Laboratory Investigation (2013) 93, 146-147

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doi:10.1038/labinvest.2012.181

Depletion of cardiac mtDNA causes cardiac dysfunction

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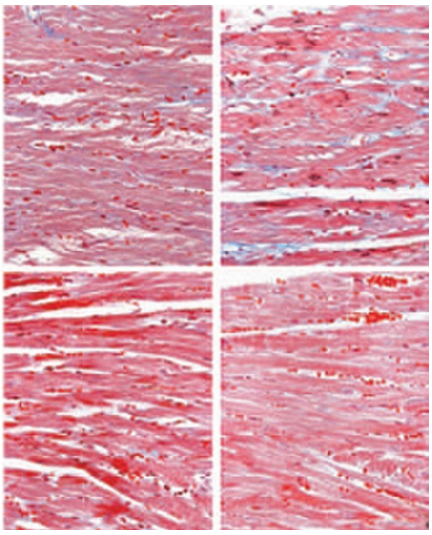

Because cardiomyocytes require substantial energy for proper function, they are sensitive to factors that impair mitochondrial energy production. Mitochondrial DNA (mtDNA) encodes key components of the electron transport chain (ETC) that are necessary for proper oxidative phosphorylation and therefore represents a potential Achilles' heel. Nucleoside reverse-transcriptase inhibitors (NRTIs) are an essential element of the therapeutic protocols used to treat HIV/AIDs patients. They inhibit HIV reverse transcriptase but have the unintended consequence of also inhibiting mitochondrial DNA polymerase-γ (pol-γ), resulting in cardiac toxicities that ultimately lead to heart failure.

To further investigate the relationship among NRTIs, mitochondrial dysfunction, and cardiomyocyte dysfunction, Koczor *et al* employed a genetically engineered mouse model (Y955C transgenic mice) that expressed a heart-specific mutant form of pol-γ containing a Y955C mutation that impaired polymerase processivity. Mice harboring this mutant form of pol-γ showed a moderate increase in left ventricular end diastolic dimension (LVEDD), confirming that pol-γ function is required for cardiac function. When Y955C transgenic mice were challenged with zidovudine (AZT; a well-known NRTI), there was a statistically significant increase in LVEDD, suggesting that underlying cardiac damage could predispose to AZT toxicity. As expected, the Y955C transgene reduced mtDNA. Both the Y955C transgene and AZT reduced basal respiration in isolated mitochondria, and the combination of the transgene and AZT reduced basal respiration further. Interestingly, it appeared that mitochondria from Y955C mice or mice treated with AZT exhibited tighter mitochondrial coupling, suggesting that the mitochondria were attempting, unsuccessfully, to compensate for deficiencies in ETC.

Adipose-derived mesenchymal stem cell therapy for ovarian damage

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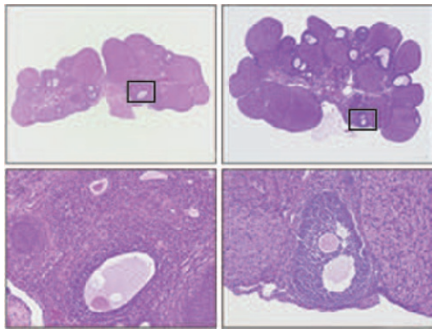

Fertility treatments have advanced dramatically since the first *in vitro*–fertilization baby was born in 1978. Yet there are situations in which fertility treatments do not work, such as dysfunctional ovarian follicles in menopausal women. The promise of stem cell therapy has given new hope to overcome these barriers. There has been some optimism about transplanting bone marrow–derived mesenchymal stem cells (BM-MSCs) into nonfunctional ovaries. However, it is more difficult to obtain BM-MSCs than adipose-derived MSCs (A-MSCs), which can be harvested from subcutaneous adipose tissue.

Given the encouraging results with BM-MSCs, Takehara *et al* asked whether A-MSCs might restore function to damaged ovaries. They generated a rat ovary-damage model using a well-known anticancer agent, cyclophosphamide, in which to study the effects of A-MSC-based therapy. They found that A-MSCs engrafted to the thecal layer area and not in the region of the granulosa cells and corpus luteum. The A-MSCs did not differentiate into thecal cells but instead were fibroblast-like cells that delivered hepatocyte growth factor, vascular endothelial growth factor, insulin-like growth factor-1, and possibly other growth factors beneficial for ovarian follicles. A-MSC-treated ovaries had increased angiogenesis and, most importantly, yielded more litters as compared with rats treated with saline. No abnormalities were detected in the F1 or F2 generation of rats treated with A-MSCs. Further studies are warranted to attempt to translate these studies for humans.

New mouse NASH model

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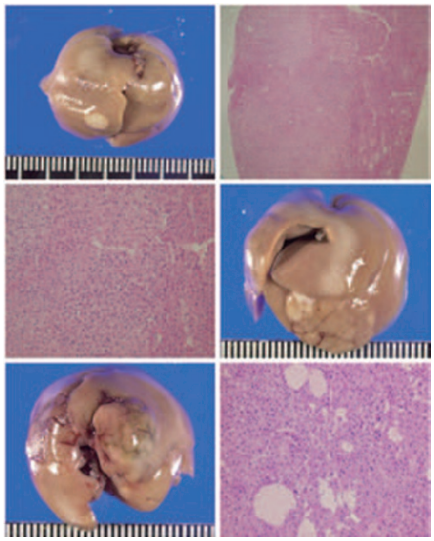
Metabolic syndrome, which has reached epidemic proportions in the United States, is characterized by the accumulation of visceral adipose tissue, which can lead to insulin resistance, hyperlipidemia, and other diseases. The pathogenesis is related to quantitative changes in pro- and anti-inflammatory cytokines secreted from adipocytes and macrophages. Metabolic syndrome manifests in the liver as nonalcoholic fatty-liver disease, which can progress to nonalcoholic steatohepatitis (NASH). NASH appears to arise through the interaction of excess accumulation of lipids and other factors such as oxidative stress, endotoxins, cytokines, and chemokines. Patients with



NASH are at risk of developing cirrhosis and hepatocellular carcinoma (HCC). To understand the pathogenesis of NASH and develop therapies, it is important to develop animal models that faithfully recapitulate the disorder's salient features with minimal manipulation. Because most of the mouse models of NASH that have been developed have been genetically engineered or require the administration of unusual diets or treatments, their validity has been challenged.

