Laboratory Investigation (2013) 93, 746-747

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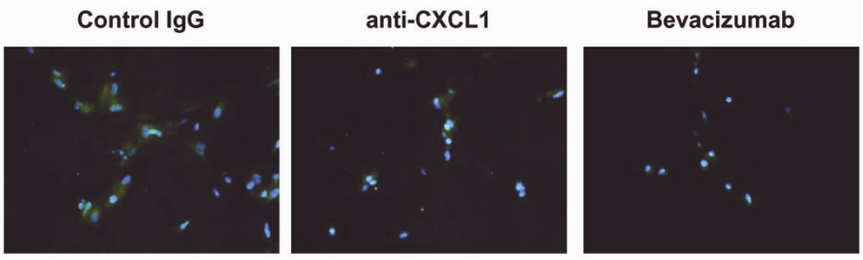
doi:10.1038/labinvest.2013.78



CXCL1 induces angiogenesis

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Tumor-induced angiogenesis is critical to support tumor formation and metastasis. Much has been learned about how tumor cells talk to endothelial cells, but the process remains poorly understood. Previous work has shown that human prostate cancer cells that overexpress Bcl-2 have increased angiogenesis when grown as xenografts. Examination of genes overexpressed by these cells has identified chemokine (C-X-C motif) ligand 1 (CXCL1), a secreted growth factor that binds the G-protein-coupled receptor CXCR2. This receptor is known to be important for inflammation, in which it acts as a chemoattractant for neutrophils. However, little is known regarding its role in angiogenesis.

Because CXCL1 is expressed strongly in prostate cancer cells that exhibit increased angiogenesis when grown as xenografts, Miyake *et al* explored its effects on angiogenesis. They discovered that CXCL1 and CXCR2 were expressed by endothelial cells and that inhibition of CXLC1 by neutralizing antibodies decreased endothelial cell viability and endothelial tube formation. Furthermore, inhibition of CXCL1 decreased endothelial cell migration. Signal transduction studies revealed that CXCL1 signaled predominantly through ERK1/2, which led to secretion of epidermal growth factor, a potent stimulator of angiogenesis. Blockade of CXCL1 in a mouse xenograft model led to decreased angiogenesis, demonstrating that CXCL1 plays a role in angiogenesis *in vivo*. Because endothelial cells produce their own CXCL1, it is not clear how the relative contributions of tumor-secreted CXCL1 and endothelial-secreted CXCL1 determine tumor-induced angiogenesis. It is possible that CXCL1 functions in both a paracrine and autocrine manner, perhaps by integrating the signals from multiple cell types.

Linking connective-tissue growth factor to inflammation

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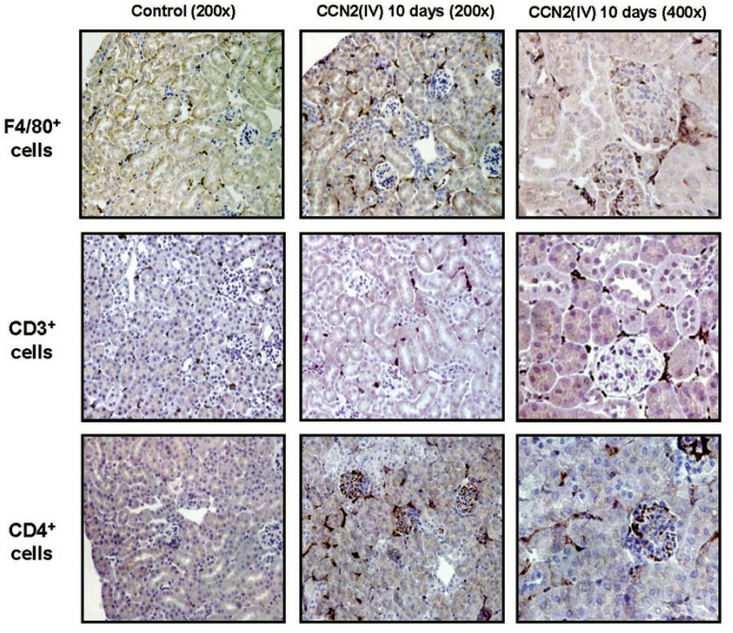
Connective-tissue growth factor (CTGF/CCN2) is a secreted matricellular protein with a variety of known biological effects in different contexts. Proteases, including matrix metalloproteinases, can process CCN2 into four fragments. One fragment, which includes a C-terminal heparin-binding domain, is known as the carboxy-terminal cystine knot domain (CCN2(IV)). CCN2 has been found to be overexpressed in almost all human diseases characterized by scarring and fibrosis and is thought to be a downstream mediator of transforming growth factor-β and angiotensin II. However, the direct contribution of CCN2 to fibrosis *in vivo* is unclear.

