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Modern Pathology

Smooth muscle–type differentiation confers a poorer prognosis in pleomorphic sarcoma

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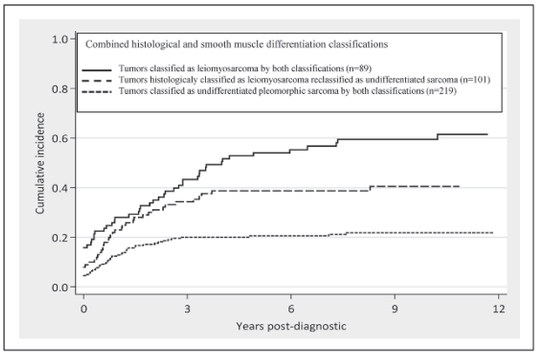

There is evidence that myogenic differentiation confers a more aggressive phenotype in poorly differentiated sarcomas. Pérot and colleagues examined a large cohort of more than 400 pleomorphic sarcomas using four smooth-muscle immunohistochemical markers: calponin, h-caldesmon, transgelin, and smooth-muscle actin. Sarcomas that displayed reactivity for all four markers had the poorest outcome (they may be pleomorphic leiomyosarcomas). Of the remaining sarcomas with partial or absent smooth-muscle phenotypes, those lacking any evidence of smooth-muscle differentiation had the best outcomes and those with partial phenotypes displayed intermediate outcomes. With respect to predicting outcome, this immunohistochemical classification system was superior to the initial histologic diagnosis, and it was significant even when other relevant clinical factors such as histologic grade, site, or sex were considered. This novel panel confirms prior studies and provides a better-defined and potentially more objective framework for assessing smooth muscle–type differentiation in sarcoma prognostication.

Productive herpes infection linked to idiopathic pulmonary fibrosis

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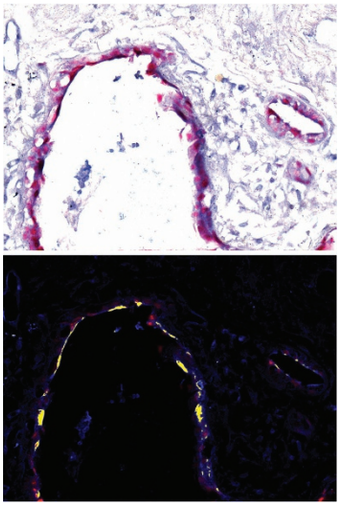
Idiopathic pulmonary fibrosis is an ultimately fatal disease that is difficult to diagnose and lacks effective therapy. On the basis of linkages with various herpesvirus types and pulmonary fibrosis in animals, Folcik *et al* used molecular methods to examine cases of idiopathic pulmonary fibrosis (IPF) and other cases of pulmonary fibrosis of known etiology. Viral genomic analysis yielded evidence of herpesvirus that was confirmed to be



herpesvirus saimiri in IPF but not in the other types of pulmonary fibrosis. The herpesvirus saimiri DNA was found specifically in the regenerating epithelia of all 21 cases of IPF. This finding suggests that IPF in humans may have a defined viral etiology. It is therefore possible that antiviral therapy might show efficacy in IPF and that analysis for viral products might aid in diagnosis and assist in directing such therapy.

Laboratory Investigation

Endothelial cells enhance bone formation by osteocytes

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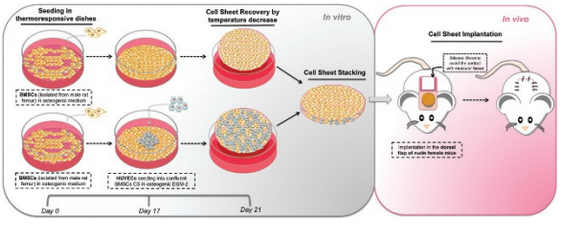

Tissue culture monolayers are a stalwart of research, but their applicability is limited by lack of supportive stromal cells. Vascularization is an active area of inquiry in three-dimensional cultures, and endothelial cells can be used for both prevascularization and neovascularization. Pirraco and colleagues present a model in which rat bone marrow stromal cells were incubated under osteogenic conditions with or without human umbilical-vein endothelial cells in stacked cell culture sheets and then transplanted into rats. These crude three-dimensional cultures showed mineralization with or without endothelial cells, but the transplants with endothelial cells showed greater osteogenicity. Neovascularization in

these implants showed incorporation of human endothelial cells. This work indicates that combining endothelial cells could increase vascularization and osteogenesis in engineered tissues that could eventually be used for bone replacement and regeneration.

