Irisin, Light My Fire
Daniel P. Kelly
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tainly a pioneer in experimentally assessing the potential magnitude of the "flexoelectric" or stress gradient–induced polarization effect. Over the last decade he has used simple and elegant beam-bending experiments to show that stress gradients alone can induce changes in electrical polarization (*6*–*8*). Although debate continues as to the absolute magnitude of flexoelectric coefficients (*9*), it is, nevertheless, generally conceded that flexoelectricity could, in the right circumstances, dominate over piezoelectricity as the primary mechanism by which applied stress might alter material polarization.

The geometry of Lu *et al*.'s experiment epitomizes the "right circumstances" for flexoelectricity (see the figure, panels A and B). The stress field is caused by a minute point contact [the tip of an atomic force microscope (AFM)]. As a result the stress field is strongly divergent close to the ferroelectric film surface, generating large field gradients; in addition, the ferroelectric film is rather thin (4.8 nm) so that appreciable stress field divergence persists throughout the entire film thickness. The orientation of the barium titanate ($BaTiO_3$) film is such that the polarization direction must lie perpendicular to the film surface. Thus, although pure mechanical pressure and piezoelectricity can suppress polarization, flexoelectricity is needed to switch the direction of polarization from up to down in a repeatable and predictable manner. Because no electric fields are applied, the switching need not be complicated by issues relating to charge injection and dielectric leakage. However, it is a little frustrating that only downward pressure can be applied to the ferroelectric film (the AFM tip can only push and not pull), and, consequently, flexoelectric polar switching can only be demonstrated in one direction. This limitation presents a drawback for any proposed future flexoelectric memory devices.

Nevertheless, Lu *et al*. have successfully illustrated the importance of nanoscience as a general tool for capitalizing on field gradient effects. The magnitude of the field gradient decays very rapidly with distance ($1/r^3$) (r is the distance away from the tip-to-surface contact point). For system behavior to be dominated by field gradient effects, objects therefore need to be both close to the field source and small in size so that the entire object is permeated by large field gradient values. These are features only offered by nanoscale materials. Furthermore, if the dimensionality of the problem can be reduced, by nanopatterning, for example, then there is potential to capitalize further on a less severely decaying field gradient than is the case in three dimensions. For example, for a point source in two dimensions, the field gradient is exactly the same as for the three-dimensional (3D) case, save for the less extreme decay with distance from the source ($1/r^2$) (see the figure, panel C).

Thus, although part of the success in the study by Lu *et al*. has been to specifically demonstrate that stress field gradients can be large enough to induce ferroelectric switching, their breakthrough is actually more general—that nanoscale systems represent the ideal environment in which to capitalize upon field gradient effects.

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MEDICINE

Irisin, Light My Fire

A newly discovered messenger system between muscle and fat tissue may explain the systemic benefits of exercise.

Daniel P. Kelly

Regular physical activity confers enormous fitness benefits. Exercise training enhances muscular endurance and strength, expends calories, and combats the development of common diseases such as obesity and type 2 diabetes. The effects of exercise are systemic and seemingly cannot be explained solely by the expenditure of calories in muscle (*1*). A recent study by Böstrom *et al*. (*2*) describes a mechanism that may elucidate how total body energy expenditure is increased by exercising muscle.

