Identification of Endothelial Stem Cells and a New Source of Pericytes

Vascular growth and remodeling are dependent on the generation of new endothelial cells from stem cells while vessel integrity and function are stabilized and maintained by embracing pericytes. For years, the cellular hierarchy and the identity of the stem cells in the endothelium remained unclear; meanwhile, the current dogma insists that pericytes are "recruited" from mesenchymal progenitors and "adhered" to the outer wall of the endothelium.

A research team led by Prof. ZENG Yi, at Institute of Biochemistry and Cell Biology (SIBCB), Shanghai Institutes for Biological Sciences (SIBS), Chinese Academy of Sciences (CAS), identified Protein C receptor-expressing (Procr$^+$) endothelial cells as vascular endothelial stem cells (VESCs) in multiple tissues, including the mammary gland, skin and retina (Figure 1).

ZENG's group adopted a series of *in vivo* approaches, including lineage tracing using genetically modified mice, cell transplantation, developmental model system as well as hindlimb ischemia injury models to investigate and characterize the behavior of Procr$^+$ VESCs inside the body system (Figure 2). The clonogenicity and endothelial properties of Procr$^+$ VESCs were also assessed through *in vitro* assays.

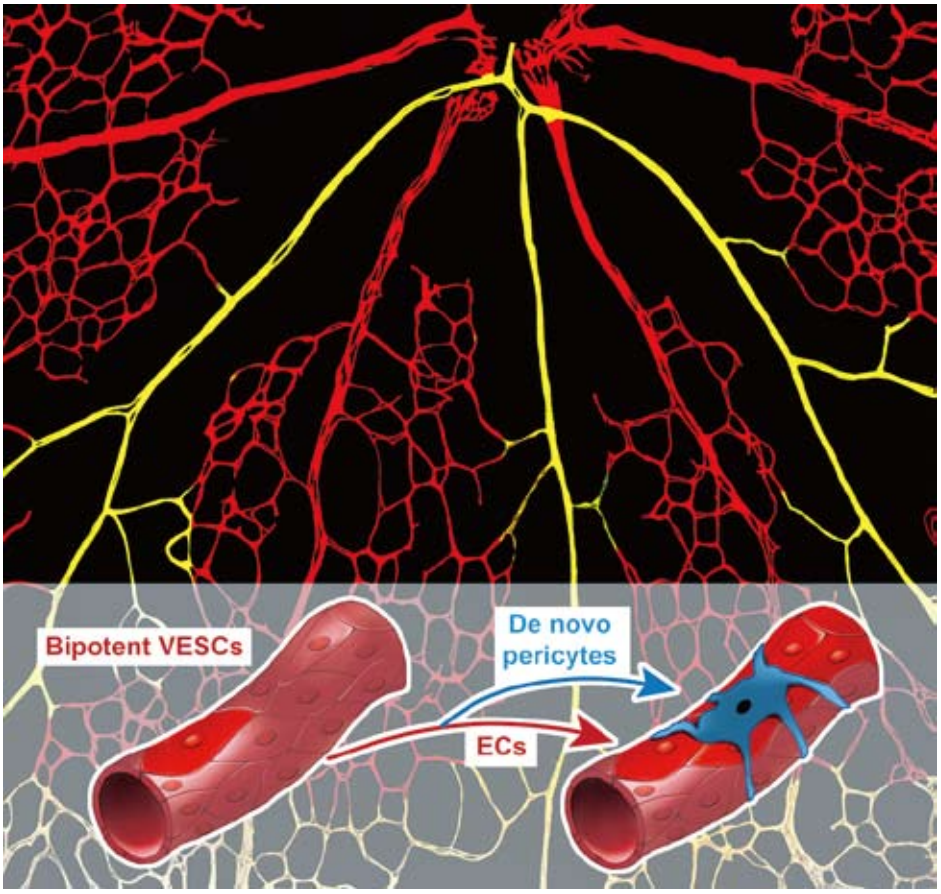

Figure 1: Identification of Procr$^+$ endothelial cells as vascular endothelial stem cells in multiple organs.

