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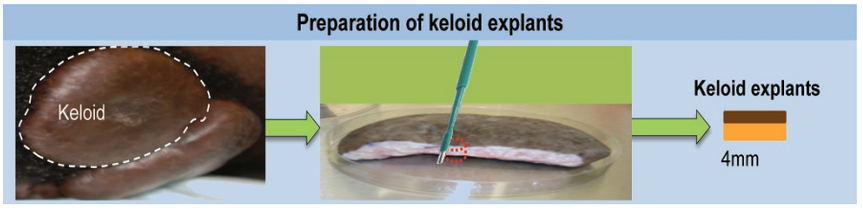

Ex vivo evaluation of antifibrotic compounds in scarring

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Keloid disease is a disfiguring fibroproliferative disorder that may represent, at least partially, an overly exuberant response to wounding, with subsequent maturation to dense fibrotic tissue with extensive collagen deposition. There is no mouse model, and cell culture of fibroblasts from keloids poorly recapitulate key aspects of the disorder. Syed and colleagues used their previously developed human keloid organ culture model, which is stable for up to six weeks. Durability of the model is important because the density of keloids takes time to resolve with treatment. The compound (−)-epigallocatechin-3-gallate (EGCG) has been shown to inhibit keloid cells in monolayer culture. Previous studies have suggested that plasminogen activator 1 is a critical regulator of keloid growth, and an interfering RNA approach is employed to inhibit its expression. The authors also used dexamethasone, the current standard of care for keloid. The two novel agents reduced keloid size through a reduction of collagen synthesis, and EGCG further induced fibroblast apoptosis, reduced the numbers of mast cells and blood vessels, and globally reduced the levels of factors known to induce fibrosis. Although not as effective in reducing collagen levels and keloid size, dexamethasone offered superior fibroblast apoptosis and cytotoxicity over the time period of these experiments. The results suggest that these two novel approaches deserve further study and could be useful in treating existing keloids or preventing their occurrence at the time of surgical removal.

A microfluidic device for gene expression studies

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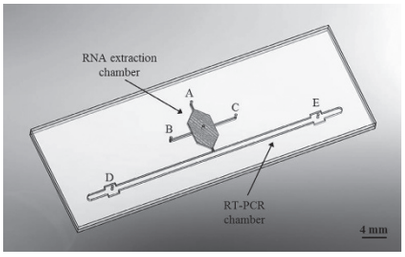

The cytochrome P450 superfamily of enzymes in the liver are involved in phase I metabolism of a variety of pharmaceutical agents. They can inactivate a drug or convert a prodrug to its active form. Exposure to certain drugs can result in genetic induction, leading to increased metabolism. Ingesting two drugs metabolized by the same P450 enzymes reduces metabolism and risk toxicities. Understanding the regulation of this superfamily is important in our contemporary environment of polypharmacy. Certain enzymes in the group metabolize particular classes of drugs; for example, CYP1A2's role in metabolizing clonapine is well known. Generally, the levels of particular P450 activities are measured by substrate-conversion assays. CYP1A2 mRNA levels can also be used to gain insights into the regulation of this enzyme in response to various stimuli.

Microfluidics technology enables microliters of liquids to be precisely moved between chambers on etched glass slides. Multiplexed PCR on such devices has many advantages in terms of avoiding contamination and efficiently processing very small amounts of nucleic acid. Although microfluidics is focused primarily on DNA, Shaw *et al* describe microfluidic extraction and purification of mRNA and reverse-transcription and quantitative PCR for CYP1A2 cDNA. This multiplexed performance on a single slide for many samples is part of the "lab on a chip" revolution consisting of disruptive technologies such as microfluidics that are forever changing the way we measure analytes in the research and clinical settings.

