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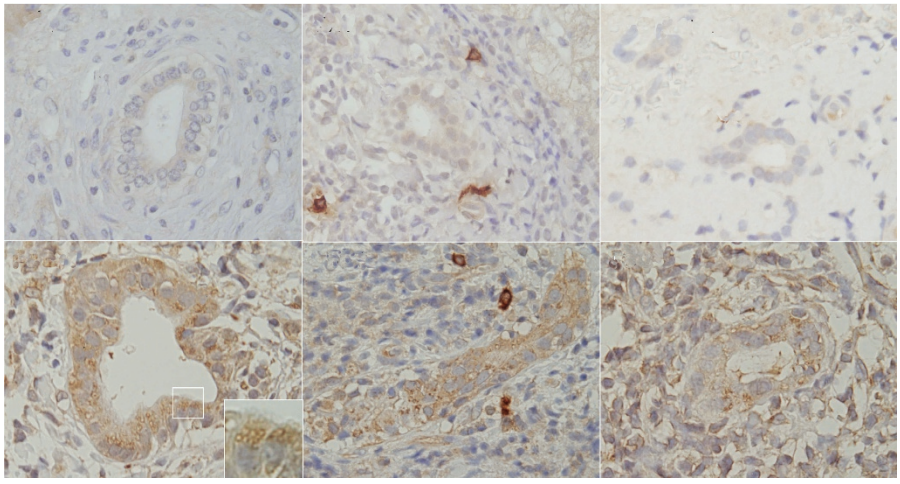

Autophagy mediates biliary epithelial senescence in primary biliary cirrhosis

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Autophagy, which literally means "self-eating," is an evolutionarily conserved process that results from various cellular stresses such as nutrient damage and activation of the endoplasmic reticulum stress pathway. It is characterized by double membrane–bound vesicles known as autophagosomes, which are the hallmark of autophagy. During stresses such as nutrient deprivation or mitochondrial damage, autophagy is activated and organelles are sequestered in autophagosomes and digested by fusion with lysosomes to either generate energy or contain collateral damage, such as induction of apoptosis due to damaged mitochondria. Recently, autophagy has been shown to mediate cellular senescence. Nakanuma and colleagues have previously observed that biliary epithelial cells (BECs) in damaged bile ducts of patients with primary biliary cirrhosis (PBC) undergo cellular senescence. In the current work by the same group, Sasaki *et al* ask whether autophagy mediates cellular senescence in BECs. They showed that markers of autophagy are identified preferentially in biliary epithelium in PBC patients as compared with normal controls, and that markers of autophagy were localized to inflamed as compared with noninflamed bile ducts. Factors known to induce cellular senescence were able to induce autophagy in BECs cultured *in vitro*. Inhibition of autophagy by pharmacological inhibitors decreased cellular senescence. The authors suggest a model whereby autophagy induces cellular senescence in response to bile duct damage. A major question related to this work is how autophagy/cellular senescence is related to the autoimmune etiology proposed for PBC.

Profibrotic monocytes in systemic sclerosis and aging

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Circulating, bone marrow–derived $CD45^+CD14^+$ monocytic precursors can give rise to profibrotic cells, including fibrocytes and alternatively activated macrophages (M2 type). These cells are known to be involved in the pathogenesis of progressive fibrotic diseases, but their relative contribution is unclear and their physiologic function in healthy subjects has been elucidated only in part. Mathai and colleagues provide novel and important information on the phenotypic and functional characteristics of the profibrotic monocytes present in increased numbers in the peripheral blood of patients suffering from systemic sclerosis with fibrotic lung involvement and in the blood of apparently normal individuals older than 60 years. In patients with systemic sclerosis, the population of circulating $CD45^+$ pro-collagen $I\alpha^+$ cells is composed predominantly of CD34-positive cells that are either CD14-negative or express this monocyte marker to varying degrees, probably reflecting various stages of maturation of fibrocytes from the $CD14^+$ precursor of the monocyte lineage. In contrast, the circulating population of $CD45^+$ pro-collagen $I\alpha^+$ cells in aged individuals is composed mainly of $CD14^+CD34^-$ and $CD14^-CD34^-$ mononuclear cells. In both groups of subjects, circulating $CD14^+$ monocytes lacking the morphological features of fibrocytes also release profibrotic cytokines and acquire the phenotype of M2-type macrophages upon *in vitro* exposure to a stimulus that does not specifically induce M2 polarization. Further investigations in this area of research may uncover pathways critically involved in the pathogenesis of systemic sclerosis and important mechanisms of normal aging.

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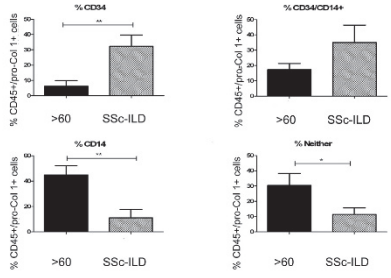