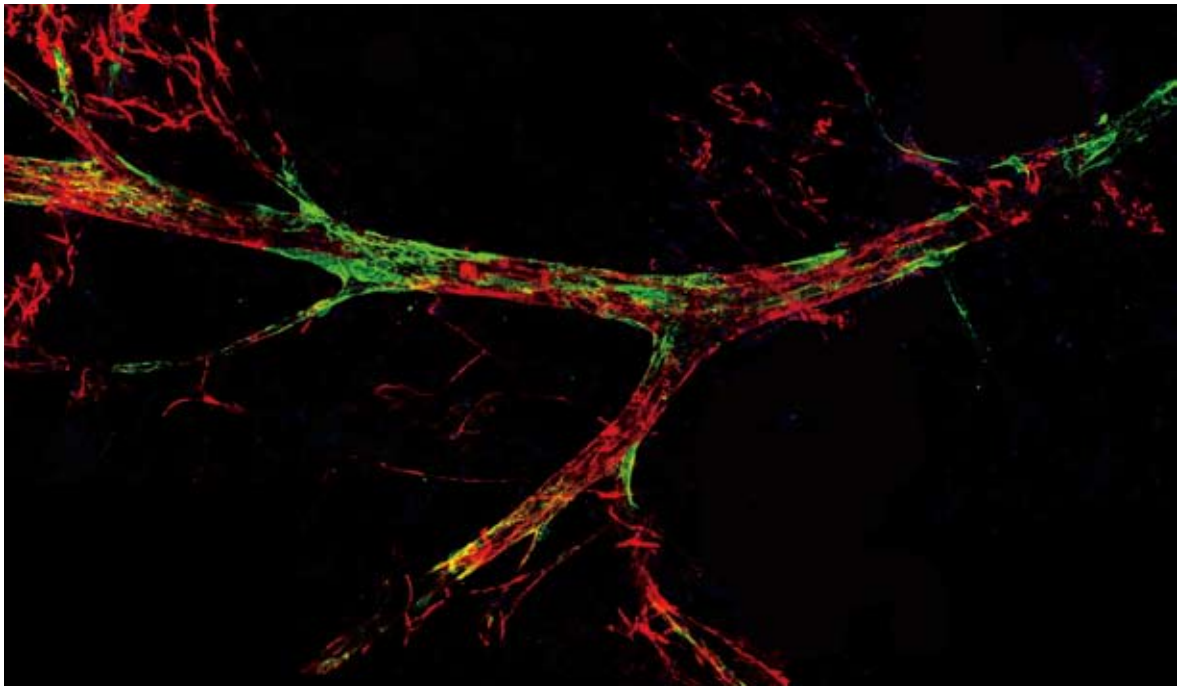

Figure 2: *In vivo* lineage tracing using genetically modified mice model to show Procr$^+$ VESCs giving rise to new endothelial cells (green) on an existing blood vessel (red).

Procr$^+$ VESCs exhibit robust clonogenicity in culture, high vessel reconstitution efficiency in transplantation, long-term clonal expansion in lineage tracing, and Endothelial-to-Mesenchymal transition (EndMT) characteristics. Remarkably, Procr$^+$ VESCs are bipotent, giving rise to *de novo* formation of endothelial cells and pericytes. This represents a novel origin of pericytes in adult angiogenesis, reshaping our understanding of blood vessel development and homeostatic process (Figure 3).

Their work establishes that 1) Procr$^+$ endothelial cells are stem cells in the vasculature of multiple organs, including the mammary gland, skin, retina and brain, and 2) Procr$^+$ VESCs give rise to both endothelial cells and pericytes during development and homeostasis. The study provides the first evidence for the de novo formation of pericytes from local endothelial stem cells. This finding challenges the current paradigm of a linear endothelial lineage, adding pericytes to the endothelial stem cells hierarchy.

This study might help locate more precise therapeutic targets for strategies to inhibit pathological angiogenesis and tumor growth, providing new insight into the cellular contribution towards fibrotic disorders.

The study, entitled "Identification of Blood Vascular Endothelial Stem Cells by The Expression of Protein C Receptor" was published in the journal *Cell Research* on July 1st, 2016, with Dr. YU Qing Cissy as first author and Prof. ZENG corresponding author of the paper.

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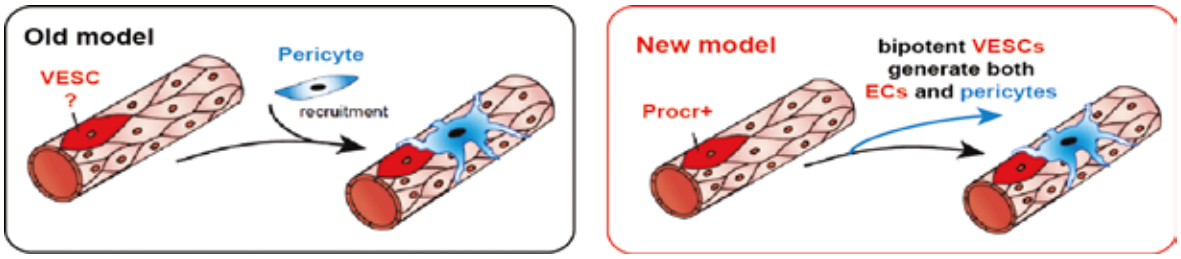

Figure 3: The traditional and updated paradigms of endothelial lineage: (Left) In the old model, the existence and cellular identity of vascular endothelial stem cells (VESCs) remained unclear. The perivascular pericytes in adult tissues were thought to have arisen from the recruitment and differentiation of mesenchymal progenitors during early development. (Right) The current study identifies Procr$^+$ endothelial cells as bipotent VESCs that give rise to both endothelial cells and *de novo* formation of pericytes. (Image provided by Prof. ZENG Yi's lab)