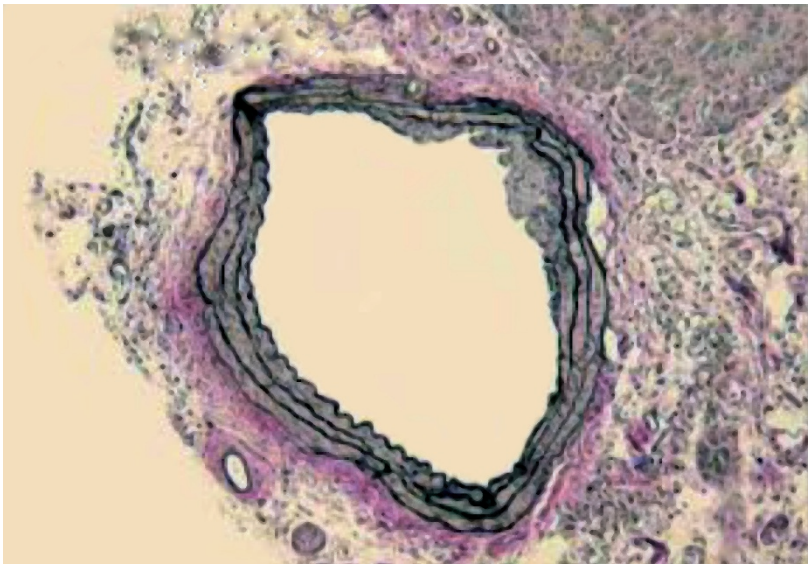
**Laboratory Investigation (2009) 89**, 254-255


# INSIDE LI

doi:10.1038/labinvest.2009.9



## Too much of a good thing?: excess collagen promotes aortic aneurysms

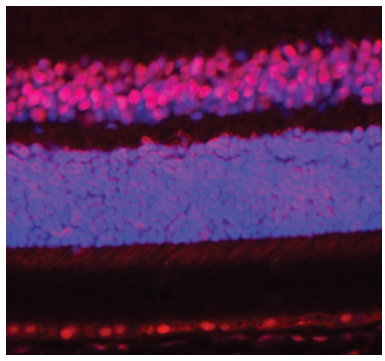
See page 315

Increasing evidence has implicated excess arterial collagen in the pathogenesis of aortic aneurysm formation, a clinically important disease with potentially disastrous consequences. However, it has not been determined whether the link is causal. To determine whether excess collagen can promote aortic aneurysm formation *in vivo*, Deguchi and colleagues devised an ingenious strategy employing genetically engineered mice. Previous work has shown that apolipoprotein E–deficient ($ApoE^{-/-}$) mice develop aortic aneurysms after infusion with angiotensin II (AngII). To examine the effect of excess collagen formation on aortic aneurysm development, the $ApoE^{-/-}$ mouse strain was intercrossed with a strain harboring a mutation in type I collagen ($Col^{R/R}$) that confers resistance to cleavage/degradation, resulting in type I collagen accumulation. Type I collagen is a major constituent of the aortic wall. After treatment with AngII, the $Col^{R/R}/ApoE^{-/-}$ mice developed more and larger aortic aneurysms than $ApoE^{-/-}$ mice with wild-type collagenase I. Furthermore, the collagen in the aneurysms of $Col^{R/R}/ApoE^{-/-}$ mice was disordered, and the aneurysms were stiffer and more prone to rupture. The data make a convincing case for a causative role for increased collagen in aortic aneurysm. Further work to identify the cause of increased collagen formation could lead to the development of therapeutic interventions aimed at decreasing collagen formation and/or increasing collagen degradation.

## Sending out an SOS: danger signals and retinal detachment

See page 278

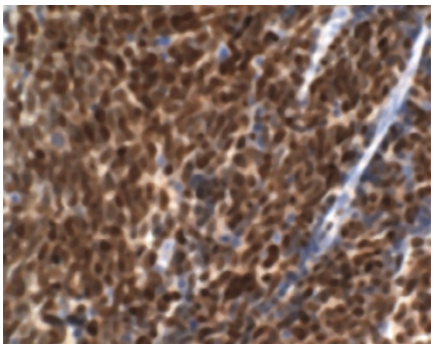
Retinal detachment, defined as the physical separation of photoreceptors from the underlying retinal pigment epithelium (RPE), is one of the major causes of human vision loss. High-mobility group box 1 protein (HMGB1) is a ubiquitous nuclear DNA–binding protein that has multiple other functions that are dependent on its cellular location. In damaged tissue, HMBG1 acts to signal the surrounding cells and the immune system and has been implicated in the pathogenesis of a variety of diseases. Arimura and colleagues have focused their attention on the roles of HMBG1 in retinal detachment. Using both *in vitro* and *in vivo* rat model studies, as well as analysis of human vitreous samples, they have shown that HMBG1 expression is increased in damaged retinal cells, presumably helping the cells to cope with damage. Furthermore, HMBG1 is released into the surrounding vitreous. Both HMBG1 and monocyte chemoattractant protein 1 (MCP1) were shown to stimulate RPE migration via the MAP kinase pathway. The authors hypothesize that RPE migration is part of the pathological wound healing response to retinal damage that contributes to retinal detachment. Although many details remain unanswered, such as the relationship of HMBG1 expression to MCP1 expression, these results provide an excellent paradigm for the development of further studies.



## PAX5 and small-cell lung cancer

See page 301

The PAX proteins are a family of nine nuclear transcription factors involved primarily in development. Increasingly, they are recognized as playing roles in the pathogenesis of various cancers. Kanteti and colleagues investigated the expression of *PAX* genes in a group of malignant upper aerodigestive neoplasms and pancreatic cancer and found that PAX5 was expressed exclusively in small-cell lung cancer (SCLC). On the basis of this finding, PAX5 expression was evaluated in other neuroendocrine tumors of the lung.