Because T helper (Th) cells—particularly Th17 cells—play an important role in chronic inflammatory diseases, Rodrigues-Díez *et al* studied the role of CCN2 with particular attention to CCN2(IV) in regulation of Th17 differentiation. They found that stimulation of naive human $CD4^+$ T cells with CCN2(IV) *in vitro* led to an increase in interleukin-17A (IL-17A)-producing Th17 cells. When CCN2(IV) was administered to mice, IL-17A did not accumulate in the peripheral circulation, but Th17 cell differentiation was promoted in the kidney. However, CCN2(IV) did not induce fibrosis or kidney dysfunction on its own. Examination of a mouse model of nonimmune inflammatory renal injury revealed elevated renal levels of CCN2 and IL-17A, suggesting that CCN2 induces Th17 cell differentiation in the kidney in this model. Overall, these results suggest that CCN2 plays an active role in sustained renal inflammation mediated by Th17 cells.



miR-206 and hypoxia-induced PH

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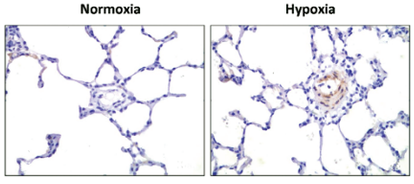

Hypoxia-induced pulmonary hypertension (PH) is characterized by pulmonary vasoconstriction and proliferation of pulmonary artery smooth muscle cells (PASMCs) that lead to structural remodeling of blood-vessel walls. PH is a common disorder resulting from chronic obstructive pulmonary disease, which is thought to be related to chronic hypoxia. Hypoxia-inducible factor-1α (HIF-1α) and four-and-a-half-LIM domain 1 (Fhl-1) play important roles in PH. Fhl-1 is thought to be directly involved in PASMC proliferation because the Fhl family of proteins has been implicated in pathways of muscle growth and differentiation and is regulated by HIF-1α in a feedback loop.

Because HIF-1α has a 5′-GGAAUG-3′'seed' region in the 3′-UTR for microRNA-206 (miR-206), Yue *et al* hypothesized that miR-206 might contribute to hypoxia-induced PH by targeting HIF-1α. Using a rat model of hypoxia-induced PH, they found that hypoxia resulted in a time-dependent increase in pulmonary artery neomuscularization that was associated with decreased levels of miR-206. Hypoxia was also associated with increased expression of HIF-1α and Fhl-1. Surprisingly, increased HIF-1α and Fhl-1 protein levels were not associated with increased HIF-1α and Fhl-1 messenger RNAs, as would be expected of miRNA-based mechanism. Although the authors cannot yet provide a reasonable explanation for how miR-206 regulates HIF-1α and Fhl-1 levels, they propose several possible mechanisms that could regulate HIF-1α and Fhl-1 protein levels involving complex networks of miRNAs. Further work will be required to determine the exact molecular mechanism(s) by which miR-206 affects the HIF-1α/Fhl-1 pathway.

