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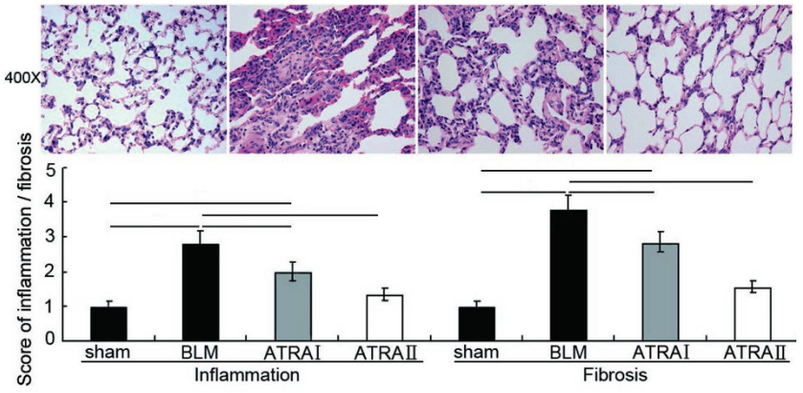

ATRA inhibits pulmonary fibrosis in a rat model

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Lung fibrosis is an aggressive disease with few treatment options, none of which has been proven to have clinical efficacy. In this disorder, lung parenchyma is replaced by fibrotic tissue that inhibits oxygen exchange in the alveoli. The disease can be caused by a variety of factors, including infection, airborne caustic agents, genetics, and certain disease conditions, although some cases lack a known cause and are considered idiopathic. Lung fibrosis may be considered a response to chronic injury. Multiple pathways drive fibrosis, but the transforming growth factor (TGF)-β1/Smad3 pathway seems to play a central role.

The effects of all-trans retinoic acid (ATRA) on lung fibrosis are debated in the literature, perhaps owing to variable dosing regimens. Song *et al* used a rat model of bleomycin-induced lung fibrosis to investigate whether ATRA can ameliorate lung fibrosis as well as whether it specifically inhibits the TGF-β1/Smad3 pathway. ATRA decreased fibrosis, inflammation, collagen deposition, α-SMA expression, and the TGF-β1/Smad3 pathway whereas E-cadherin expression increased—all in an apparently dose-dependent fashion. Given this set of changes, the authors suggest that ATRA may, at least in part, inhibit fibrosis by blocking an epithelial-to-mesenchymal transition (EMT)-like process in the lung. This conjecture is supported by decreases in Snail and Twist protein expression with ATRA treatment. Other factors associated with EMT, such as HMGA2, ZEB1, and ZEB2, were also reduced. ATRA is currently used effectively as an oral medication for promyelocytic leukemia and other diseases, and this study suggests that it may also have efficacy for the treatment of lung fibrosis.

Mechanism of renal osteodystrophy

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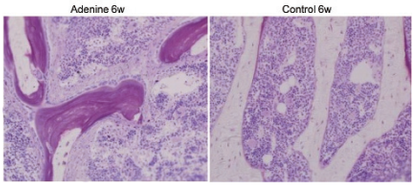

Renal osteodystrophy (ROD) is a disorder of bone that results from chronic kidney disease (CKD). Typical histological findings in ROD include increased numbers of osteoblasts and osteoclasts with peritrabecular fibrosis and increased osteoid tissue, consistent with a severe defect in mineralization. Clinically, ROD is characterized by joint pain and high risk of bone fracture. Recent reports have correlated bone strength with intra- and intermolecular collagen crosslinks catalyzed by lysyl oxidase (LOX). The risk of bone fracture increases when LOX activity is decreased in bone. Advanced glycation end products (AGEs) are carbohydrate modifications of proteins. AGEs accumulate in long-lived tissues such as bone and have been implicated causally in several bone disorders.

On the basis of these findings, Aoki *et al* investigated the relationship among LOX activity, AGEs, and ROD in a rat model of CKD. They found that the bones of rats with ROD harbored irregularities of bone collagen fibril alignment and fibrils with increased diameters. Examination of LOX activity revealed a decrease in *Lox* mRNA and Lox protein expression, which was associated with increased AGEs in peritrabecular osteoblasts, suggesting that ROD may be caused by the accumulation of AGEs. Because defects in osteoblast differentiation are also thought to contribute to ROD, the authors examined osteoblast differentiation in their ROD model. Exposure of osteoblasts to AGE-modified bovine serum albumin *in vitro* resulted in decreased *Spp1* mRNA, a marker of osteoblast differentiation. These results support a model in which ROD is caused not only by decreased bone-mineral density but also by suppressed osteoblast differentiation and collagen fibril abnormalities caused by decreased LOX expression regulated by AGEs.

Autoantibodies to VE-cadherin in autoimmune diseases

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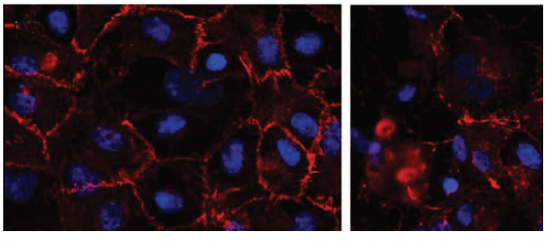
Autoimmune diseases are frequently associated with idiopathic systemic vasculitis, which is linked to early mortality. Endothelial integrity is maintained by specialized structures known as adherens junctions, which are composed of vascular



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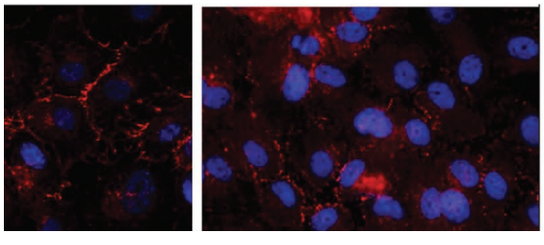
endothelial (VE)-cadherin. VE-cadherin has been implicated in virtually all functions of endothelial cells, including migration, survival, contact-induced growth inhibition, vascular integrity, and assembly into tubular structures. Knockout of VE-cadherin in mice results in embryonic lethality due to severely impaired vascular assembly. Structural modifications in VE-cadherin are associated with vascular permeability in several pathologic conditions, and result in the protein's extracellular domain (soluble VE-cadherin) becoming detectable in serum from patients with rheumatoid arthritis. Soluble VE-cadherin could lead to the development of autoantibodies.