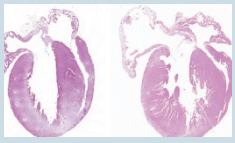


PAX5 was identified in 27% of carcinoid, 55% of large-cell neuroendocrine cancer, and 66% of SCLC tumor tissue samples. An increase in *PAX5* gene copy number was seen in 70% of SCLC samples. However, no gene rearrangements/translocations involving *PAX5* were identified. Furthermore, activating mutations in *PAX5* do not appear to play a role in SCLC.

Since c-Met is important in the pathogenesis of SCLC, the relationship between PAX5 and c-Met was also investigated. PAX5 was found to positively regulate c-Met expression, and inhibition of PAX5 by small interfering RNA led to a decrease in c-Met expression. Furthermore, SU11274, a c-Met inhibitor, and SN38, a potent topoisomerase I inhibitor, were found to synergize therapeutically with *PAX5* knockdown, suggesting that targeting PAX5 could be useful therapeutically. Finally, it was suggested that PAX5 and PAX8 could be diagnostically useful to distinguish between SCLC and non-small-cell lung cancer (NSCLC) given that NSCLC did not express PAX5 but uniformly expressed PAX8.

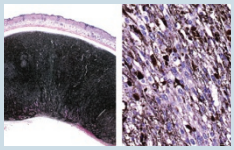
# nature.com/pathology

**Cell signaling and cardiac hypertrophy** The extracellular regulated kinases ERK1 and ERK2 (ERK1/2) are known to play important roles in cardiac hypertrophy. However, we do not yet fully understand how generic signal transducing mechanisms such as ERK1/2 signaling can lead to cardiac hypertrophy and other specific phenotypic consequences. In a recent article in *Nature Medicine*, Lorenz and colleagues pieced together a plausible mechanism for the specificity of ERK1/2 activation in cardiac hypertrophy. It turns out that receptor tyrosine kinase input is transduced through G protein βγ subunits released from activated $G_q$, resulting in ERK1/2 autophosphorylation on Thr188 and translocation to the nucleus to phosphorylate nuclear targets involved in cardiac hypertrophy. This elegant mechanism is explored in a variety of cell culture and transgenic mouse models and in failing human hearts. The findings have the potential to translate into therapeutic strategies for modifying cardiac hypertrophy.



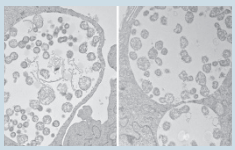
*Nature Medicine* 2009;15:75–83; doi:10.1038/nm.1893

**Genetic basis of uveal melanoma and blue nevi** Uveal melanomas are an uncommon subset of melanomas that originate from the choroidal plexus of the eye. In contrast to melanoma in sun-exposed skin, *BRAF* and *NRAS* mutations are not found within uveal melanomas. Another subset of melanocytic neoplasms that do not show such mutations is blue nevi. Previous work has shown that hypermorphic *Gnaq* mouse mutations lead to hyperpigmented mice with increased intradermal melanocytes. This led Van Raamsdonk and colleagues to wonder, in a recent letter in *Nature*, whether a subset of human nevi/melanomas might contain *GNAQ* mutations. DNA sequence analysis identified *GNAQ* mutations exclusively in codon 209 in 83% of blue nevi, 50% of malignant blue nevi, and 46% of uveal melanomas. The mutations were oncogenic and tumorigenic in nude mice and resulted in increased mitogen-activated protein kinase signaling, suggesting a therapeutic strategy for the treatment of uveal melanoma.



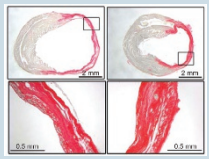
*Nature* 2009;457:599–602; doi:10.1038/nature07586

**Subversion of the Golgi by *Chlamydia*** Intracellular pathogens frequently learn to exploit their host cell environment. In a recent letter in *Nature*, Heuer and colleagues identified a particularly striking example involving the intracellular pathogen *Chlamydia trachomatis*. They found that *Chlamydia* induces cleavage of a Golgi matrix protein, golgin-84, leading to Golgi fragmentation. Golgin-84 appears to be cleaved by both inflammatory caspases and calpains. The overall goal of Golgi fragmentation seems to be the transport of sphingolipids to the bacterial inclusion, which enhances chlamydial growth regulation, development, and reproduction. The involvement of host cell caspases and calpains highlights potential targets for therapy.



*Nature*, published online 7 December 2008; doi:10.1038/nature07578

**New insights into mechanism of fibrosis in myocardial infarction** Secreted Frizzled-related proteins (sFRPs) have been thought to function mainly as inhibitors of Wnt-mediated signal transduction. However, recent studies in *Xenopus* and zebrafish suggested that FRPs might also function as inhibitors of Tolloid (TLD) family metalloproteinases. In a recent article in *Nature Cell Biology*, Kobayashi and colleagues investigated the ability of mammalian sFRP2 to inhibit cleavage of substrates of TLD-like proteinases. In contrast to what was found with *Xenopus* and zebrafish FRPs, they found that sFRP2 actually enhanced cleavage of procollagen C proteinase activity, a TLD-like proteinase activity. On the basis of these results, they sought to determine the relevance of sFRP2 function *in vivo*. Evaluation of a myocardial infarction (MI) model in an sFRP2 knockout mouse revealed significantly less fibrosis after MI and improved heart function compared with FRP2 wild-type mice. Since post-MI myocardial fibrosis contributes significantly to the morbidity and mortality associated with MI, inhibition of fibrosis through antagonism of sFRP2 function might have significant clinical benefit.



*Nature Cell Biology* 2009;11:46–55; doi:10.1038/ncb1811