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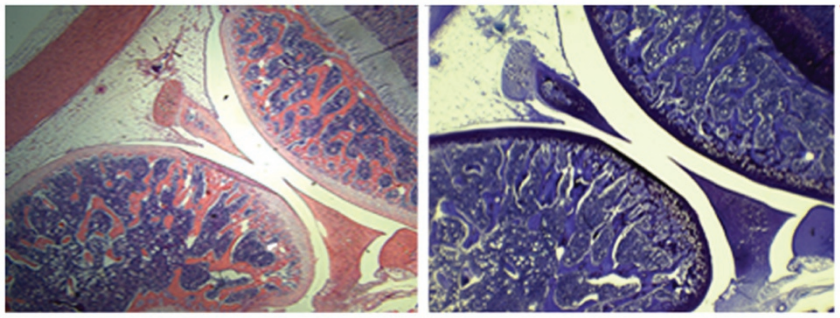


TGF-β1 induces arthrofibrosis and chondrometaplasia *in vivo*

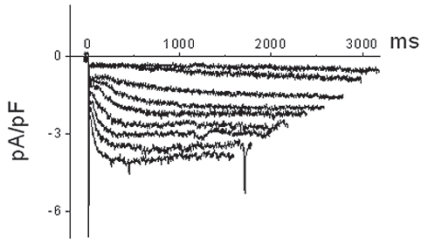
See page 1615

Arthrofibrosis is characterized by the production of excess fibrous tissue within joints, which leads to chronic pain and loss of motion. Although the etiology is unknown, the onset of arthrofibrosis is associated with injury, surgery, diabetes, and immobilization. Transforming growth factor-β1 (TGF-β1) has been implicated as having an important role in many types of pathologic fibrosis throughout the body; it is thought to orchestrate its effects primarily through Smad signaling by targeting the production of extracellular matrix proteins (ECMs) and other proteins, such as connective-tissue growth factor.

To test the hypothesis that expression of TGF-β1 drives arthrofibrosis, Watson *et al* used a recombinant adenovirus to deliver and express TGF-β1 in the joints of athymic nude rats. They found that the rats rapidly developed pathologic fibrosis which, as it advanced, underwent chondrometaplasia and invaded structures within the joint. This process paralleled arthrofibrosis in humans very well. To study the underlying molecular events, the authors analyzed RNA expression from fibrotic tissues. They discovered that many genes were overexpressed in fibrotic tissues, including laminins and ECM proteins. Interestingly, as the cells underwent chondrometaplasia, there was a parallel increase in genes involved in chondrocyte differentiation and maturation. There was also evidence to support the conclusion that the proliferating fibroblasts that generated the fibrous tissue originated locally from the joint, not from circulating stem cells. This arthrofibrosis model is certain to yield many insights into the biology of arthrofibrosis as well as supply a much-needed model with which to test various therapeutic strategies.

Examination of postnatal hearts after exposure to carbon monoxide

See page 1582



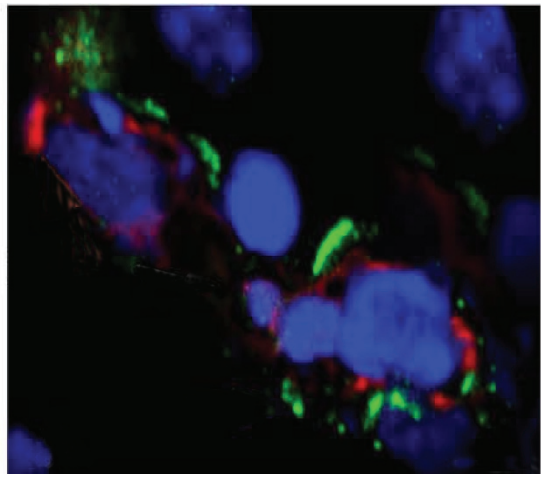
Maternal smoking during pregnancy is the most important independent risk factor for sudden infant death syndrome (SIDS). Maternal smoking exposes the fetus to a number of toxic chemicals, including carbon monoxide (CO). CO has a fourfold higher affinity for fetal than maternal hemoglobin. To model the effects of CO on the fetus, Sartiani *et al* exposed pregnant rats to CO, which they had previously found to delay cardiomyocyte maturation.

