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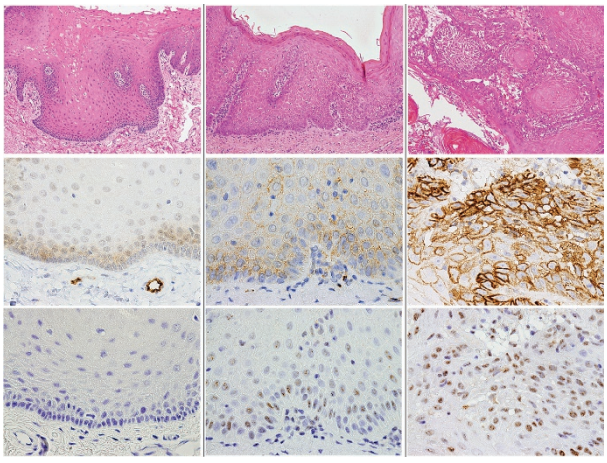

Inhibition of mTOR signaling in vascular tumors

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There has been considerable focus on signal transduction pathways in endothelial cells due to an interest in inhibiting the angiogenesis associated with various nonneoplastic and neoplastic diseases. Less attention has been paid to neoplasms with endothelial differentiation, which range from benign hemangiomas to fully malignant angiosarcomas. Mechanistic (mammalian) target of rapamycin (mTOR) signaling is a critical signal transduction pathway that lies downstream of growth factors such as vascular endothelial growth factor and is thus poised to integrate growth factor signaling in vascular tumors. mTOR inhibitors such as rapamycin (sirolimus) are used as potent immunosuppressive agents and have been studied in the context of various neoplasms, including vascular tumors.

On the basis of preliminary success with rapamycin in the treatment of vascular tumors, Du *et al* investigated the role of mTOR signaling in several vascular tumor models. They found that mTOR signaling was activated in both benign and malignant vascular tumor samples. In particular, S6 ribosomal protein (S6) was phosphorylated. Evaluation of vascular tumor primary cell cultures and cell lines revealed activation of both mTOR complex-1 and mTOR complex-2 targets, suggesting that mTOR signaling is functionally important. Genetic inhibition of S6 by lentiviral-mediated short hairpin RNA knockdown inhibited migration and proliferation in a hemangioendothelioma cell line. Furthermore, rapamycin inhibited proliferation and angiogenesis in infantile hemangioma explants. Perhaps the most significant experiment was the use of topical rapamycin to inhibit vascular tumor growth in a mouse model. Topical rapamycin has excellent potential as a therapy for cutaneous vascular tumors such as infantile hemangiomas, which frequently occur on the face and other areas where surgery might be difficult.

Osteopontin prolongs hepatic fibrosis

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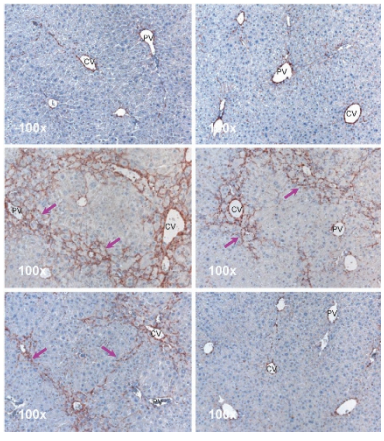
Liver fibrosis represents a significant disease burden. Most chronic liver diseases eventually enter the final pathway of cirrhosis. A better understanding is needed of the circumstances under which liver fibrosis can resolve and the underlying mechanisms of the resolution. Osteopontin, a key regulator of tissue remodeling in several systems, may have relevance to this process. In previous work, Nieto's group showed that osteopontin is profibrogenic by promoting both hepatic stellate cell activation and deposition of extracellular matrix, including collagen I expression. In an extension of this work, the group now demonstrates that osteopontin can delay the resolution of fibrosis by sustaining the synthesis of collagen I, a critical profibrogenic protein. Liver fibrosis was induced by administering thioacetamide to both wild-type and osteopontin-null transgenic mice, and the production and resolution of fibrosis were studied closely. In the mice lacking osteopontin, histology showed a lack of centrilobular and parenchymal necrosis as compared with the wild-type animals. Less fibrillar collagen I was detected by immunostaining. In a more mechanistic view, the levels of collagen I and tissue inhibitor of metalloproteinase-1 (TIMP-1) were both reduced. The latter—a regulator of fibrosis—is secreted by activated hepatic stellate cells, in which it apparently acts in an autocrine and/or paracrine loop



mediated through the bcl-2 pathway to prevent necrosis of the cells. A decrease in TIMP-1 levels is associated with resolution of fibrosis, perhaps due in part to the clearing of hepatic stellate cells. Hence, osteopontin appears to be an important regulator of hepatic fibrosis, and determining how to inhibit this pathway is certainly an aim of interest.

