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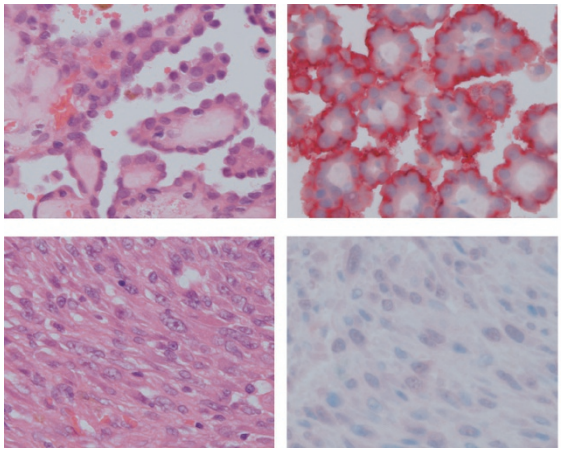

Loss of *CDKN2A/2B* in iron-induced rat mesothelioma model

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Mesothelioma, a malignant neoplasm arising from mesothelial cells, is an aggressive and devastating cancer associated with exposure to asbestos fibers. One hypothesis regarding the pathogenesis of asbestos-mediated mesothelioma—the oxidative stress theory—proposes that mineral substances in asbestos are phagocytosed by macrophages, which are unable to ingest them, resulting in the generation of massive amounts of DNA-damaging reactive oxygen species. Asbestos fibers are rich in iron, and it is known that asbestos fibers with higher amounts of iron are more carcinogenic. To more fully elucidate the mechanisms of carcinogenesis of mesothelioma, Hu and colleagues used a rat model in which iron is delivered intraperitoneally to induce peritoneal mesothelioma.

The authors observed that rats developed two morphologically distinct types of mesothelioma: papillary epithelioid mesothelioma (EM), which arose from the region of the tunica vaginalis and expanded upward, and sarcomatoid mesothelioma (SM), which was associated with intra-abdominal organs such as the stomach and spleen. The sarcomatoid mesotheliomas were much more aggressive; they usually resulted in death due to intestinal obstruction. Array-based comparative genomic hybridization analyses revealed that EMs were comparatively simple genetically and SMs were much more complex. Notably, loss of *CDKN2A/2B* was frequently observed, a finding that is also characteristic of human mesothelioma. Hu *et al*. present DNA-based evidence that the iron treatments result in oxidative DNA damage. They conclude that this model will be useful for studying how oxidative DNA damage catalyzed by iron leads to deletion of *CDKN2A/2B*.

Putting the brakes on inflammatory cell motility

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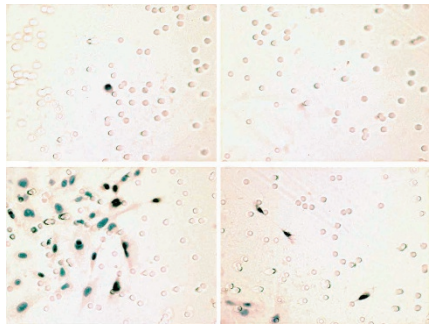
Inflammation is initiated by release of proinflammatory substances in response to tissue injury or to pathogens. To produce an effective response, leukocytes exit the circulation and invade and migrate through tissues to travel to the site of injury or infection, where they participate in the inflammatory response. Motility, which is absolutely critical to the function of leukocytes, is mediated through the interaction of nonmuscle myosin II (NMII), an adenosine triphosphate–driven molecular motor, with the actin cytoskeleton. In order to investigate the role of motility in inflammation, Si and colleagues used blebbistatin, a small-molecule NMII inhibitor, both *in vitro* and *in vivo*.

The authors found that blebbistatin induced actinomyosin disassembly in a human leukemia cell line, a human T-lymphocyte cell line, and a rat macrophage cell line. Furthermore, blebbistatin inhibited migration and invasion of cytokine-stimulated rat macrophage cells *in vitro*. *In vivo* administration of blebbistatin suppressed acute inflammation in a tumor necrosis factor–induced acute kidney inflammation rat model and in a rat obstructive nephropathy model.



Examination of rat kidneys revealed that blebbistatin directly affected the ability of macrophages to infiltrate the kidney. In summary, these important studies highlight the requirement of cell motility in the inflammatory response and suggest that blebbistatin might be effective in the reduction of excessive inflammation, which can lead to chronic renal injury.

Estrogen opposes Fas-mediated bone loss

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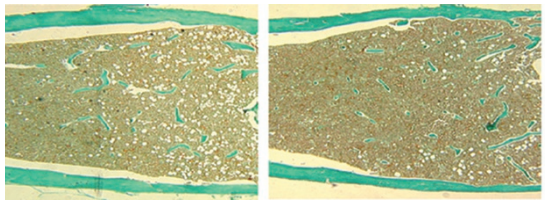
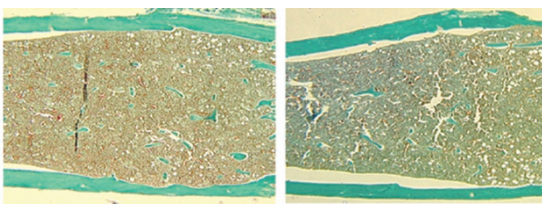
Osteoporosis, which is characterized by loss of bone mass, is thought to affect as



many as 28 million Americans and is a risk factor for fractures after falling in the elderly. Such fractures often result in serious morbidity and can even lead to death. Osteoporosis is a problem in postmenopausal women in particular, as estrogen is important in regulating bone mass. Bone mass is maintained through the opposing forces of bone formation, mediated by osteoblasts, and bone loss, mediated by osteoclasts. Previous work has shown that human postmenopausal osteoblasts constitutively express Fas, a death receptor that activates the extrinsic apoptosis pathway. In addition, Fas has been shown to inhibit osteoblast differentiation. On the basis of these findings, Kovacic and colleagues asked whether the effects of estrogen on bone mass were mediated through Fas.