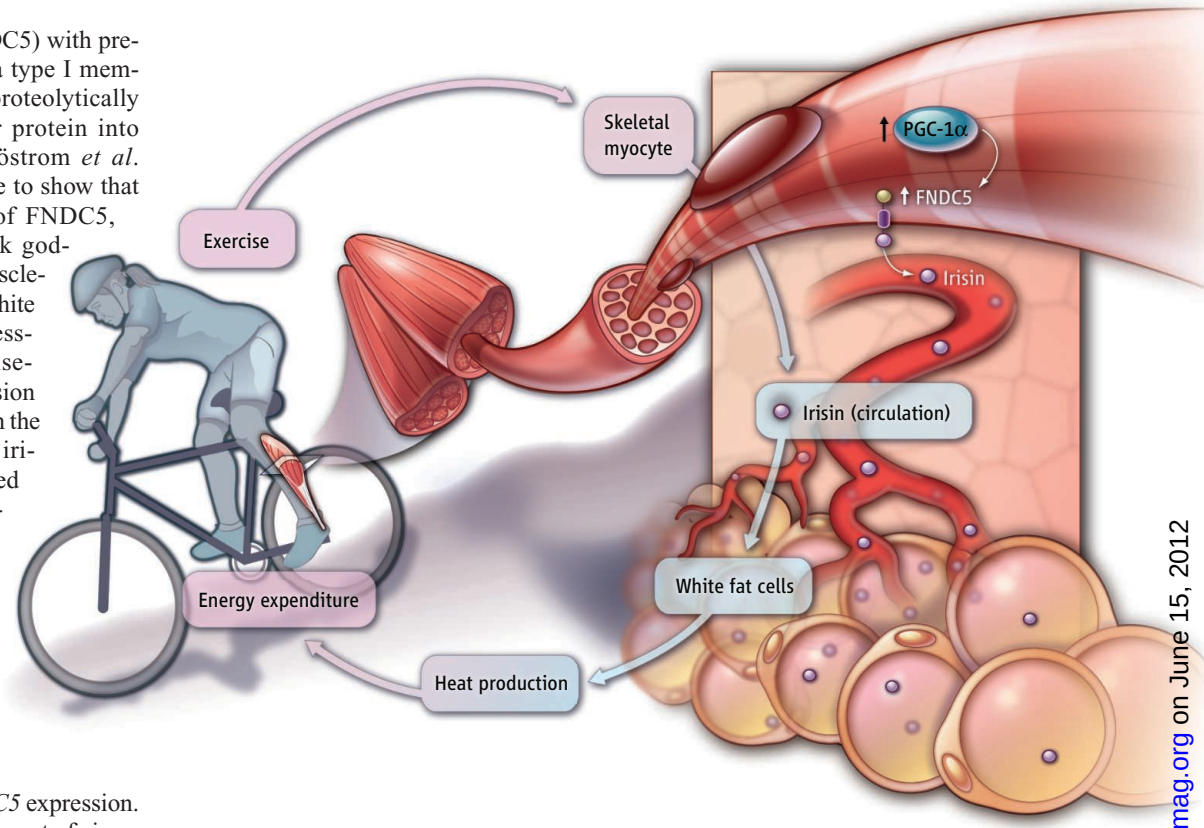
Exercise training results in adaptive structural and metabolic changes in skeletal muscle, including a change in the type of muscle fiber, mitochondrial biogenesis, and angiogenesis (*3*). Substantial progress has been made in delineating the molecular regulatory circuitry involved in the exercise-induced changes in muscle structure and function. Notably, the expression of a gene transcriptional co-regulator called peroxisome proliferator–activated receptor γ (PPARγ) coactivator 1α (PGC-1α) is induced in muscle in response to exercise in rodents and humans (*4*, *5*). In mice, PGC-1α activates and orchestrates genes that mediate the adaptive changes of exercise-trained muscle (*6*, *7*). Mice engineered to overexpress PGC-1α in skeletal muscle show increased exercise endurance, vascularity, and mitochondrial capacity to produce adenosine 5′-triphosphate (ATP) in the absence of exercise (*6*). In addition, such mice exhibit relative resistance to age-related obesity, insulin resistance, and diabetes (*8*).

Investigation of the subcutaneous fat tissue depots in the muscle-specific PGC-1α–overexpressing mice revealed a surprising finding (*2*). Specifically, the white fat cells displayed signatures of brown fat cells, a feature referred to as "browning." Unlike white adipose, which simply stores fat, brown fat is specialized to uncouple mitochondrial respiration, allowing for the generation of heat. Thus, brown fat serves an important thermogenic function for rodents and all species that hibernate. Interestingly, humans also have functional brown fat (*9*–*12*). The surprising observation that white fat in the PGC-1α–overexpressing mice exhibited browning suggests that muscle activity during exercise triggers remodeling of distant subcutaneous adipose tissue depots. Consistent with this hypothesis, exercise may activate thermogenic programs in fat tissue (*13*).