Wnt/β-catenin signaling in rhabdomyosarcoma

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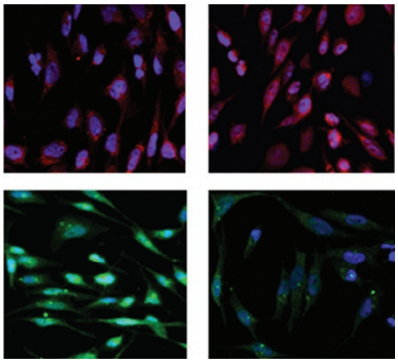
The Wnt pathway affects both proliferation and differentiation in numerous mammalian developmental processes and other studied cell models. It is specifically known to mediate myogenic differentiation in certain cellular systems. Annavarapu



and colleagues therefore examined the role of this pathway in both alveolar and embryonal rhabdomyosarcomas (RMS), aggressive mesenchymal tumors showing rhabdomyogenic differentiation. A little over half of the human RMS samples expressed β-catenin—primarily in the cytoplasm/membrane, with only rare cases showing nuclear accumulation. Other members of the Wnt pathway were expressed as well, indicating an intact signaling cascade. Application of the pathway agonist Wnt3a had differential effects in alveolar and embryonal cell lines. Wnt3a promoted nuclear accumulation of β-catenin in both tumor cell types, mediated by the binding and inactivation of the T-cell factor/lymphoid-enhancing factor DNA regulator that binds and inhibits transcriptional regulators. Expression of certain expected genes, such as *CYCD1* and *MYC*, was not demonstrated. Wnt3a treatment was associated with a paradoxical decrease in proliferation only in alveolar cell lines; there was no effect on embryonal cells. No increase in apoptosis was noted. Induction of myogenic differentiation markers was observed. Thus, contrary to intuition, increased β-catenin signaling seems to exert a tumor-suppressive function in alveolar RMS. This suggests that clinically available agents (e.g., lithium chloride) that promote activation of β-catenin by inhibiting the inactivating function of the GSK3β kinase, thereby promoting β-catenin destruction in the proteosome, could be of interest for further study. This work highlights an interesting inhibitory role for the canonical Wnt pathway in alveolar Wnt that certainly warrants elucidation.

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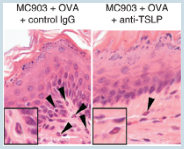
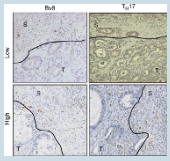
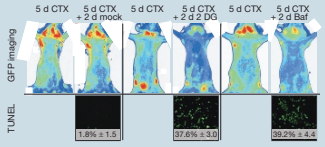


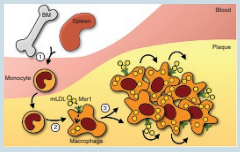
It's the basophils that promote eosinophilic esophagitis Recent work has identified an association between a gain-of-function polymorphism in the gene that encodes thymic stromal lymphopoietin (TSLP) and the development of eosinophilic esophagitis (EoE), a food allergy–associated inflammatory disease characterized by esophageal eosinophilia and inflammation. To investigate the pathogenesis of EoE, Noti *et al*, as described in a recent article in *Nature Medicine*, developed a mouse model of EoE. Surprisingly, they found that disease symptoms arose independently of immunoglobulin E (IgE) but were dependent on TSLP and basophils. These observations may explain the failure of previous clinical trials targeting IgE. In addition to providing a mouse model that faithfully recapitulates many of the salient features of EoE, these studies indicate that interfering with TSLP and basophils could lead to a treatment for EoE.
Nature Medicine 2013;19:1005–1013; doi:10.1038/nm.3281



New mechanism of resistance to antiangiogenic therapy In a recent article in *Nature Medicine*, Chung *et al* hypothesized that tumor-mediated antiangiogenic therapy resistance could be mediated by signaling events within the tumor microenvironment. They found that cancer cell lines that were resistant to antiangiogenesis therapies secreted interleukin (IL)-17A in comparison with tumor cell lines that were sensitive, suggesting that IL-17A might mediate resistance. Further experiments demonstrated that IL-17 and tumor-infiltrating T helper type 17 cells induced expression of granulocyte colony–stimulating factor from tumor-associated fibroblasts, which led to the recruitment of myeloid cells that promoted vascular endothelial growth factor–independent tumorigenesis. They also showed the importance of this pathway in antiangiogenic therapy resistance in several but not all cancer types; it therefore has broad clinical significance. This is the first report of cross-talk between adaptive and innate immunity in mediating therapeutic resistance.
Nature Medicine, published online 4 August 2013; doi:10.1038/nm.3291



Additional metabolic targeting of senescent cancer cells increases apoptosis Since the description of the Warburg effect more than 50 years ago, alterations in metabolism have increasingly been shown to be important for cancer. In a *Nature* letter, Dörr and colleagues demonstrate that therapy-induced senescence (TIS) is associated with increased use of glucose and elevated ATP production using a *myc*-driven mouse lymphoma model. This is due to massive proteotoxic stress termed senescence-associated secretory phenotype (SASP). These senescent cells were much more sensitive to inhibition of glucose metabolism or autophagy that led to apoptosis mediated by endoplasmic reticulum–related dysfunction. This effect was not seen when SASP was not present in an animal model in which this response pathway is not available. This study suggests that rational combinations of chemotherapy and inhibition of glucose utilization and/or autophagy could have clinical efficacy.
Nature, published online 14 August 2013; doi:10.1038/nature12437



Macrophage recruitment is less prominent than local proliferation in atherosclerosis In atherogenesis, macrophages accumulate within and expand the arterial wall in the context of a well-studied inflammatory response. Much previous work has focused on the early signaling events required to attract peripheral macrophages and other cells to this environment, which led to the belief that macrophages in the plaque were derived primarily from the peripheral blood. Using a mouse model, Robbins and colleagues reexamined this assumption in a study reported in a letter in *Nature Medicine*. In their system, macrophages replenish themselves in about 4 weeks, primarily as a result of local macrophage proliferation rather than infiltration from the blood and/or bone marrow. The local microenvironment stimulates this proliferation using the scavenger receptor A. Thus, interference with local macrophage proliferation may represent a productive avenue to inhibiting progression of atherosclerosis.
Nature Medicine, published online 11 August 2013; doi:10.1038/nm.3258