esterification and LD formation could also be relevant in other tumor types. For instance, clear cell renal cell carcinomas (ccRRCs) are characterized by the presence of glycogen stores and abundant LDs (Straub et al., 2010). Indeed, ccRCCs display vastly elevated levels of free cholesterol and cholesteryl esters compared to normal kidney tissue (Gebhard et al., 1987). Targeting cholesterol esterification could thus also have benefits in other cancer types. Interestingly, ACAT inhibitors have already undergone toxicological analysis and are used in humans. Avasimibe, the agent used to inhibit ACAT in this study, is currently undergoing clinical trials for the treatment of hyperlipidemia and atherosclerosis. Like statins or metformin, this may provide another example of a drug originally developed to target metabolic diseases that can be repurposed for the treatment, and possibly prevention, of cancer. Old drugs could indeed perform new tricks when used in the appropriate setting (Gronich and Rennert, 2013).

However, there are also cautionary notes raised by the work presented in this paper. Interestingly, supplementation of culture medium with exogenous low-density lipoprotein (LDL) or arachidonic acid rescued the toxicity of ACAT inhibitors (Figure 1). Although the authors did not investigate the effect of exogenous lipids in vivo, this result suggests that dietary regimens that produce elevated levels of circulating LDL or AA could restrict ACAT inhibitor efficacy (Yue et al., 2014). This observation complements previous results demonstrating that the lipolytic enzyme monoacylglycerol lipase (MAGL) is important in aggressive cancers and that its ablation resulted in reduced tumor growth. However, this effect was completely lost when mice were fed a high-fat diet (Nomura et al., 2010). The impact of diet on the metabolism of cancer cells is an urgent issue. Dietary regimens should be considered during preclinical research and then be translated into the clinic if potential targets in cancer metabolism are to fulfill their promise.

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BAT Thermogenesis: Linking Shivering to Exercise

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The thermogenic capacity of brown adipose tissue (BAT) in response to cold is relatively well established in humans. Several hormones and factors are involved in this response, and Lee et al. (2014) now provide evidence for a role of irisin and FGF21 in BAT thermogenic activity in humans.

In response to low-temperature exposure or prolonged stay in a mild cold environment, warm-blooded animals may initiate shivering, a muscular response aimed at maintaining the proper body temperature. However, before the surrounding temperature decreases enough to activate shivering, a nonshivering phase occurs, in which brown adipose tissue (BAT) is activated for heat production. This response involves rapid (within minutes) activation of signal transduction via neuronal pathways and heat release via UCP-1 induction in BAT sites such as the supraclavicular region (Symonds et al., 2012). Among the known factors and hormones involved in this response is norepinephrine (NE), which mediates the activation of the sympathetic nervous system. NE induces fibroblast growth factor 21 (FGF21) gene transcription and release in BAT (Hondares et al., 2011), which, in turn promotes lipolysis by the activation of hormone sensitive lipase (HSL). Consequently, the intracellular lipids released by lipolysis within brown adipocytes are directed to active mitochondria for heat