Tsumura Suzuki obese diabetes (TSOD) mice are an inbred strain in which the males spontaneously develop type 2 diabetes mellitus and moderate obesity. Nishida *et al* wondered whether TSOD mice might make a good NASH model. Examination of the livers of TSOD male mice revealed that they developed most of the histological hallmarks of NASH. There was minimal hepatic fibrosis and no progression to cirrhosis. However, the mice developed multifocal dysplastic nodules and lesions suggestive of HCC. Interestingly, steatosis appeared to decrease at about the same time the dysplastic nodules were arising. It appears that TSOD mice are a valuable tool with which to study the development of NASH and the evolution from dysplastic nodules to HCC, as well as to test possible interventions.

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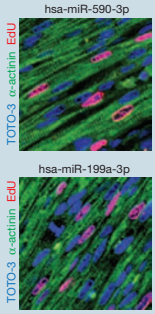
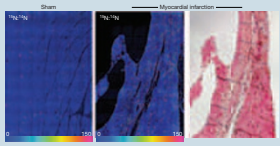
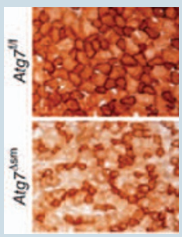


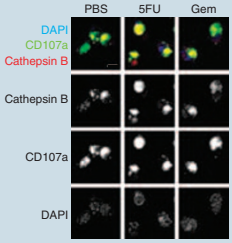
miRNAs induce cardiac regeneration To identify microRNAs (miRNAs) that were able to induce proliferation of cardiomyocytes (CMs), Eulalio *et al*, as described in a recent article in *Nature*, screened a library of miRNAs for the ability to increase proliferation in neonatal mouse and rat CMs. Surprisingly, some of the miRNAs also induced proliferation in postnatal CMs *in vitro*. Because of the limited ability of the heart to replace CMs lost after cardiac damage, the authors expressed these miRNAs in a mouse model of myocardial infarction. They found that, as compared with controls, ventricular wall thickness and cardiac function were preserved in mice that expressed miRNAs that induced proliferation in postnatal CMs *in vitro*. The authors concluded that these miRNAs promote proliferation of already differentiated CMs, thus enhancing the limited potential of these cells to proliferate after cardiac damage.
Nature 2012;492:376–381; doi:10.1038/nature11739



Renewal of the heart by preexisting cardiomyocytes Recent studies have demonstrated that heart cells are generated in adult mammals. However, the capacity for generation and the source of these cells are unknown. As reported in a recent letter in *Nature*, Senyo *et al* have identified a source and determined the frequency of cardiac myocytes generated in adult mammals. Using multi-isotope imaging mass spectrometry and lineage tracing in genetically engineered mice, they demonstrated that, contrary to what some researchers have thought, cardiomyocytes arise from pre-existing cardiomyocytes, not cardiac stem cells. Also, the capacity for renewal is relatively limited, amounting to a rate of 0.76% of cardiac cells per year. This number goes up slightly in areas adjacent to injured heart muscle, but not much, which might explain why hearts are not able to replace much damaged cardiac tissue after injury.
Nature, published online 5 December 2012; doi:10.1038/nature11682



Autophagy deficiency protects from obesity and insulin resistance Autophagy is an evolutionarily conserved process for degradation of aggregated proteins and recycling of organelles or nutrients that appears to be involved in many aspects of cellular homeostasis. To determine the metabolic role of autophagy in skeletal muscle, Kim *et al* generated a skeletal muscle–specific autophagy-deficient mouse. In the study, recently published in *Nature Medicine*, the authors found that autophagy deficiency in skeletal muscle caused mitochondrial stress which resulted in the secretion of fibroblast growth factor 21 (Fgf21). Fgf21, which the authors termed a mitokine, increased β-oxidation in white adipose tissue, which resulted in protection from insulin resistance induced by a high-fat diet. Mice with skeletal muscle–specific autophagy deficiency showed a pronounced decrease in fat mass, a resistance to obesity, and improved insulin deficiency.
Nature Medicine, published online 2 December 2012; doi:10.1038/nm.3014



The "dark side" of chemotherapy Chemotherapy acts directly on tumor cells, but it is nonselective and acts on nonneoplastic cells as well. In a study recently reported in *Nature Medicine*, Bruchard *et al* explored the "dark side" of chemotherapy that actually supports cancer instead of fighting it. They demonstrated that gemcitabine (Gem) and 5-fluorouracil (5FU) are toxic to myeloid-derived suppressor cells (MDSCs), immature myeloid cells that suppress T-cell activation. While some MDSCs die, others release interleukin-1β (IL-1β) as a result of lysosomal damage and subsequent activation of the NOD-like receptor family, pyrin domain containing–3 protein (NLRP3)-dependent caspase-1 activation complex (the inflammasome). IL-1β caused secretion of IL-17 by $CD4^+$ T cells, which blunted the antitumor immune response. The authors suggested that combining 5FU or Gem with IL-1β or NLRP3 inflammasome inhibitors might enhance their effectiveness.
Nature Medicine, published online 2 December 2012; doi:10.1038/nm.2999