Using an ovariectomized mouse model, the authors studied the effects of estrogen withdrawal in wild-type and Fas-deficient knockout mice. They demonstrated that the effects of estrogen were mediated through Fas. Interestingly, bone loss was not seen in ovariectomized Fas-deficient mice, as opposed to wild-type mice, which developed rapid loss of bone density. Fas appeared to be a positive regulator of osteoclastogenesis, but it had a negative effect on osteoblastogenesis. Whereas the effect on osteoblasts appeared to be direct, leading to decreased osteoblastic differentiation and increased apoptosis, the effect on osteoclastogenesis appeared to be indirect. Further work will be required to define the precise mechanisms involved in the estrogen-mediated regulation of osteoclasts and osteoblasts through Fas.



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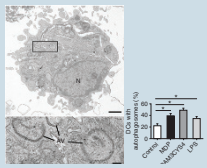
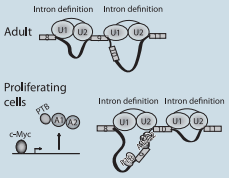


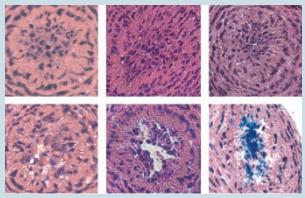
Defects in autophagy linked to Crohn's disease Polymorphisms within nucleotide-binding oligomerization domain–containing-2 (NOD2), an intracellular pattern-recognition receptor, are associated with Crohn's disease (CD). Recent large-scale population studies have identified two additional CD-susceptibility variants, ATG16L1 and GTPase family M, which function in autophagy, a cellular digestion process involved in many cellular processes, including bacterial defense. To link these CD-susceptibility variants into one common pathway, Cooney and colleagues, reporting in a recent article in *Nature Medicine*, demonstrated that NOD2 induced autophagy in dendritic cells (DCs) in response to its bacterial ligand. Furthermore, DCs from patients with defects in either NOD2 or ATG16L1 were functionally impaired. The authors suggested a mechanism whereby NOD2 influences bacterial degradation and interacts with the major histocompatibility complex class II antigen-presentation machinery within DCs.

Nature Medicine 2010;16:90–97; doi:10.1038/nm.2069



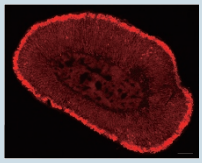
Mechanism of pyruvate kinase mRNA splicing in cancer Whereas normal, quiescent cells extract energy from glucose primarily by oxidative phosphorylation, tumor cells consume glucose more rapidly, converting it to lactate (the "Warburg effect"). Recently, it has been shown that aerobic glycolysis is mediated through the generation of distinct isoforms of pyruvate kinase (PKM) generated by alternative splicing. PKM1 includes exon 9, whereas PKM2 uses exon 10. In a recent letter in *Nature*, David and colleagues report their finding that three heterogeneous nuclear ribonucleoproteins bind to sequences flanking exon 9, resulting in inhibition of exon 9 splicing and subsequent splicing to exon 10. These results indicate a plausible mechanism through which tumor oncogenes can ensure aerobic glycolysis in actively proliferating tumor cells.

Nature 2010;463:364–368; doi:10.1038/nature08697



Platelets play crucial role in postnatal closing of ductus arteriosus Failure of the ductus arteriosus (DA) to close after birth is the most common form of congenital heart disease in preterm infants. DA closure is a two-step process. In the first step, "provisional" closure results from smooth muscle contraction, which constricts the DA. This is followed by anatomical remodeling of the lumen and permanent closure. In a recent article in *Nature Medicine*, Echtler and colleagues hypothesized that platelets might have an important function in permanent closure of the DA. They found that platelets aggregated abundantly in the DA and that mice harboring platelets with functional defects had higher rates of patent DA than littermate controls. Retrospective examination of a cohort of preterm infants revealed that low platelet counts were associated with a 13-fold increase in the risk of failure of the DA to close postnatally.

Nature Medicine 2010;16:75–82; doi:10.1038/nm.2060



Defects in the circadian clock expose the importance of Hsd3b6 in salt-sensitive hypertension The circadian clock is thought to control the expression of 10% of the transcriptome. Using a *Cry*-null mouse model that lacks the core clock components, Doi and colleagues, as described in a recent article in *Nature Medicine*, sought to understand why plasma aldosterone levels were chronically elevated in these mice. Utilizing expression arrays, they showed that type VI 3β-hydroxyl-steroid dehydrogenase (Hsd3b6), encoding a key protein in aldosterone biosynthesis, was elevated specifically in aldosterone-producing cells. Furthermore, *Cry*-null mice had salt-sensitive hypertension that was reduced by an Hsd3b6 inhibitor. The clinical attributes of these mice share many similarities with a human condition known as idiopathic aldosteronism. Importantly, the authors identified the human homologue of *Hsd3b6, HSD3B1*, an important step in determining whether *HSD3B1* is involved in salt-sensitive hypertension and idiopathic hyperaldosteronism in humans.

Nature Medicine 2010;16:67–74; doi:10.1038/nm.2061