

METABOLISM

Get that myokine burn

Cell Metab. 19, 96–108 (2014)

Exercise is protective against obesity and type 2 diabetes. Peroxisome proliferator-activated receptor- γ coactivator 1 α (PGC-1 α) controls metabolic adaptation to exercise in muscle and can lead to the expression of brown adipocyte-specific genes in white adipose tissue (WAT). Roberts *et al.* employed a metabolomics approach to identify small molecule metabolites secreted from PGC-1 α -expressing muscle that contribute to these protective phenotypes. In media from cultured mouse myoblasts overexpressing PGC-1 α , β -aminoisobutyric acid (BAIBA) was enriched compared with media from normal myoblasts. In cultured human pluripotent cells differentiated into WAT, BAIBA led to increased expression of brown fat-specific genes and raised the basal rate of oxygen consumption. In mice, BAIBA led to augmented expression of brown adipocyte-specific genes and hepatic β oxidation genes—including peroxisome proliferator-activated receptor α (PPAR α)—and decreased body fat and improved glucose tolerance. In cultured hepatocytes, BAIBA raised the rate of maximal oxygen consumption and expression of β oxidation genes. A small molecule inhibitor of PPAR α abrogated these effects, indicating that BAIBA mediated its effects via PPAR α . Taken together, these data suggest exercise-induced release of BAIBA from skeletal muscle can promote the expression of brown adipocyte-specific genes in fat and stimulate β oxidation via PPAR α in the liver, and these molecular changes are at least partially responsible for the beneficial effects of exercise.

AD

METHODOLOGY

A bright ruler

Biophys. J. 105, 2724–2732 (2013)

BARON CHANDA



Techniques such as Förster resonance energy transfer (FRET) and chemical crosslinking have been used successfully to monitor molecular distances, but these can be limited by considerations such as the distances that can be measured (~10–100 Å in FRET) and the physical and dynamic properties of the fluorescent groups used. Jarecki *et al.* developed a strategy that combines the concepts of these two approaches in which their limitations can be mitigated by each other. The authors generated “tethered quenchers” where the short-range quencher nitroxide radical on one end of a molecule quenches a fluorophore on another end by collisional quenching. They first calibrated the approach by generating a series of probes with varied lengths (PEG units) between the quencher and fluorophore on different lengths of polyproline, which are known to form rigid helices of fixed lengths. The authors ultimately determined that the features of quenching report on the length of the quencher, thereby providing a ruler for studying the distances between two unknown molecular points in the range of 4–30 Å. Molecular dynamics simulations provided further validation. Next, the authors used an environmentally sensitive

fluorophore in their quencher to read out the Shaker K⁺ channel’s activation state and provide support for the ‘resting-state’ model where the transitions between channel opening and closing are asymmetric. ‘Tethered quenchers’ should find utility in even more complex systems such as large protein complexes.

MB

METALS

Ascorbate opens the door

J. Biol. Chem. doi:10.1074/jbc.M113.514828

STEPHANE MARI



Iron concentration must be carefully controlled *in vivo* to enable enzyme function but prevent oxidative stress. Plant roots import iron first by generation of Fe(III) via acidification, followed by reduction to Fe(II) by the enzyme ferric chelate reductase and uptake by a metal transporter. However, the mechanisms used in other parts of the plant for these processes are less clear. Grillet *et al.* now explore this question in seeds from the pea *Pisum sativum*. XANES spectroscopy of the embryo sac liquid, which directly feeds the seed, was consistent with a 4:1 Fe(III)/Fe(II) ratio, with citrate as a predominant ligand for the Fe(III) species. Mass spectrometry further identified the Fe(III) complexes as tri-iron compounds with varying proportions of citrate and malate

ligands. In contrast, Fe(II) was complexed by nicotianamine, an aminopropyl polymer previously linked to iron transport in plants, demonstrating the use of different ligands for the two metal oxidation states. The authors confirmed the embryos were capable of reducing iron and, surprisingly, discovered this activity persisted when embryos were removed, suggesting the active ingredient was excreted from the cells. Indeed, mass spectrometry, influx assays with iron chelators and ascorbate oxidase, and knockout of metabolic genes confirmed that the small molecule ascorbic acid plays a central role in iron reduction and uptake. These results, which were also confirmed in *Arabidopsis thaliana*, provide new insights into iron speciation and transport.

CG

NEURODEGENERATION

In need of nucleosides

Nat. Cell Biol. doi:10.1038/ncb2901

Parkinson’s disease (PD) is a progressive neurological disorder that results in the loss of dopaminergic neurons and has been associated with mitochondrial defects. Mutations in PTEN-induced kinase 1 (PINK1), which is linked to early-onset PD, also disrupts mitochondrial homeostasis, but the identity of the metabolic pathways that are altered remained unknown. Tufi *et al.* performed microarray analysis on *Drosophila pink1* mutants and observed increased transcripts for genes involved in nucleotide biosynthesis and salvaging. In particular, deoxyribonucleoside kinase (dNK), which converts deoxyribonucleosides (dNs) into their monophosphate forms, was upregulated in *pink1* mutants. Ubiquitous expression of *dNK* increased mitochondrial biogenesis and DNA synthesis, resulting in greater production of ATP and increased oxygen consumption. Neuronal overexpression of *dNK* was sufficient to prevent the loss of dopaminergic neurons and rescued a large majority of mitochondrial defects and motor impairments observed in *pink1* mutants. Finally, *pink1*-mutant flies fed a diet of either dNs or folic acid exhibited an increase in nucleotide metabolism that could rescue both mitochondrial and neuronal defects. Application of dNs or folic acid to PINK1-knockdown human neuroblastoma cells also restored mitochondrial membrane potential and improved respiration. This work implicates nucleotide metabolism as an important response pathway that can protect against neurodegeneration.

GM

Written by Mirella Bucci, Amy Donner, Catherine Goodman, Grant Miura and Terry L. Sheppard