To investigate the molecular mechanism responsible for delayed cardiomyocyte maturation, the authors examined gene expression patterns in the hearts of offspring of female rats that were exposed to CO at several time points after birth. They found dramatic alterations in the gene expression profile, particularly in genes within pathways controlling the cell cycle and excitation–contraction coupling. Because cardiomyocytes stop proliferating soon after birth, changes in genes controlling the cell cycle could have deleterious effects on cardiomyocyte maturation and function. Changes in genes involved in excitation–contraction could be responsible for generating fatal arrhythmias, which would be consistent with SIDS. Electrophysiological evaluation of cardiomyocytes from CO-exposed rats demonstrated abnormalities consistent with delayed maturation. Much work remains to be done, but these fascinating studies provide a framework in which to dissect the important downstream effects of fetal CO exposure.

Mechanism of blood–brain-barrier defects in mdx mice

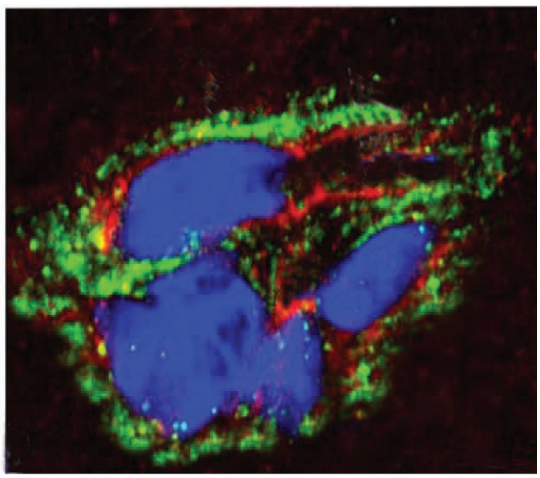
See page 1645

Duchenne muscular dystrophy (DMD), which affects one in 3,500 males, is an X-linked recessive form of muscular dystrophy characterized by severe



muscle degeneration, eventually leading to death. DMD is caused by a mutation in the dystrophin gene at Xp21, which encodes the dystrophin protein. This is a large protein that is at the core of a protein complex that connects the cytoskeleton to the extracellular matrix through the cell membrane. All DMD patients experience muscle wasting, but a smaller subgroup experiences cognitive defects that have been linked to defects in the blood–brain barrier (BBB), a functional barrier that prevents the diffusion of large molecules across the capillary wall into the cerebrospinal fluid of the brain. Central to the function of the BBB are glial cells that interact with endothelial cells through perivascular endfeet. The BBB is known to be abnormal in mdx mice, a mouse model of DMD.

Nico *et al* hypothesized that dystrophin-associated proteins (DAPs) might be altered in mdx mice, which would link DAPs to BBB function. They demonstrated that several DAPs had reduced RNA expression and protein levels on basement membrane and glial endfeet and that the basement membrane was thickened and discontinuous. These results suggest that dystrophin deficiency results in DAP defects. Further studies are necessary to determine whether basement membrane defects result in DAP alterations or if they are caused directly by changes in the basement membrane.



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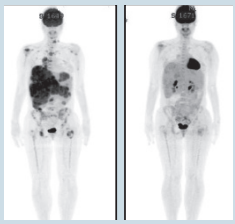
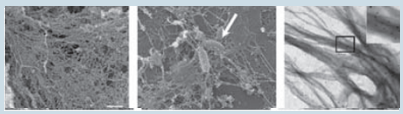
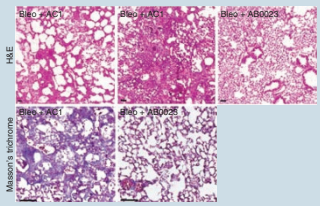