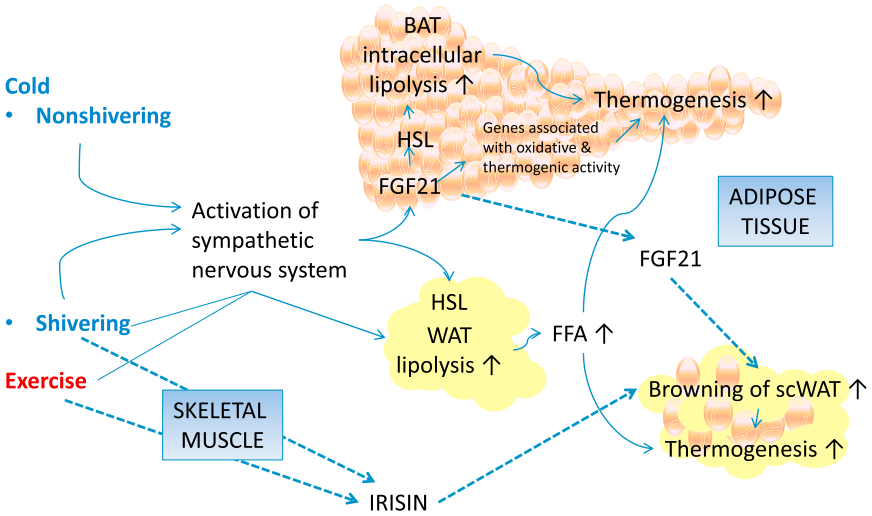

Figure 1. The Effects of Cold (Nonshivering and Shivering) and Exercise on FGF21 and Irisin
Cold induces both nonshivering and shivering thermogenesis. Shivering and exercise involve skeletal muscle, while nonshivering effects are directed to brown adipose tissue (BAT). Both cold and exercise activate the sympathetic nervous system, and the resulting noradrenergic stimulus induces lipolysis both in BAT and in white adipose tissue (WAT). Fibroblast growth factor 21 (FGF21), which is activated by norepinephrine, induces hormone-sensitive lipase (HSL) and other genes associated with oxidative and thermogenic activity, thus leading to increased thermogenesis in BAT. FGF21 also induces browning in subcutaneous WAT in cooperation with irisin, which is secreted by the muscles as a result of shivering or exercise. Excess fatty acids from the enhanced lipolysis are oxidized and consumed in BAT and subcutaneous WAT (scWAT).

production. Interestingly, exercise also promotes adipose tissue- mediated thermogenesis via secretion of the myokine irisin. Lee et al. (2014) now show that shivering is also associated with irisin secretion, thus linking exercise- and cold-induced thermogenesis.

Myokines are released from muscles in response to exercise. They signal to other organs an increased need for fuel, activating glycogenolysis in muscle, and gradually increasing lipolysis in adipose tissue (Stich et al., 2000). Indeed, repeated exercise bouts (cycling or swimming) in mice result in an increased adipocyte UCP1 expression, specifically in inguinal subcutaneous adipose tissue (Boström et al., 2012). Irisin was one of the first myokines found to activate such adipose tissue browning in rodents in response to exercise (Boström et al., 2012). These effects are mediated by the transcriptional coactivator PGC1-α, which is activated by exercise and in turn induces expression of the FNDC5 gene and membrane protein; FNDC5 is then cleaved to release irisin (Boström et al., 2012).

In a recent paper, Lee et al. (2014) describe the effects of cold, shivering, and exercise on FGF21 and irisin. They show that exposure to cold increases plasma FGF21 and serum irisin in healthy human volunteers and that induction of irisin is associated with more intense shivering, as determined using electromyography (EMG), a technique for measuring muscle electrical activity. The concentration of irisin in serum increases on average from 10 to 20 ng/ml during cold exposure. It remains unchanged after a maximal exercise test, in which volunteers exercise to exhaustion, but increases from an average of 10 up to 30 ng/ml after a submaximal exercise test, in which volunteers exercise at a lower intensity for the same or longer periods of time (Lee et al., 2014). Thus, shivering induces irisin secretion at levels almost comparable to those induced by exercise, suggesting that shivering links exercise- and cold-induced thermogenesis.

Lee et al. then tested the effects of the two cytokines on adipocytes. They used irisin and FGF21 to treat in vitro human neck adipocytes, which have BAT-like characteristics, and primary human subcutaneous and omental adipocytes, typically without BAT characteristics. Both irisin and FGF21, and especially their combination, resulted in significant heat production in neck and subcutaneous adipocytes—although to a lesser extent in the subcutaneous adipocytes—but omental adipocytes did not respond to the treatment. These results may reflect the browning capacity of certain adipocytes, namely those that are anatomically situated where they can be exposed to environmental cold. These adipocytes may be activated by cytokines to produce heat, in order to maintain proper body temperature, but they may also be harnessed to burn excess fatty acids produced by systemic lipolysis in white adipose tissue (WAT) in response to both cold and exercise. Both cold and exercise activate the sympathetic nervous system, through which NE stimulates HSL in WAT, resulting in breakdown of triglyceride stores (Figure 1).

