27. Molinero A, Fernandez-Perez A, Mogas A, Giralt M, Comes G, Fernandez-Gayol O *et al.*: **Role of muscle IL-6 in gender-specific metabolism in mice**. *PLoS One* 2017, **12**:e0173675.

28. •• Timper K, Denson JL, Steculorum SM, Heilinger C, Engstrom-Ruud L, Wunderlich CM *et al.*: **IL-6 improves energy and glucose homeostasis in obesity via enhanced central IL-6 trans-signaling**. *Cell Rep* 2017, **19**:267-280.
A murine study unravelling the effects of IL-6 on appetite regulation.

29. Islam H, Townsend LK, McKie GL, Medeiros PJ, Gurd BJ, Hazell TJ: **Potential involvement of lactate and interleukin-6 in the appetite-regulatory hormonal response to an acute exercise bout**. *J Appl Physiol (1985)* 2017, **123**:614-623.

30. Moore SC, Lee IM, Weiderpass E, Campbell PT, Sampson JN, Kitahara CM *et al.*: **Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults**. *JAMA Intern Med* 2016, **176**:816-825.

31. •• Pedersen L, Idorn M, Olofsson GH, Lauenborg B, Nookaew I, Hansen RH *et al.*: **Voluntary running suppresses tumor growth through epinephrine- and IL-6-dependent NK cell mobilization and redistribution**. *Cell Metab* 2016, **23**:554-562.
Exercise inhibits tumor growth in mice. The mechanisms involved epinephrine, IL-6 and naturel killer cells.

32. •• Christensen JF, Simonsen C, Hojman P: **Exercise training in cancer control and treatment**. *Compr Physiol* 2018, **9**:165-205.
A most comprehensive literature review of studies regarding exercise training in cancer patients.

33. Thorsson V, Gibbs DL, Brown SD, Wolf D, Bortone DS, Ou Yang TH *et al.*: **The immune landscape of cancer**. *Immunity* 2018, **48**:812-830.e14.

34. Dethlefsen C, Lillelund C, Midtgaard J, Andersen C, Pedersen BK, Christensen JF *et al.*: **Exercise regulates breast cancer cell viability: systemic training adaptations versus acute exercise responses**. *Breast Cancer Res Treat* 2016, **159**:469-479.

35. Hojman P, Dethlefsen C, Brandt C, Hansen J, Pedersen L, Pedersen BK: **Exercise-induced muscle-derived cytokines inhibit mammary cancer cell growth**. *Am J Physiol Endocrinol Metab* 2011, **301**:E504-E510.

36. Aoi W, Naito Y, Takagi T, Tanimura Y, Takanami Y, Kawai Y *et al.*: **A novel myokine, secreted protein acidic and rich in cysteine (SPARC), suppresses colon tumorigenesis via regular exercise**. *Gut* 2013, **62**:882-889.

37. Dethlefsen C, Hansen LS, Lillelund C, Andersen C, Gehl J, Christensen JF *et al.*: **Exercise-induced catecholamines activate the hippo tumor suppressor pathway to reduce risks of breast cancer development**. *Cancer Res* 2017, **77**:4894-4904.