RNA-Seq reveals altered cytoskeletal genes in cardiomyocytes in heart failure

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Heart failure has been known to induce perturbations of the cardiomyocyte cytoskeleton, which regulates contractile properties and other signaling pathways in these cells. Herrer *et al* used RNA-sequencing analysis (RNA-Seq) to examine the gene expression signature of left ventricular samples of dilated and ischemic cardiomyopathies during cardiac transplantation and compared these with healthy donor hearts. Although approximately 60 genes were differentially expressed in these cardiomyopathies versus normal heart, a common signature of downregulation of MYLK4 and RHOU messenger RNA (mRNA) and protein with upregulation of ANKRD1 mRNA and protein was noted. Overall, there were similarities between ischemic and dilated cardiomyopathies at the cytoskeletal level, perhaps indicating partial convergence of these two etiologies in a final common pathway for heart failure. Further study of these cytoskeletal proteins and their function in cardiomyocytes could provide insights into the physiology of normal heart and the pathophysiology of heart failure.

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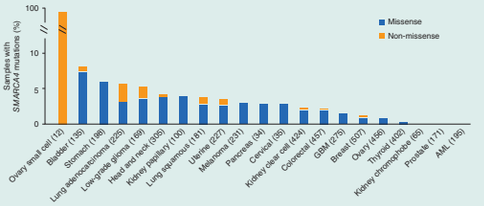
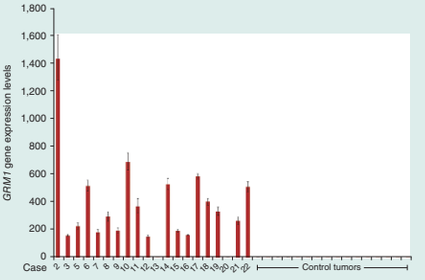
Small-cell carcinoma of the ovary harbors recurrent *SMARCA4* mutations



In a report published in *Nature Genetics*, Jelinic and colleagues studied small-cell carcinoma of the ovary and found biallelic inactivating SMARCB4 mutations in every tumor. Similar results were reported by Ramos *et al* and Witkowski *et al* in the same journal. The pathogenic mechanisms leading to small-cell carcinoma of the ovary had previously been obscure. Loss of SMARCA4 protein in the nucleus was noted in cases with nonsense mutations predicting expression of truncated protein, suggesting that SMARCA4 is a tumor suppressor. *SMARCA4* mutations have been reported in other tumors, but only at single-digit prevalence. SMARCA4 protein is part of the SWI/SNF complexes that serve as master regulators of gene expression through chromatin remodeling. *SMARCA4* mutation appears to be a defining molecular derangement in small-cell carcinoma of the ovary.

Nature Genetics 2014;46:424–426; doi:10.1038/ng.2922; *Nature Genetics* 2014;46:427–429; doi:10.1038/ng.2928; *Nature Genetics* 2014;46:438–443; doi:10.1038/ng.2931

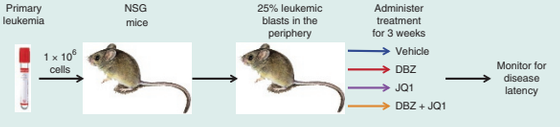
Rejuvenating stems cells in muscles restores strength lost in aging and injury



Chondromyxoid fibroma is a cartilaginous bone tumor that recapitulates various stages of chondrogenesis. Nord and colleagues, in a study published in *Nature Genetics*, demonstrated that 90% of these tumors show characteristic fusion events that place *GRM1* under the control of various strong promoters. *GRM1* encodes a glutamate receptor, and fusions result in massive overexpression. This aberrant glutamate signaling appears to be a critical molecular driver of chondromyxoid fibroma tumorigenesis. Increased expression of *GRM1* (as well as potentially activating missense mutations) can be oncogenic in other tumors. Normal human cartilage expresses protein from *GRM1* and other glutamate receptor genes as well, indicating a potential role in normal cartilage development and tissue homeostasis. Inhibitors of GRM1 signaling are clinically available, but, because chondromyxoid fibroma is a benign tumor amenable to surgical excision, therapeutic targeting may not be relevant. GRM1 expression could aid in the diagnosis of chondromyxoid fibroma.

Nature Genetics 2014;46:474–477; doi:10.1038/ng.2927

Epigenetic changes underlying targeted therapy resistance in T-ALL



Some cases of T-cell acute lymphoblastic leukemia (T-ALL) are associated with activating mutations in *NOTCH1* that act as a molecular driver. γ-Secretase inhibitors (GSIs) can interrupt NOTCH1 signaling and have therapeutic efficacy. However, as with most single-agent targeted therapies, resistance ensues. In this *Nature Genetics* paper, Knoechel and colleagues describe their use of a mouse model xenograft model with human T-ALL to demonstrate that a subpopulation of cells resistant to GSI (termed "persister" cells) exist prior to treatment. These persister cells rapidly expand in the population when NOTCH1 signaling is inhibited by GSIs. A knockdown screen identified chromatin regulator genes, including *BRD4*, as key mediators of GSI resistance. BRD4 can occupy enhancers of critical T-ALL genes such as *MYC* and *BCL2*. Inhibition of BRD4 by the inhibitor JQ1 when combined with a GSI increased the effectiveness of GSI inhibition, essentially preventing or delaying epigenetic resistance and suggesting the feasibility of clinical application.

Nature Genetics 2014;46:364–370; doi:10.1038/ng.2913

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