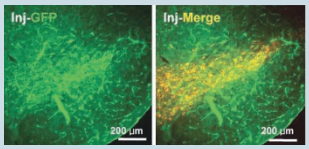
Breakthrough in melanoma therapy The protein kinase B-RAF is frequently mutated in malignant melanoma. PLX4032 is a B-RAF kinase inhibitor that preferentially inhibits the mutant form of B-RAF. In a recent letter in *Nature*, Bollag *et al* describe the initial clinical evaluation of PLX4032 in a cohort of metastatic melanoma patients. They found that at the maximal tolerated dose (MTD) PLX4032 inhibited mutant B-RAF. Furthermore, two-thirds of patients treated at the MTD exhibited tumor regressions quantified as partial responses, and 2 of 32 patients exhibited a complete response. The median progression-free survival was estimated to be at least 7 months. However, many patients experienced tumor regrowth. In order to increase the duration of response, combination therapies with other targeted agents, immunotherapy, or traditional chemotherapy will be explored.
Nature, published online 7 September 2010; doi:10.1038/nature09454



Novel insight into cystic fibrosis pathogenesis Neutrophil extracellular traps (NETs) consist of nuclear DNA decorated with characteristic granule proteins. Recently, neutrophils have been shown to capture bacteria extracellularly through NET formation (NETosis). In a recent letter in *Nature Medicine*, Marcos and colleagues report their discovery of the mechanism of NETosis in neutrophils. They found that the G protein–coupled chemokine receptor CXCR2 mediated NET formation through an Src family kinase and, to a lesser extent, mitogen-activated protein kinase signal transduction mechanism. When the authors examined airway fluids from patients with cystic fibrosis, they found that airway NETosis was inversely associated with pulmonary function. Using a mouse cystic fibrosis model, they found that blockade of CXCR2 in airway neutrophils decreased NETosis and reduced the severity of disease without impairing the antibacterial actions of neutrophils.
Nature Medicine 2010;16:1018–1023; doi:10.1038/nm.2209



Therapeutic effect of inhibition of lysyl oxidase–like-2 in various diseases Lysyl oxidase–like-2 (LOX2) modifies the extracellular matrix by promoting crosslinking of fibrillar collagen I, a major component of desmoplastic cancer stroma and fibrosis associated with diseases such as hepatic and pulmonary fibrosis. To understand whether LOX2 might play a role in these pathologic processes, Barry-Hamilton *et al*, in work described in *Nature Medicine*, asked whether inhibition of LOX2 would inhibit them. They demonstrated that inhibition of LOX2 with AB0023, an inhibitory antibody, was effective in treating primary and metastatic xenograft cancer models and mouse hepatic and pulmonary fibrosis models. Because LOX2 does not appear to be expressed highly in normal tissues, inhibitors of LOX2 such as AB0023 hold great promise for the treatment of cancer and diseases characterized by pathologic fibrosis.
Nature Medicine 2010;16:1009–1017; doi:10.1038/nm.2208



Preventive strategy for Parkinson's disease Parkinson's disease (PD) is a common and devastating neurodegenerative disease for which there is no effective means of prevention or treatment. Individuals with mutations in leucine-rich repeat kinase-2 (LRKK2) develop PD that is indistinguishable from sporadic, non-LRKK2-associated PD. In a recent Brief Communication in *Nature Medicine*, Dawson and colleagues investigated whether inhibition of LRKK2 would inhibit PD in a mouse model. They identified several inhibitors that selectively inhibited mutated forms of LRKK2 and showed that they were protective against neurotoxicity *in vitro* and *in vivo*. Interestingly, the substrate of LRKK2 that is responsible for the neurotoxicity has not been identified. Further studies aimed at identification of this substrate(s) will be useful in elucidating the pathogenesis of PD. Additionally, this work highlights LRKK2 as a therapeutic target for the prevention of PD.
Nature Medicine 2010;16:998–1000; doi:10.1038/nm.2199