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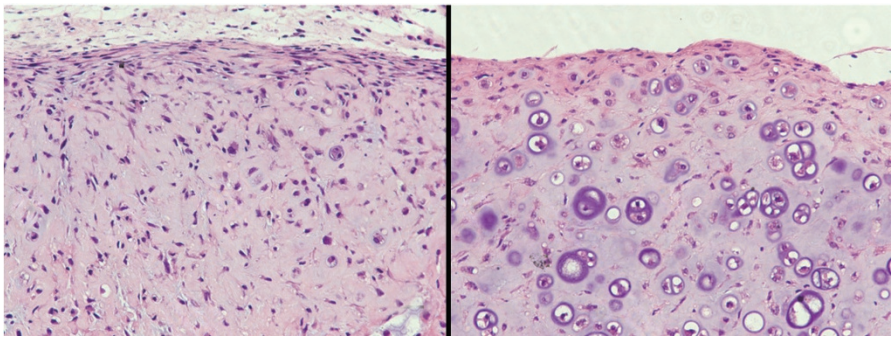

Toward manipulation of β-catenin for articular cartilage regeneration

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Articular cartilage is critical to normal joint function. Without it, joints are painful and have limited motion. The current treatment for severe degenerative joint disease/osteoarthritis, which is characterized by loss of articular cartilage, is prosthetic joint replacement. While there has been considerable improvement in prosthetic joints, they still suffer from issues of wear, requiring eventual replacement. Furthermore, infection associated with surgery is a major clinical problem, resulting in considerable morbidity and cost. It would be advantageous to be able to manipulate articular cartilage medically for therapeutic purposes. The superficial zone (SFZ) within articular cartilage contains a distinct cell population that is critical for joint mechanics and lubrication and is thought to contain cartilage progenitor cells. Therefore, the SFZ holds potential in maintaining and regenerating articular cartilage. Because SFZ cells express members of the Wnt signaling pathway, including β-catenin, making this pathway an attractive target to manipulate the SFZ for therapeutic purposes, Yasuhara *et al* investigated Wnt/β-catenin signaling in SFZ cells.

The authors demonstrated that cartilage-specific overexpression of β-catenin resulted in thickened articular cartilage whereas deletion of β-catenin had the opposite effect. Culture of purified SFZ cells showed cells with features of progenitor cells. Treatment with Wnt3a, a stimulator of Wnt/β-catenin signaling, maintained SFZ morphology and gene expression and facilitated proliferation. When SFZ cells were transplanted into athymic mice, they formed ectopic tissue masses that exhibited cartilaginous differentiation that was inhibited by administration of Wnt3a. In summary, the SFZ contains cells with features of progenitor cells that can differentiate along the cartilage lineage. Control of this process by modulating Wnt/β-catenin signaling shows promise for articular cartilage maintenance/regeneration therapy.

Syk as a therapeutic target in neutrophil-mediated glomerulonephritis

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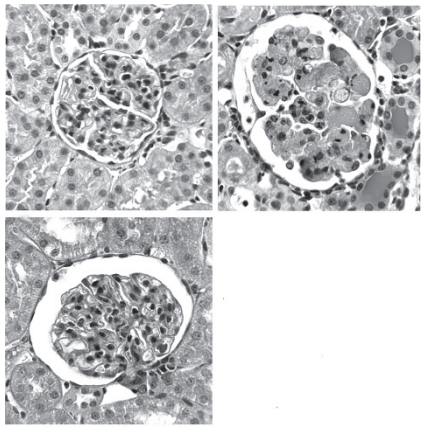

Glomerular antibody deposition can cause acute podocyte injury and proteinuria through Fc-receptor dependent recruitment and activation of circulating neutrophils and monocytes. c-Jun amino terminal kinase (JNK) and p38 mitogen–activated protein kinase (MAPK) are activated downstream of Fc-receptor activation. However, a link between JNK and MAPK activation and Fc-receptor activation has not been established. Spleen tyrosine kinase (Syk), a nonreceptor tyrosine kinase expressed in B cells of the immune system, is known to link Fc-receptor activation to downstream signaling, making it an attractive therapeutic target in immune-based diseases such as rheumatoid arthritis. Because of its potential therapeutic importance, Ryan *et al* sought to understand the relationship between Syk and JNK/MAPK activation in antibody-dependent neutrophil-mediated glomerulonephritis.