How *B. burgdorferi* hides in chronic infection

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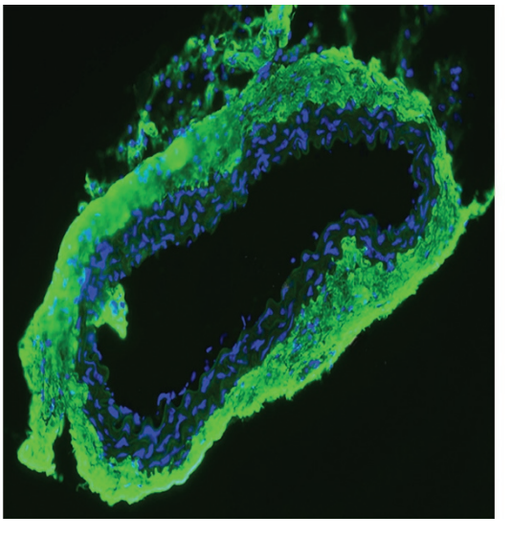
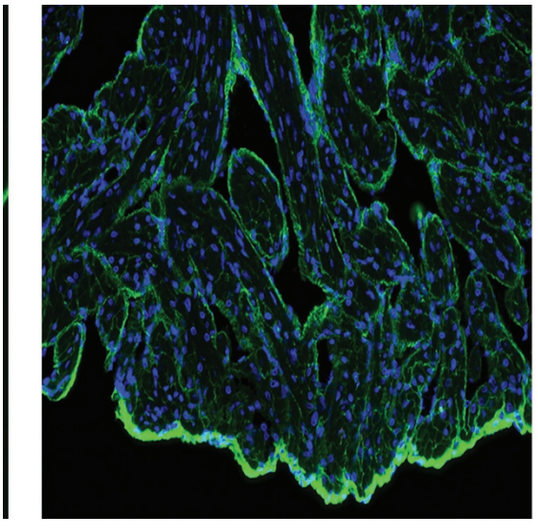
Borrelia burgdorferi is a tick-transmitted spirochete that causes Lyme disease. Ticks infect a host by depositing *B. burgdorferi* into the dermis, where it proliferates and then disseminates to other tissues. Acquired immunity reduces *B. burgdorferi* levels but is followed by low-level chronic infection, which persists for years and acts as a reservoir for future recrudescence. In chronic infection, *B. burgdorferi* is restricted to the extracellular matrix (ECM) of a subset of tissues and organs. Interactions



with the ECM are mediated by a class of proteins known as adhesins. *B. burgdorferi* encodes a large number of adhesins, including decorin-binding proteins A and B. Previously, investigators had observed a direct relationship between the numbers of persisting *B. burgdorferi* and decorin expression levels in collagen-rich tissues.

To further elucidate the mechanism and purpose of *B. burgdorferi* tissue restriction in chronic infection, Imai *et al* used a mouse model of persistent *B. burgdorferi* infection. Examining the connective tissue at the base of the heart, the authors found that *B. burgdorferi*–specific antibodies drove the spirochete into the tunica adventia, whereupon antibody clearance and subsequent recrudescence led to reinfection of tissues that had been cleared by the immune system. In accord with previous work, *B. burgdorferi* and decorin colocalized in the tunica adventitia and not in nearby ECM, which was decorin-poor. The authors suggest that decorin probably "protects" *B. burgdorferi* from antibody clearance by binding to an immunogenic epitope that prevents interaction with and clearance by the immune system. This study highlights the complex relationship between infectious agents and the immune system and provides mechanistic insight into how *B. burgdorferi* evades the immune system, resulting in chronic infection.



