

(Abstract Example)

Hemo-Vasculogenesis In The Kidney And Heart

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Background: The close relationship between endothelial and hematopoietic precursors during early development of the vascular system suggested the possibility of a common precursor, the hemangioblast, for both cell types. Whether similar or related progenitors for endothelial and hematopoietic cells are present during organogenesis is unclear. Sphingosine 1-phosphate receptor 1 (S1P1) is one of the five G-protein coupled receptors activated by Sphingosine 1-phosphate (S1P), which is a crucial sphingolipid in many biological processes, including vascular development. Deletion of S1P1 in mice results in embryonic lethality at E12.5-14.5 due to failure of migration and/or differentiation of vascular smooth muscle cells (vSMCs) and pericytes. S1P1 functions autonomously in endothelial cells (ECs) as an inhibitor of angiogenesis. However, due to the early lethality, the role of S1P1 in kidney vascular development and heart development has not been determined.

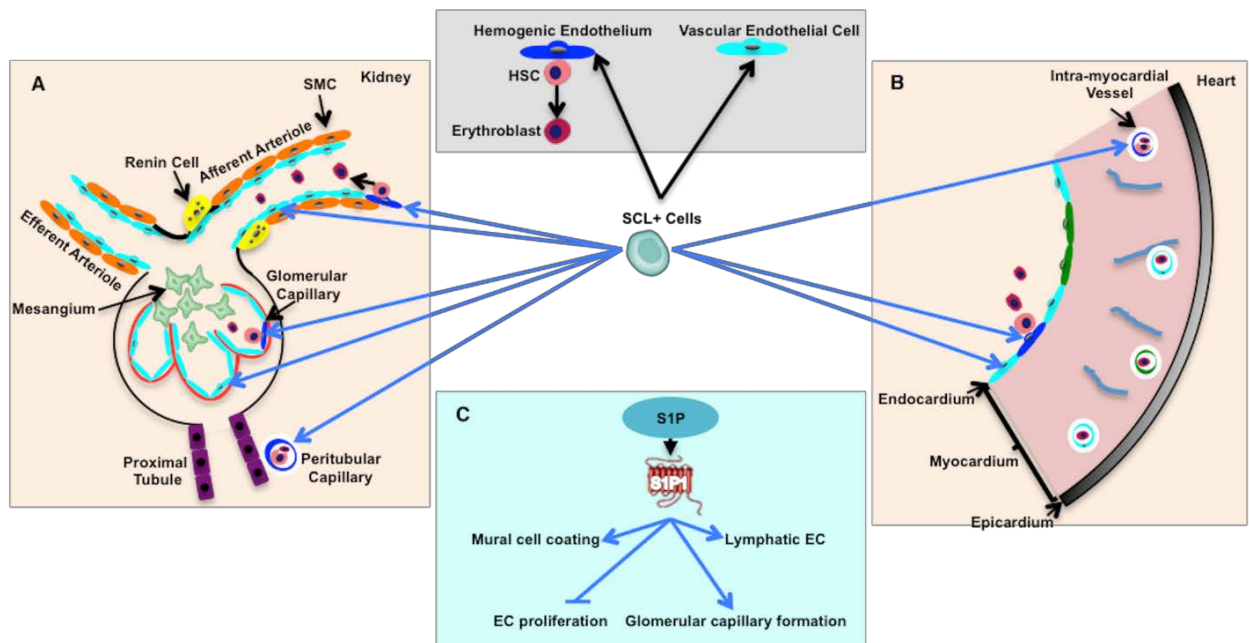
Objective: To define whether the prevascular embryonic kidney and heart possess hemangioblasts and the role of Sphingosine 1-phosphate (S1P) signaling in the development of the kidney vasculature and heart.

Design/Methods: Using tamoxifen inducible transgenic mice that specifically label endothelial and hematopoietic precursors, we performed fate-tracing studies combined with hematopoietic colony forming assays, embryonic kidney/heart cross-transplantation and *in vitro* organ culture studies.

Results: 1) We identified a multipotential progenitor, marked by the expression of the helix-loop-helix transcription factor stem cell leukemia (*SCL/Tal1*). During organogenesis of the kidney and heart, *SCL+* progenitors give rise to endothelium, endocardium and blood precursors with multipotential colony forming capacity. 2) We identified blood and blood vessels derived from the *SCL+* precursors within transplanted embryonic kidney suggesting that these precursors originate *in situ* in avascular organs and contribute to the hemo-vasculogenesis, the concomitant formation of blood and vessels. 3) Genetic ablation of the *SCL+* precursors led to abnormal vascular development in both kidney and heart. 4) Mouse embryos with conditional knockout of *S1P1* in ECs derived from *SCL+* progenitors (*EC-S1P1KO*) developed abnormal heart, severe edema, hemorrhages and die at E14.5 to E16.5. 5) *EC-S1P1KO* embryos showed kidney vascular abnormalities including dilation of arteries, veins and glomerular capillaries, endothelial hyperplasia, disruptions of vSMC coating of arteries and arterioles and absence of lymphatic endothelium. 6) The transplanted kidneys of *EC-S1P1KO* mice also developed vascular alterations revealing the intrinsic requirement of *S1P1* for renal vascular development. 7) The embryonic kidney culture experiments show improved vascular development when exposed to S1P.

Conclusions: Our data showed that vascular endothelium and blood cells originate *in situ* from *SCL+* precursors in the mouse prevascular embryonic kidney and early heart. The *S1P-S1P1* signaling pathway controls the development and assembly of the kidney vasculature and development of the heart during mouse early embryogenesis.

Concept Figure



Summary

- **Objective:** 1) Define whether the early embryonic kidney and heart possess progenitors that differentiate into vessels and blood cells. 2) Determine the fate of those progenitors and the role of Sphingosine 1-phosphate (S1P) in their differentiation during development of the kidney vasculature and heart.
- **Conclusions:** Our studies show that *SCL*⁺ progenitors originate and differentiate within the early embryonic kidney and heart by hemo-vasculogenesis, the concomitant generation of blood and vessels. Furthermore, the S1P signaling pathway is crucial for kidney vascular development and heart development.
- **Implications for Children:** The temporary hemogenic (blood forming) function of the kidney and heart may serve as a crucial transition before the establishment of their connection to the general circulation. This fundamental finding will have additional implications for our understanding of cardiovascular diseases in children and adults and our capability to perform tissue engineering.

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