The authors found that Syk was activated both in a rat model of antibody-dependent inflammation-mediated glomerulonephritis and in human postinfectious glomerulonephritis biopsy specimens. Syk inhibition by a small-molecule Syk inhibitor resulted in loss of JNK and MAPK activation, linking Syk activation to JNK/MAPK activation. Importantly, Syk-inhibitor therapy in a rat model of antibody-dependent inflammation-mediated glomerulonephritis resulted in reduction of glomerular inflammation, which was associated with diminished podocyte loss and prevention of proteinuria. These results warrant a more thorough examination of Syk activation in human glomerular diseases and suggest that Syk inhibition by small-molecule Syk inhibitors should be explored therapeutically in the treatment of immune-mediated glomerulonephritis.

Frataxin in astrocytic tumors

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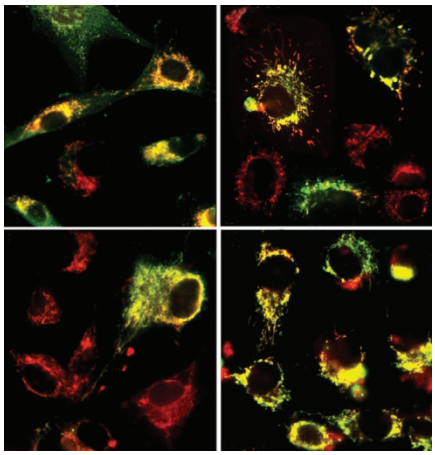
Friedreich's ataxia is characterized by neuronal degeneration and heart failure, which are caused by loss of transcription of the *frataxin* gene due to a trinucleotide repeat expansion. Frataxin (FXN) is a mitochondrial protein involved in iron–sulfur-cluster biogenesis, serving to bind and transfer iron to key electron transport complexes and cytochrome C. In cancer,

there is mounting evidence that FXN functions as a tumor suppressor. Mice with hepatocyte-specific FXN deletion develop liver tumors, and FXN expression is associated with decreased growth rates in colon cancer cell lines. The growing body of literature about the relationship of FXN to cancer prompted Kirches *et al* to study the role of FXN in astrocytic tumors/glioblastoma cell lines.



In contrast to what they expected, the investigators found that enforced expression of FXN in glioblastoma cell lines did not exhibit any mitochondrial phenotypes and resulted in increased proliferation under growth factor–restricted and hypoxic conditions, appearing to function as an oncogene instead of a tumor suppressor. Increased FXN expression was also associated with an increase in cytoplasmic reactive oxygen species (ROS), due to decreased H_2O_2-converting enzymes and glutathione levels. The fact that increased ROS levels were associated with expression of FXN suggested to the authors that glioblastoma cells with increased FXN levels might be more sensitive to cellular stressors. They demonstrated that FXN-expressing glioblastoma cells were more sensitive to alkylating agents and compounds that induce apoptosis; antioxidants reversed this sensitivity. Thus, the increased proliferation of FXN-expressing glioblastoma cells comes at a cost of increased sensitivity to chemotherapeutic agents.