The above results suggest that FGF21 and irisin function in concert during cold and shivering. In addition, FGF21 has a dual role inducing beneficial changes in adipose tissue. Cold temperature induces FGF21 expression and release from BAT both in rodents (Hondares et al., 2011) and in humans (Lee et al., 2013, Lee et al., 2014). The released FGF21 has endocrine effects on WAT (i.e., browning) but may also have autocrine effects (Potthoff et al., 2012). Interestingly, FGF21 release may in turn depend on the presence of BAT. Under normal temperature conditions, FGF21 shows a diurnal rhythm with plasma concentrations ranging on average between 50 and 100 pg/ml, being highest in the morning (Lee et al., 2013). This rhythm is blunted by cold exposure. Now Lee et al. show that FGF21 diurnal variation is more effectively blunted in human subjects with detectable BAT, suggesting that FGF21 secretion during cold exposure may require functionally active BAT.

Why would the signal from muscle recruit adipocytes for browning? Irisin levels are not elevated immediately after an exercise bout (Boström et al., 2012), and now Lee et al. (2014) show that maximal exercise does not produce as significant an irisin response as submaximal exercise, suggesting that exercise intensity rather than time determines the irisin response. This may reflect the different metabolic milieu that characterizes these two conditions: glucose and insulin concentrations are higher after maximal exercise compared to cold or

submaximal exercise, while fatty acid (FA) concentrations are not affected by maximal exercise but increase after submaximal exercise (Lee et al., 2014) and exposure to cold, at least in BAT positive subjects (Orava et al., 2013). In this context, shivering may be regarded as "low-intensity minimal exercise," which may be important for the irisin response (Lee et al., 2014). The resulting browning of subcutaneous WAT may help meet the need for excess oxidation sites for released FAs in response to cold, acting in concert with heat production. Alternatively, submaximal exercise may be regarded as "high-intensity shivering," leading to similar responses including the activation of thermogenesis along with the oxidation of glucose and FAs in working muscles.

Overall, the results by Lee et al. (2014) suggest that irisin and FGF21— induced by submaximal exercise, shivering or cold—collaborate in promoting the browning of adipose tissue in order to meet the increased demand for fat (and/or glucose) oxidation. In the future, it will be interesting to explore how these signals linking muscle and adipose tissue are regulated in obesity and whether they could function as a treatment for subjects with nonfunctional BAT. Moreover, these two players, though important, are only part of the puzzle, and new factors will likely add to our understanding of muscle-adipose communication and the possibilities for treatment.

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Independent Control of Aging and Axon Regeneration

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Axon regeneration capacity often declines with age. One might assume that loss of regeneration is an obvious consequence of organismal aging. However, in the latest issue of *Neuron*, Byrne et al. (2014) demonstrate that regeneration ability and aging are regulated cell-autonomously within neurons, and can be decoupled.

In animals, the juvenile state is often associated with better tissue-repair ability. Ample evidence suggests that this is also the case for axon regeneration, an essential step of neural repair after brain and spinal cord injury. For example, in contrast to immature neurons with robust growth ability, the terminally differentiated neurons in the adult mammalian central nervous system possess limited regenerative regrowth after injury. Such aging-associated decline of regenerative growth has also been observed in the mammalian peripheral nervous system and other species. These observations suggest a possible connection between axon regeneration ability and aging. However, this issue has never been formally tested due to the complexity of the system. In an attempt to address this question, Byrne and colleagues analyze how aging affects axon regeneration in *C. elegans,* and find that age-dependent decline of axon regeneration ability is independent of the life span of the animals. (Byrne et al., 2014).

C. elegans is a particularly well-adapted model to address the relationship between axon regeneration and aging. Axon regeneration can be easily assessed in vivo by laser axotomy, and *C. elegans* is a leading model for aging study. Byrne and colleagues first observe a 3-fold decrease in axon regeneration capacity between young and old adult worms, corroborating the hypothesis of age-dependent decline of regeneration. They then ask whether conditions that delay aging and increase lifespan could overcome this effect. They therefore assess the regeneration capacity of old worms in three different mutants known to increase life span (*sir-2.1*, *eat-2*, and *daf-2*) (Figure 1). They observe that only the mutation in *daf-2*, the worm homolog