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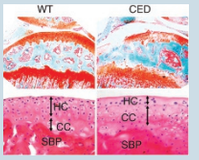
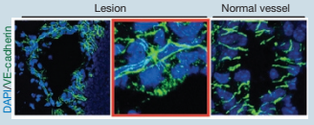
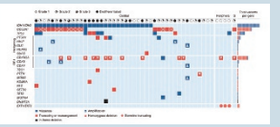


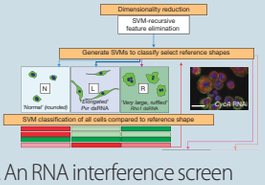
Role of TGF-β signaling in osteoarthritis Osteoarthritis is predicted to affect 67 million people in the United States by 2030. Currently, there is no effective medical therapy; joint replacement is the major treatment. Accumulating evidence suggests that transforming growth factor-β1 (TGF-β1) plays an important role in the pathogenesis of osteoarthritis. This prompted Zhen and colleagues, as described in a recent article in *Nature Medicine,* to study its mechanism of action. Although osteoarthritis is characterized by degeneration of articular cartilage, the authors found that early changes in osteoarthritis were in subchondral bone in a mouse model, where increased numbers of osteoclasts led to elevated levels of TGF-β1, which recruited mesenchymal stem cells (MSCs). MSCs stimulated bone formation and angiogenesis, which preceded articular cartilage degeneration. These results suggest that modulation of TGF-β1 levels in subchondral bone may be a therapeutic strategy in osteoarthritis.
Nature Medicine 2013;19:704–712; doi:10.1038/nm.3143



Endothelial-to-mesenchymal transition in vascular dysplasia Cerebral cavernous malformation (CCM) is a vascular dysplasia that is characterized by irregular cerebral blood vessels and often leads to cerebral hemorrhages. CCM is caused by loss-of-function mutations in any one of three *CCM* genes. To understand how loss of *CCM* function contributes to CCM, Maddaluno *et al*, as reported in a recent letter in *Nature,* generated endothelial-specific tamoxifen-inducible *Ccm1* loss-of-function mice that recapitulated the important features of CCM. They found that loss of Ccm1 in endothelial cells led to an endothelial-to-mesenchymal transition (EndMT), which was mediated by activation of transforming growth factor-β (TGF-β) signaling. EndMT is characterized by altered junction organization, loss of cell polarity, and increased cell proliferation and migratory capacity. The authors found that inhibition of TGF-β signaling reduced the number of vascular malformations and prevented leakage.
Nature 2013;498:492–496; doi:10.1038/nature12207



Frequent mutation of COL2A1 in chondrosarcoma In a study recently described in *Nature Genetics*, whole-exome sequencing of chondrosarcomas revealed a mutational burden per case ranging from 1 to 115, proportional to tumor grade. As expected, the authors identified *IDH1* or *IDH2* (~60%) and *TP53* (20%) mutations. The RB1 tumor suppressor pathway was often disrupted (for example, by *CDKN2A* mutations), and activating mutations in the Hedgehog pathway were demonstrated. The big surprise was the variety of insertions, deletions, and rearrangements of the *COL2A1* gene (37% in all) encoding the major structural collagen in cartilage. Applied metrics suggested selection for mutations that disrupt the coding frame. *COL2A1* mutations underlie a variety of congenital skeletal disorders, but these are not characterized by increased chondrosarcoma incidence. Only time will tell whether disruption of this truncated protein is involved in chondrosarcomagenesis, perhaps in a dominant negative fashion.
Nature Genetics, published online 16 June 2013; doi:10.1038/ng.2668



Cells have a limited repertoire of discrete shapes Cell shape—a critical factor in diagnostic pathology—influences cells' ability to function in diverse environments and facilitates neoplastic function. Recent work reported in *Nature Cell Biology* used *Drosophila* hemocytes in culture and image analysis to demonstrate that these cells adopt only five basic reference shapes. An RNA interference screen offered evidence that certain signaling pathways regulate the balance between discrete states rather than creating novel shapes, in effect reducing the complexity to a smaller number of shapes. Using melanoma cell lines, the authors found that growth on deformable collagen I matrices produced populations of rounded and elongated (or spindled) cells. Melanoma cells with loss of functional Pten protein tended to adopt a more spindled morphology at the expense of rounded cells.
Nature Cell Biology 2013;15:860–871; doi:10.1038/ncb2764