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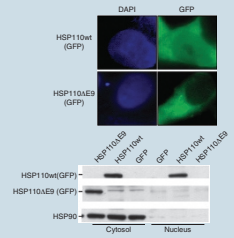
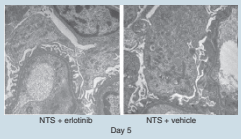
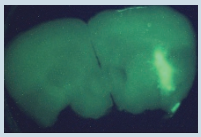


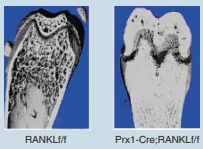
Achilles' heel in colorectal carcinoma Colorectal carcinomas (CRCs) showing microsatellite instability (MSI) are characterized by defects in DNA mismatch repair. MSI CRCs have a good prognosis and better response to chemotherapy than do other CRCs. In a recent article in *Nature Medicine,* Dorard and colleagues report the discovery of one factor to explain the difference in prognosis and response to chemotherapy. They demonstrated an altered form of heat shock protein (HSP) 110 that arose through deletion of a T_{17} mononucleotide repeat located in intron 8, which led to expression of an altered HSP110 transcript that produced a truncated version of HSP110 lacking a substrate binding domain. This altered HSP110, designated HSP110ΔE9, acts in a dominant negative fashion to inhibit wild-type HSP110. The fact that not all MSI CRCs have HSP110ΔE9 allowed the authors to demonstrate that its presence correlates with better prognosis and response to chemotherapy.
Nature Medicine 2011;17:1283–1289; doi:10.1038/nm.2457



Central role of EGFR signaling in rapidly progressive crescentic glomerulonephritis Rapidly progressive glomerulonephritis (RPGN) is a life-threatening form of renal disease. Heparin-binding epidermal growth factor–like growth factor (HB-EGF) has been implicated in RPGN, but its precise role has not been defined. As described in a recent article in *Nature Medicine,* Bollée *et al* demonstrated that HB-EGF is central to the pathogenesis of RPGN; HB-EGF is induced early in the pathogenesis of a mouse model of RPGN, where it binds to epidermal growth factor receptor (EGFR)—primarily on podocytes—to promote glomerular injury. Blockade of EGFR, either genetically in podocytes or systemically by EGFR small-molecule inhibitors, prevents severe RPGN and even attenuates glomerular injury when given after onset of the disease. These results clearly support further study of clinically available EGFR inhibitors in the treatment of RPGN.
Nature Medicine 2011;17:1242–1250; doi:10.1038/nm.2491



Etiology of brain tumor–associated epilepsy Peritumoral seizures are an early and common symptom in patients with glioma. Approximately one-third of patients develop recurrent seizures known as tumor-associated epilepsy. Recently, elevated peritumoral glutamate levels have been associated with tumor-associated epilepsy. As recently described in *Nature Medicine,* Buckingham *et al* hypothesized that glutamate release from glioma cells through system x_c^-, an Na^+-independent cystine–glutamate transporter, leads to epileptic activity. They showed that glutamate receptor–bearing peritumoral neurons had a reduced activation threshold due to glutamate secreted by human glioma cells in a mouse model. Inhibition of glutamate release by sulfasalazine, a Food and Drug Administration–approved system x_c^- inhibitor, reduced epileptic activity in glioma-bearing mice, suggesting that sulfasalazine may be useful in treating human glioma patients with tumor-associated epilepsy.
Nature Medicine 2011;17:1269–1274; doi:10.1038/nm.2453



Throwing old dogma a new bone Resorption of cartilage and bone is critical for skeletal development and bone remodeling. Osteoclasts are primarily responsible for resorption of mineralized cartilage and bone. Receptor activator of nuclear factor-κB ligand (RANKL) is essential for osteoclast development, function, and survival. According to prevailing dogma, RANKL is produced by osteoblasts on the bone surface or in the bone marrow during cartilage and bone remodeling. This dogma was recently challenged in an article by Xiong *et al* and a separate brief communication by Nakashima *et al*, both in *Nature Medicine*. Utilizing highly purified populations of osteocytes and elegant lineage-specific mouse models that deleted *Tnfsf*11 encoding RANKL in osteoblast- or osteocyte-specific lineages, the two groups demonstrated that osteocytes produce the bulk of RANKL in response to bone stresses that stimulate osteoclasts. Xiong *et al* also showed that hypertrophic chondrocytes were responsible for producing RANKL required for remodeling of cartilage.
Nature Medicine 2011;17:1235–1241; doi:10.1038/nm.2448 and 2011;17:1231–1234; doi:10.1038/nm.2452