How does exercise, as modeled by PGC-1α overexpression in muscle, cause changes in remote fat tissue depots? Profiling of muscle genes activated by PGC-1α identified a factor called fibronectin type

Diabetes and Obesity Research Center, Sanford-Burnham Medical Research Institute, Orlando, FL 32827, USA. E-mail: dkelly@sanfordburnham.org

III domain containing 5 (FNDC5) with predicted structural features of a type I membrane protein that could be proteolytically cleaved to release a smaller protein into the bloodstream. Indeed, Böstrom *et al*. offer several lines of evidence to show that a secreted protein product of FNDC5, named irisin (after the Greek goddess messenger Iris), is the muscle-derived factor that acts upon white fat in the PGC-1α–overexpressing mice. One is that exercise-induced *FNDC5* gene expression in muscle caused an increase in the concentration of circulating irisin. In addition, irisin activated oxygen consumption and thermogenesis in white fat cells in culture. Further, injection of an adenoviral vector expressing irisin into mice resulted in browning of subcutaneous white fat and increased total body energy expenditure. These results support the model that exercise induces muscle *FNDC5* expression. This response increases the amount of circulating irisin, the factor that activates adipocyte thermogenic programs, thereby leading to mitochondrial heat production and energy expenditure (see the figure).



The myocyte-adipocyte connection. The proposed irisin messenger system is depicted for humans [but characterized in mice (*2*)]. Exercise and energy expenditure induces the transcriptional regulator PGC-1α in the skeletal myocyte, which in turn drives the production of the membrane protein FNDC5. The circulating factor irisin, cleaved from FNDC5, activates thermogenic programs in white adipose tissue ("browning"), including mitochondrial biogenesis and the expression of uncoupling protein 1 (UCP1), leading to mitochondrial heat production and energy expenditure.

The fascinating results of Böstrom *et al*. raise a theoretical conundrum: Why would physical activity induce a program that burns fat stores? This would seemingly lead to a cycle that would deplete available fuel stores for exercising muscle. Although the answer is not immediately apparent, it is possible that this mechanism evolved as a primitive survival response. For example, Böstrom *et al*. note that increased muscle activity generates heat through shivering and futile metabolic cycles, providing a defense against a cold environment. Perhaps irisin serves as a first messenger to rapidly increase thermogenic capacity by boosting respiratory uncoupling in adipose tissue. Similarly, increased physical activity is necessary for the organism to travel to a new habitat, often requiring long periods of exposure to harsher (colder) environments. In this latter scenario, exercising muscle would trigger the secretion of irisin as a signal to increase total body thermogenic defenses. However, the lack of irisin action on brown adipose tissue depots, as observed by Böstrom *et al*., would seem to be inconsistent with this thermogenic theory. It is also possible that this cross-organ signaling mechanism is involved in the dynamic control of body weight, providing an adaptive response that allows the organism to rapidly switch to an endurance phenotype by triggering weight loss. Indeed, Böstrom *et al*. found that administration of irisin modestly reduced both weight gain and the development of insulin resistance in mice fed a high-fat diet.

Does this pathway represent a broader metabolic regulatory network involving other organs that use energy? And are other messengers involved? Notably, FNDC5 is abundant in heart muscle. Interestingly, heart-derived natriuretic peptides activate white adipose thermogenic programs (*14*). The results of Böstrom *et al*. suggest the intriguing possibility that organs involved in high energy-expending activity, such as skeletal and heart muscle, send signals to fuel storage depots.

What is the role of irisin in humans? Irisin is highly conserved across species, and exercise increases circulating irisin concentrations in humans (*2*). It may be that irisin links physical activity to energy metabolic homeostasis, including weight control. Delineating the function of this interorgan messenger system in humans will be necessary to determine whether irisin and related factors are rational targets for therapeutic approaches aimed at disease states caused by chronic caloric excess, such as obesity and diabetes.

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