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VEGFR-3 plays an important role in early lymphangiogenesis and can be inhibited by a neutralizing antibody

Angiogenesis and lymphangiogenesis are critical processes for solid tumor growth, invasion, and metastasis. Many recent studies have provided insights into the normal molecular regulation of lymphangiogenesis. One of the key mechanisms of lymphangiogenesis in the embryo is sprouting of lymphatic vessels from pre-existing veins. It involves expression of lymphatic endothelium-specific marker 1 (LYVE-1) in the endothelial cells of the pre-existing veins. LYVE-1 expression sensitizes these cells to the lymphatic inductive signals. Following induction, Prox-1 is expressed in some of these cells, which are now committed to undergo lymphatic differentiation and start budding from veins. Subsequently, these cells express vascular endothelial growth factor receptor 3 (VEGFR-3) to stabilize lymphangiogenesis. In normal adult tissues and tumors, many believe that lymphangiogenesis is primarily regulated by vascular endothelial growth factor (VEGF) C and D which bind and activate VEGF receptor 3 (VEGFR-3).

Pytowski *et al*[1] demonstrated that lymphangiogenesis could be specifically and completely blocked, by inhibiting the activation of VEGFR-3 by VEGF-C. Using a novel monoclonal VEGFR-3 neutralizing antibody, mF4-31C1, lymphatic growth was prevented in normal mice and mice recently implanted with human breast carcinoma cells, without affecting the pre-existing lymphatic vessels. Peak VEGF-C expression was seen only during the earliest stages of lymphangiogenesis with much less expression during the later stages of lymphatic capillary organization and functional integration; therefore, they concluded that the role of VEGFR-3 signaling was not important for the survival of mature adult lymphatic vessels.

It is currently unknown whether VEGFR-3 neutralizing antibody can reduce the density or the size of existing lymphatic vessels in human tumors. Specifically, although lymphatic dissemination of tumors factors heavily into their metastatic spread, it remains to be seen whether therapeutic inhibition of lymphangiogenesis would be useful. Successful therapeutic reduction of lymphatic vessel density would be predicated on a requirement for continuous VEGF-C signaling in their usual maintenance. This has not yet been demonstrated, but should be a valuable area for future investigation.

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Reference

1 Pytowski B, Goldman J, Persaud K, *et al*. Complete and specific inhibition of adult lymphatic regeneration by a novel VEGFR-3 neutralizing antibody. J Natl Cancer Inst 2005;97:14–21.

The multifunctionality of hepatic stellate cells upon activation

Hepatic stellate cells (HSCs), perisinusoidal retinoid-storing mesenchymal cells located in the space of Disse, play a pivotal role in hepatic regeneration and fibrosis in response to hepatic injury. Upon stimulation under either physiological or pathological conditions, HSCs undergo morphological and biological activation, resulting in the acquisition of a contractile 'myofibroblast' phenotype, production of extracellular matrix (ECM) components including collagen, proteoglycan and adhesive glycoproteins, matrix metalloprotease, upregulated expression of profibrotic growth receptors, and secretion of the corresponding profibrotic growth factors. Tissue growth factor β1 (TGF β1) and platelet-derived growth factor (PDGF) figure prominently. These secreted profibrotic growth factors act in an autocrine and paracrine fashion to further increase ECM production and collagen deposition. Although these profibrotic growth factors may act upon different intracellular signaling pathways, it seems that hepatic fibrogenesis is well regulated regardless of the inciting activators. How HSCs orchestrate hepatic fibrogenesis upon activation, however, is still unclear. A recent study conducted by **Campbell *et al***[1] has shed light upon this question. The investigators established two *in vivo* systems to study how HSCs respond to PDGF C, a newly identified member of the PDGF ligand family. Mice with transient expression of PDGF C carried by an adenovirus vector showed robust pericellular collagen deposition by activated HSCs, as expected. To determine the long-term effect of a profibrotic environment, transgenic mice stably expressing constituitively activated PDGF C under control of a proximal mouse albumin enhancer/promoter were studied. HSCs were activated, without evidence of liver damage or injury. Livers developed steatosis and significant fibrosis. The fibrosis, manifest first by deposition of abundant collagen, began at 6 weeks of age, progressed with age, and eventually resulted in large liver volume, severe fibrosis, and development of dysplasia and foci of well-differentiated hepatocellular carcinoma. The mechanism of the hepatic fibrogenesis in the PDGF C transgenic mice was attributed to activation of several key profibrotic genes, specifically TIMP-1 and -2 and

TGF β1, and induction of their own autocrine cytokine receptors (PDGFR α and β). This engendered activation of intracellular signaling pathways involving ERK-1/-2 and PKB/AKT. The data from this study thus indicate that the hepatic fibrosis and steatosis arising from constituitive activation of HSCs is similar to liver damage or injuries seen in some forms of chronic human liver disease including fatty liver diseases. The eventual outcome of hepatocellular carcinoma is itself a critical observation which merits further investigation. An interesting addition to the above findings is the report in this issue by **Zhou *et al***[2] that HSCs express the plasma zinc metalloprotease, ADAMTS13, the protein deficiency of which causes thrombotic thrombocytopenic purpura (TTP). Thus, hepatic stellate cells exhibit a stunning portfolio of attributes when they become activated, including regulation through autocrine and paracrine profibrotic cytokines; production of extracellular matrix; contractility; influence on hepatocyte lipid metabolism and potential risk of neoplasia; and production of a key antithrombotic plasma protease.

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References

1 Campbell JS, Hughes SD, Gilbertson DG, *et al*. Platelet-derived growth factor C induces liver fibrosis, steatosis, and hepatocellular carcinoma. Proc Natl Acad Sci USA 2005:102: 3389–3394.

2 Zhou W, Inada M, Lee T-P, *et al*. ADAMTS13 is expressed in hepatic stellate cells. Lab Invest 2005;85:780–788.