In this issue

By John Ashkenas, Science Editor

Tailoring mitochondria to the cell's needs

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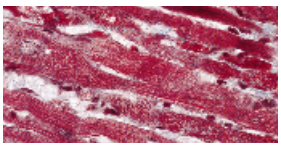
Cells increase their complement of mitochondria in response to rising metabolic demands or altered physiological conditions. This biosynthetic process is complicated, in part because mitochondrial composition varies between cell types. All cells depend on mitochondrial oxidative phosphorylation (OXPHOS), but some — notably adult cardiac myocytes — are specialized for metabolizing fatty acids in their mitochondria. Most other cells, including those in the neonatal heart, rely on the reducing power generated as glucose is metabolized in the cytoplasm. Likewise, mitochondria in brown adipose tissue (BAT), but not in most other cells, contain high levels of uncoupling proteins that allow OXPHOS to generate heat rather than ATP.

Lehman et al. now show that the transcriptional coactivator PGC-1 is limiting for mitochondrial proliferation in cardiac muscle, and they argue that this factor helps direct quantitative and qualitative changes in the mitochondrial population of various cells. PGC-1 interacts with PPARα in heart cells (and with PPARγ or other transcription factors elsewhere) to activate mitochondrial biogenesis. PGC-1 and PPARγ mediate BAT's response to cold, but in cardiac myocytes, as Lehman and colleagues now show, PGC-1 and PPARα activate mitochondrial proliferation during fasting and at other times when fatty acid oxidation becomes increasingly important to meet the heart's energy needs. Overexpressing PGC-1 in cardiac cells increases cells' capacity to carry out fatty acid oxidation and coupled OXPHOS. Because this transgene activates a different set of genes and functions in BAT, the authors suggest that pairing of PGC-1with PPARα specifies the expression of cardiac mitochondrial components.

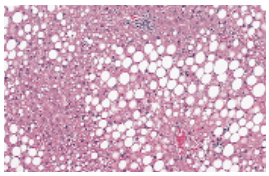


The importance of maintaining tight control over this regulatory system is seen in the phenotype of transgenic mice expressing PGC-1 constitutively in the heart. These animals show a dramatic proliferation of cardiac mitochondria but develop dilated cardiomyopathy and die at an early age. How increased mitochondrial function might alter heart development is still unknown.

Free radicals in alcoholic liver disease

(See article on pages 867–872)

The fatty degeneration of the liver characteristically seen in alcoholics has been ascribed to cellular damage mediated by free radicals. Here, Kono et al. identify the macrophage enzyme NADPH oxidase as the source of these troublesome compounds, and they confirm that free radicals are required in the pathogenesis of alcohol-induced liver disease. Covalent adducts, derived in part from the oxidation of ethanol itself, are found in bile from normal mice receiving alcohol on a chronic basis. However, similarly treated mice lacking NADPH oxidase show fewer such adducts, and these animals prove to be completely resistant to liver injury. This same group showed previously that ethanol promotes the release of bacterial endotoxin from the intestine into the circulation, causing liver macrophages (Kupffer cells) to respond with inflammatory modulators. Presumably in response to this bacterial product, activated Kupffer cells in alcohol-fed mice produce the pro-apoptotic protein TNF-α, an effect that is blocked in NADPH oxidase–deficient mice but could promote hepatocyte killing in wild-type animals. Whether free radicals are also harmful because of direct cytotoxicity, independent of the effects of TNF-α, is not resolved here.



Alcohol and bone fragility

(See article on pages 887–895)

In addition to liver disease, alcoholics are at risk of other ailments, including fragile bones. Osteopenia in these individuals might be explained by a deficit in osteoblast-dependent bone deposition, an excess of osteoclast-dependent bone resorption, or both. Dai et al. show here that these effects each contribute to bone fragility in mice exposed over 4 months to ethanol in their drinking water. They also show that IL-6, a known inducer of osteoclast formation, is required for ethanol's effects on bone resorption. Since ethanol can induce IL-6 expression in cultured marrow stromal cells, Dai and coworkers compared the differentiation of marrow cells from wild-type and *IL6*$^{-/-}$ knockout mice. IL-6–deficient cultures failed to accumulate osteoclast precursors in response to ethanol or to upregulate expression of RANK ligand, which promotes the formation of mature osteoclasts. By several measures, bone mass was better maintained in alcohol-fed *IL6*$^{-/-}$ mice than in wild-type animals, suggesting that the loss of osteoclast induction improves the mechanical strength of the bone. The residual effects of alcohol on bone mass in IL-6–deficient animals might be explained by loss of bone deposition. Alcohol feeding did not interfere with osteoblast proliferation, but it did cause a significant block in osteoblast function in both genotypes, as seen in calcium retention in cultured osteoblasts. Hence, reduced bone deposition is largely IL-6–independent but would be expected to act in concert with an IL-6–dependent increase in bone turnover to weaken the bones, increasing the high incidence of fractures among alcoholics.