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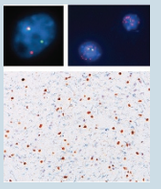
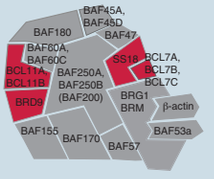


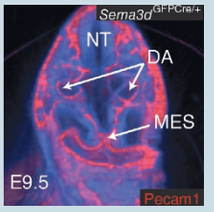
Genetic alterations in pediatric low-grade gliomas Low-grade gliomas (LGGs) include World Health Organization (WHO) grade I pilocytic astrocytomas, WHO grade II diffuse gliomas, and low-grade glioneural tumors. To determine the spectrum of underlying genetic mutations in pediatric LGGs, Zhang *et al* performed whole-genome sequencing, as recently described in *Nature Genetics*. They found that most tumors were characterized by a single functional mutation, suggesting that LGGs are genetically simple and driven primarily by a single dominant mutation. This also implies that targeting these aberrations pharmacologically should be useful. Pilocytic astrocytomas were characterized by *KIAA1549-BRAF* fusions, which activated the MAPK/ERK pathway. The authors also identified a previously unreported duplication of the *FGFR1* tyrosine kinase domain–encoding region, which encoded a constitutively active FGFR1 protein that also activated the MAPK/ERK pathway in 24% of diffuse WHO grade II gliomas.

Nature Genetics 2013;45:602–612; doi:10.1038/ng.2611



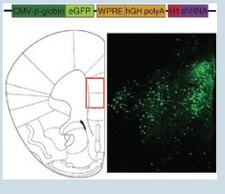
Role of mammalian SWI/SNF complexes in cancer As reported in a recent analysis in *Nature Genetics*, Kadoch *et al* explored the role of mammalian SWI/SNF (mSWI/SNF) complexes in cancer. Using an affinity purification–mass spectrometry–based approach, they identified several new subunits of the mSWI/SNF complexes. On the basis of these results, they searched 44 published genome and/or exome sequencing studies to develop a global understanding of the mutational frequencies of various mSWI/SNF subunits. Overall, they found that mSWI/SNF was mutated in 19.6% of all cancer types analyzed, including a broad spectrum of both solid tumors and hematopoietic malignancies. When mSWI/SNF mutations were compared with other tumor suppressors, the authors found that mSWI/SNF-subunit gene mutations were generally mutually exclusive from *TP53* and *PTEN* mutations, suggesting a role similar to that of other tumor suppressors in cancer.

Nature Genetics 2013;45:592–601; doi:10.1038/ng.2628



Mechanism of anomalous pulmonary venous connections Semaphorins were originally identified as axon guidance molecules but are thought to play a role in development of the cardiovascular system. To determine the role of semaphorin 3d in cardiovascular development, Degenhardt *et al*, as described in a recent letter in *Nature Medicine*, generated a *Sema3d* knockout mouse. They found that homozygous *Sema3d* $^{-/-}$ null mice had anomalous pulmonary venous connection (APVC), a condition in which there is improper connection of some or all of the pulmonary veins to the right atrium or systemic venous system, resulting in a left-to-right shunt. The mortality in humans of total APVC (TAPVC), if untreated, is 80%. Analysis of individuals with TAPVC revealed a phenylalanine-to-leucine substitution at position 602 of semaphorin 3d, suggesting a link with human TAPVC.

Nature Medicine, published online 12 May 2013; doi:10.1038/nm.3185



Mice provide insight into major depressive disorder To investigate the mechanisms that underlie major depressive disorder (MDD), Cao *et al*, as described in a recent letter in *Nature Medicine*, used a mouse model of chronic social defeat stress (CSDS) that mimics symptoms of human depression. They found that mice that were susceptible to CSDS had decreased concentrations of ATP in the prefrontal cortex and hippocampus, two candidate sites thought to be involved in MDD. Further elegant studies with a variety of genetically engineered mouse models convincingly demonstrated that ATP stored within astrocytes is released to decrease depressive symptoms, suggesting that astrocytic ATP release has a pivotal role in the biological mechanisms of MDD. The authors propose that understanding the mechanisms that underlie the antidepressant-like effect of ATP may allow the identification of new targets for the treatment of depression.

Nature Medicine, published online 5 May 2013; doi:10.1038/nm.3162