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INSIDE LAB INVEST

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TGF-β regulates glucose-induced senescence of mesothelial cells in dialysis patients

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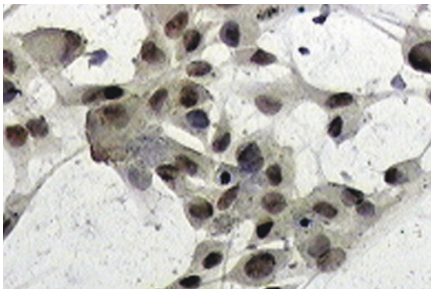

Continuous ambulatory peritoneal dialysis (CAPD) is an attractive treatment alternative for patients with chronic renal failure. However, there are growing concerns about the possible long-term effects of peritoneal dialysis fluids (PDFs) on the integrity and function of the peritoneal membrane. Despite improvements in the manufacturing of PDFs, glucose remains the preferred osmotic agent even with its possible unfavorable effects. It has been observed that peritoneal alterations in dialysis patients—including basement membrane thickening, vasculopathy, and accumulation of glycation end products—are similar to those seen in diabetics. Previous studies have demonstrated hypertrophy, reduced density, and reduced proliferative potential of mesothelial cells in rodents chronically exposed to glucose-containing PDF. These findings suggest that mesothelial cells may undergo accelerated senescence in response to high glucose concentrations. In this issue, Ksiazek *et al* examine the effect of high glucose concentration on primary cultures of human peritoneal mesothelial cells (HPMCs) obtained from non-uremic, nondiabetic patients undergoing elective abdominal surgery. Mesothelial cells grown under high-glucose conditions (30 mM) showed reduced cell proliferation and increased expression of the cell-cycle inhibitors p21Waf1 and p27Kip1 when compared with cells grown in standard medium (5mM glucose). Senescence-associated mesothelial cell hypertrophy was observed under high-glucose conditions along with increased expression of the senescence marker SA-β-Gal. HPMCs exposed to high glucose expressed and released increased TGF-β1, and exposure to exogenous TGF-β1 induced a senescent phenotype in these cells. The glucose-induced expression of SA-β-Gal was inhibited by antibodies to TGF-β1. These results suggest that high glucose in PDF may stimulate a senescence-like phenotype in peritoneal mesothelial cells and that this effect is mediated by a TGF-β1 pathway.

Mitochondrial POLG mutation, mtDNA depletion, and cardiomyopathy

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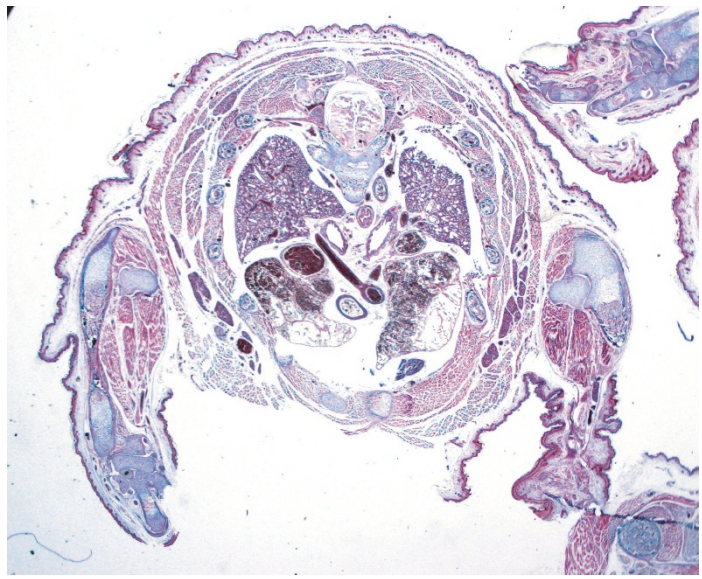
Mitochondria have their own genome, mitochondrial DNA (mtDNA), and most cells in the body contain from 10^3 to 10^4 copes of mtDNA. Mammalian mtDNA encodes 13 proteins essential for electron transport complexes as well as 22 tRNAs and 2 rRNAs necessary for the translation of these 13 proteins. Thus, mtDNA is essential for oxidative phosphorylation, and a loss of mtDNA will result in mitochondrial respiratory defects. mtDNA replication is catalyzed by DNA polymerase γ (Pol γ), which is encoded by the nuclear gene *POLG*. It is well known that pathogenic mutations in *POLG* cause a wide range of human diseases, including chronic progressive external ophthalmoplegia (CPEO), peripheral neuropathy, and parkinsonism. In clinical patients, Y955C is the most common and severe autosomal dominant mutation in the *POLG* gene. It is known that Y955C exhibits <1% of wild-type polymerase activity and works as a dominant mutation. To clarify the pathogeneic role of the Y955C mutant of *POLG*, Lewis *et al* generated transgenic mice expressing human Y955C *POLG* under the control of a cardiomyocyte-specific promoter (the alpha myosin heavy-chain promoter). The hearts of the transgenic mice were dysfunctional, demonstrating cardiomegaly, myocytolysis, and cardiomyocyte hypertrophy, and the animals died prematurely. Moreover, the study demonstrated depleted mtDNA in the transgenic heart accompanied by enhanced oxidative stress and ultrastructural abnormalities in mitochondria. The data clearly prove that the Y955C *POLG* mutation can indeed cause mtDNA depletion in animals and leads to myopathy and muscle dysfunction.