It has previously been shown that polyclonal and monoclonal antibodies directed against VE-cadherin can affect the stability of endothelial cell–cell cohesion, leading to vascular permeability and hemorrhage. Hence, Bouillet *et al* hypothesized that circulating autoantibodies to VE-cadherin (AAVEs) could contribute to the vasculopathies associated with autoimmune diseases. Using a unique antibody-capture enzyme-linked immunosorbent assay, they screened serum from many patients with autoimmune diseases including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis, and Behçet's disease (BD). They found significantly higher levels of AAVEs in patients with RA, SLE, and BD. When the authors incubated a monolayer of endothelial cells with purified immunoglobulin G from a BD patient, they observed cell retraction, redistribution of VE-cadherin, and numerous intercellular gaps. These results suggest that AAVEs may be specific biomarkers for endothelial injury in autoimmune diseases.



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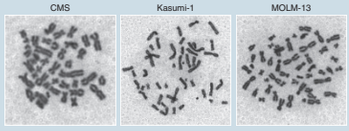
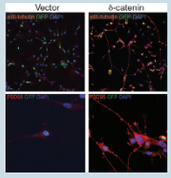
Cohesin mutations in myeloid neoplasms



Cohesin is a multimeric protein complex thought to be involved in the cohesion of sister chromatids during cell division, postreplicative DNA repair, and the regulation of global gene expression. Mutations in cohesin genes have increasingly been identified in various cancers, with the general hypothesis that defective cohesin complexes promote aneuploidy. Given the identification of cohesin mutations in rare cases of myeloid neoplasms in previous studies, Kon *et al*, as described in a recent letter in *Nature Genetics*, used high-throughput sequencing to identify mutations of nine cohesin or cohesin-related genes in 581 primary myeloid neoplasm specimens. They found significant numbers of mutations or deletions in four cohesin genes in a variety of myeloid neoplasms. Their data lead them to favor the idea that cohesin mutations participate in leukemogenesis through the deregulated expression of genes involved in myeloid development and differentiation and not through the development of aneuploidy.

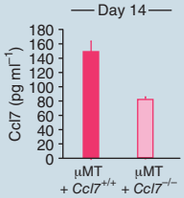
Nature Genetics 2013;45:1232–1237; doi:10.1038/ng.2731



Driver mutations in glioblastoma In order to identify new driver mutations in glioblastoma multiforme (GBM), Frattini *et al*, as recently reported in *Nature Genetics*, developed an algorithm that computes the frequency, magnitude, and focality of copy-number variations (CNVs) at any locus in the human genome with the somatic mutation rate for genes residing at that location. This algorithm integrates into one score the two genetic hallmarks of driver cancer genes: focality of CNVs and point mutations. Their analysis identified nearly all genes known to have functional relevance in GBM as well as 18 new genes of potential functional importance. The algorithm is not specific for GBM and can be used to identify driver mutations in other cancers with complex genetic landscapes.

Nature Genetics 2013;45:1141–1149; doi:10.1038/ng.2734

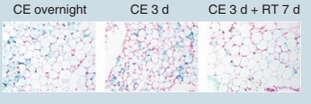
B lymphocytes induce additional damage after heart attack



Inflammation following acute myocardial infarction (AMI) is induced by exposure ligands from damaged tissue that activate the innate immune system. However, using a mouse model of acute myocardial infarction (AMI), Zouggari *et al* further demonstrated that B lymphocytes migrating to postischemic tissues signal through Ccl7 and Ly6Chi to mobilize monocytes to myocardial tissue, causing further damage and loss of function. Depletion of mature B cells, due to either genetic deficiency or antibody binding, prevented both signaling and increased damage. In human AMI patients, high circulating concentrations of CCL7 or BAFF (required for maintenance of mature B cells) correlated with both risk of death and recurrent AMI. These studies expand our understanding of AMI pathogenesis and suggest additional biomarkers for prognosis and risk assessment as well as avenues of therapeutic intervention.

Nature Medicine, published online 15 September 2013; doi:10.1038/nm.3284

Adipogenesis can now be followed in detail Widespread obesity, a scourge of the Western diet, has been much investigated given causative associations such as the differential expanse of visceral adipose tissue over subcutaneous stores with diabetes and cardiovascular disease. Wang *et al* have produced a helpful tool in the form of their ApidoChaser mouse, which can be used to study adipogenesis and adipose-tissue regulation in detail. Using this mouse, which employs a doxycycline-inducible LacZ promoter to trace mature adipocytes, the authors found that adipose tissue from different regions form at different stages of development and behave differently under the influence of a high-fat diet. Subcutaneous fat grew primarily through hypertrophy out to 2 months, whereas perigonadal fat quickly showed rapid adipogenesis. The authors also demonstrated that beige adipocytes do not transdifferentiate from white adipocytes during cold exposure but develop independently from precursor cells.



Nature Medicine, published online 1 September 2013; doi:10.1038/nm.3324

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