α9 Integrin blockade and wound healing

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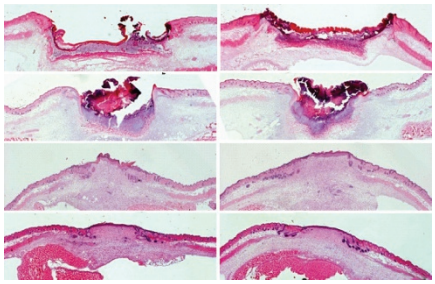
Wound healing can be broken down into three discrete phases: an initial inflammatory response and

re-epithelialization, formation of granulation tissue and accompanying neovascularization, and, finally, wound contraction. Although much progress has been made in understanding the basic mechanisms of wound healing, many questions remain. There has recently been considerable progress in our understanding of the role of extracellular matrix (ECM) in wound healing. Increasingly, the ECM is appreciated to be a dynamic structure that continually remodels in response to various stimuli. Integrins (cell surface receptors) have been shown to mediate a variety of cell–ECM interactions. Recently, α9 (also known as α9β1) integrin has been shown to be present on the surface of



keratinocytes within wound tissue. To elucidate the role of α9 integrin in wound healing, Nakayama and colleagues sought to determine what would happen when they blocked the action of α9 integrin with a blocking monoclonal antibody in a murine wound healing model. Surprisingly, they discovered that α9 integrin blockade specifically affected the middle granulation tissue phase of wound healing. They attributed the defect to deficiencies in dermal fibrocyte migration; dermal fibrocytes were found to have α9 integrin on their surface. Furthermore, they investigated whether bone marrow–derived circulating fibrocytes might be the ultimate source of the fibrocytes found in granulation tissue. However, these cells did not possess α9 integrin, suggesting that bone marrow is not the ultimate source of these fibrocytes.

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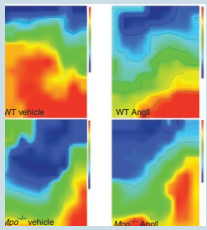
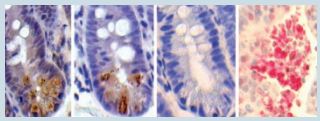
Myeloperoxidase is a primary mediator of atrial fibrillation



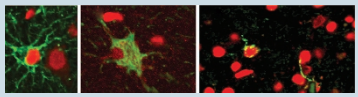
Atrial fibrillation (AF) is the most common arrhythmia in humans. Considerable evidence suggests that AF is an inflammatory disorder. Mechanistically, AF appears to be induced by inflammatory-mediated atrial fibrosis, which is induced by the action of matrix metalloproteinases (MMPs) on extracellular matrix. Recent reports suggest that leukocyte-derived myeloperoxidase (MPO) is a crucial regulator of MMPs by generating hypochlorous acid. On the basis of these findings, Baldus and colleagues, as described in a recent letter in *Nature Medicine*, investigated the contribution of MPO to atrial fibrillation. They showed that MPO-deficient mice developed less atrial fibrosis and AF in response to angiotensin II, an effector of atrial remodeling and fibrosis. Continuous infusion of MPO in MPO-deficient mice restored their vulnerability to atrial fibrosis and AF. These results suggest that MPO may be a therapeutic target for the treatment of AF.
Nature Medicine 2010;16:470–474; doi:10.1038/nm.2124

Chemoprevention by induction of apoptosis in APC-deficient colorectal carcinoma cells

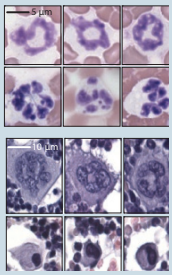


Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) is a membrane-bound TNF-family ligand that induces apoptosis in cancer cells but not in normal cells. To test the potential of TRAIL in the prevention of cancer, Wu and colleagues explored the possibility that TRAIL might induce apoptosis in premalignant primary adenoma cells from Apc^{Min} mice. Although TRAIL alone failed to induce apoptosis, TRAIL combined with all-*trans*-retinal acetate (RAc) sensitized premalignant primary adenoma cells to apoptosis. Furthermore, short-term, noncontinuous TRAIL and RAc therapy inhibited the growth of intestinal polyps and prolonged survival in Apc^{Min} mice and induced apoptosis in explanted human polyps from patients with human familial adenomatous polyposis. Together these results provide strong evidence that TRAIL and RAc cotreatment might be a useful chemopreventive strategy in patients with human adenomatous polyposis.
Nature 2010;464:1058–1061; doi:10.1038/nature08871

TLR4 and HMGB1 are involved in neuronal seizure formation



Toll-like receptors (TLRs) have a key role in pathogen recognition by recognizing pathogen-associated molecules that trigger TLR signaling and trigger inflammation by inducing transcription of inflammatory cytokines. Recent work has shown that TLRs can bind molecules released by injured tissue such as high-mobility group box-1 (HMGB1), which is released by necrotic cells. In a recent article in *Nature Medicine*, Vezzani and colleagues show that proconvulsive stimuli lead to HMBG1 and TLR4 activation, contributing to seizures in different mouse models of acute and chronic seizures. Their results suggest that targeting the HMBG1–TLR4 axis might be useful in the treatment of refractory epilepsy.
Nature Medicine 2010;16:413–419; doi:10.1038/nm.2127



The bone microenvironment can contribute to myelodysplasia and leukemia As reported recently in *Nature*, Scadden and colleagues sought to understand the influence of the bone microenvironment on hematopoietic development. In a mouse model in which osteoblastic differentiation was impaired by osteoprogenitor specific deletion of *Dicer1*, they discovered that mice developed myelodysplastic syndrome (MDS) and, rarely, secondary acute myeloid leukemia (AML). Analysis showed that the bone marrow and leukemias did not harbor *Dicer1* deletions, confirming that the dysplasia and leukemia were secondary to impaired bone microenvironment. Expression analysis of osteolineage cells from *Dicer1*-deficient mice showed significant downregulation of the Schwachman-Bodian-Diamond syndrome (*Sbds*) gene. This is of considerable interest because inactivating mutations of human *SBDS* are associated with a syndrome of skeletal abnormalities, bone marrow failure, and a propensity to develop MDS and AML, suggesting that the findings seen in the mouse models might also apply to humans.
Nature 2010;464: 852–857; doi:10.1038/nature08851