Not all c-kit mutations can be corrected by imatinib

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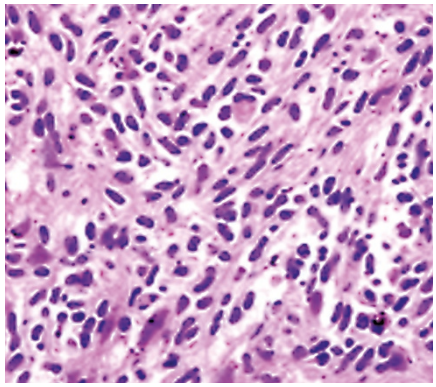

KIT-activating mutations are the driving force of human mast cell neoplasms and gastrointestinal stromal tumors (GISTs). In mast cell neoplasms, KIT mutations were found in the tyrosine kinase II domain, particularly confined to the codon 816. However, in some cases, mutations involving KIT juxtamembrane domain (JM) have also been reported. In this issue, Nakagomi and Hirota reported and characterized a rare KIT-JM missense mutation, Val559Ile, in aggressive systematic mastocytosis. The KIT codon 559 is a major "hot spot" for missense mutations in GISTs. A KIT tyrosine kinase inhibitor, imatinib mesylate, has been successfully used in the treatment of clinically advanced, metastatic GISTs. Based on *in vitro* experiments and clinical studies, KIT-JM mutants, including common Val559Asp KIT mutant, do not show resistance to imatinib. In the current study, *in vitro* experiments demonstrated that Val559Ile KIT mutant is resistant to imatinib. These results add a significant piece to the puzzle of mutational KIT activation and tyrosine kinase inhibition, indicating that different substitutions at the same KIT-JM codon lead to differences in imatinib sensitivity. Further studies in this area may help us understand how structural changes of KIT-JM affect inhibition of KIT tyrosine kinase domains. Jerzy Lasota, Armed Forces Institute of Pathology, Washington, DC

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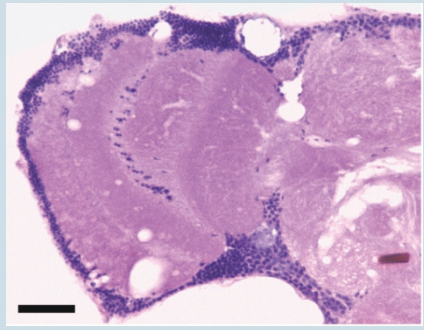
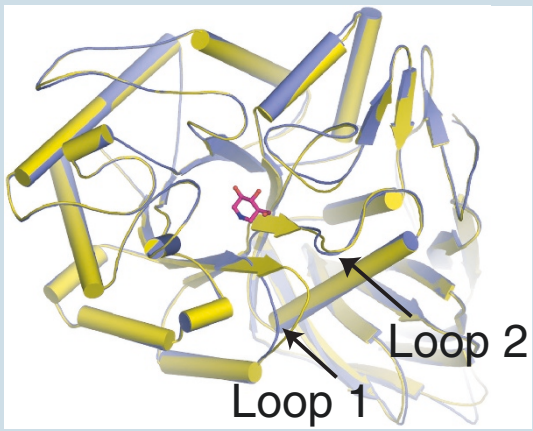
Untangling Alzheimer's disease



Recent research has provided new insight Alzheimer's disease (AD). Hyperphosphorylated forms of the microtubule-associated protein tau accumulate in AD, and the extent of accumulation correlates with neuronal loss. A recent *Nature Cell Biology* article reported that interaction between tau and actin may be critical to neurotoxicity. Tau also interacts with amyloid β peptide (Aβ), a neurotoxic protein linked to AD. A *Nature Genetics* study found that APP is targeted to Aβ-generating compartments when the SORL1 sorting receptor is underexpressed. SORL1 variants were associated with familial late-onset AD, suggesting that SORL1 dysfunction contributes to AD.

Nature Cell Biology, 24 December 2006; doi: 10.1038/ncb1528
Nature Genetics, 14 January 2007; doi: 10.1038/ng1943



A chemical chaperone provides novel therapeutic opportunities in Gaucher's disease Gaucher's disease (GD) results from mutations of the lysosomal enzyme acid β-glucosidase (GCase) that interfere with trafficking, stability and/or intrinsic activity. A letter in *Nature Chemical Biology* reported that binding of isofagomine (IFG) to N370S GCase, one of the two most prevalent GD-associated mutations, increases GCase activity and corrects trafficking. Crystallography suggested that IFG locks GCase in a substrate-bound conformation. Beyond the potential for GD therapy, these data suggest that other diseases characterized by protein misfolding or mistrafficking may also be treated with small molecules that stabilize specific protein conformations.

Nature Chemical Biology 2007, 3: 101-107.

***H. pylori*, a more daunting foe than the British Empire** Explanations for Napoleon Bonaparte's death have ranged from arsenic poisoning to inappropriate medical treatment. A case report, including autopsy data, in *Nature Clinical Practice Gastroenterology & Hepatology*, has concluded that Napoleon's demise was due to *H. pylori*-associated gastritis and gastric adenocarcinoma. Could the gastritis be why Napoleon was often painted with his hand to his gut?

Nature Clinical Practice Gastroenterology & Hepatology 2007, 4: 52-57.