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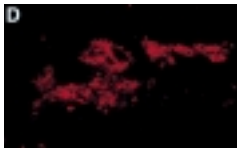
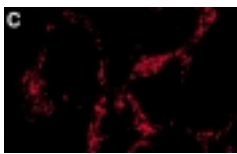
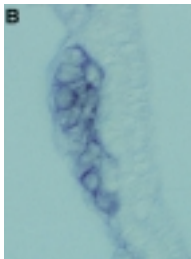
Cancer Cell Biology

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A) Whole mount RNA hybridization of mouse embryo with a probe to the vascular marker flk-1, a receptor for VEGF. B) Mouse embryo blood island reacted with antibody to PECAM, a vascular marker. C-D) In vitro differentiation of wild-type (C) and VEGF mutant (D) ES cells, followed by immunostaining for PECAM. VEGF mutant cells express PECAM but do not form intact vessels.

We are interested in the molecular controls that govern blood vessel formation. The vasculature is one of the first organ systems to form and function during embryonic development, and it changes extensively as development proceeds to meet the changing needs of the fetus. We study how blood vessels are formed during mouse development because it is fascinating, and because I believe that many molecular processes used during embryonic blood vessel formation are reused when blood vessels are formed inappropriately by a

solid tumor. Tumor angiogenesis is one important factor in the growth and spread of cancer and one that is increasingly a target of new cancer therapies. One aspect of our work uses a model in which mouse embryonic stem cells differentiate in the incubator to form several cell types.

Because they form blood vessels in this model, we can use it to study the early processes. We recently obtained some cells with a targeted mutation in a gene called VEGF. VEGF is critical to blood vessel formation in the embryo, and we showed that lack of VEGF prevents differentiation of blood vessels as stem cells differentiate. Moreover, the mutant cultures that lack VEGF accumulate cells that express different markers from mature endothelial cells that are found in blood vessels, and we hypothesize that these cells are precursors that are prevented from maturing by the mutation. We plan to study these cells to better understand how endothelial cells are formed and how they are incorporated into blood vessels. We will learn more precisely where the block in development occurs in the absence of VEGF. We have also initiated in vivo studies to complement our culture assays.

We are also interested in how blood vessels interact with hematopoietic cells. Macrophages are blood cells that help with the immune response in the adult. Macrophages also form during development before the need for an immune system. They have phagocytic properties, which means they can "eat" dead cells. Because they are associated with areas of change in the embryo, they are thought to help with tissue remodeling - for example, they congregate between the digits of the developing hand where the tissue is being degraded. We are interested in how macrophages move from the blood vessels where they are made to areas of remodeling. We recently showed that macrophages form in the blood vessels made from mouse embryonic stem cells that differentiate in vitro. They also migrate out from the vessels and congregate in areas that may be remodeling. Our recent preliminary data suggests that molecules that control trafficking of macrophages from blood vessels to the tissues in adults may also be important during macrophage movements during development.

We also have made and obtained embryonic stem cells with mutations that result in macrophage defects, and we are analyzing their phenotype upon differentiation.

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