Figure legends

Figure 1. Stepwise development of vessels of the three circulations. In the extraembryonic yolk sac, mesodermal precursor cells aggregate to form blood Island, the site of development of endothelial and primitive blood cells. Within the blood island, centrally located cells become primitive blood cells whereas outer cells give rise to endothelial cells (ECs). ECs then form the vascular primary plexus, which is subsequently remodeled to form the yolk sac vasculature. In the embryo proper, mesodermal precursor cells differentiate into the vascular primary plexus and major vessels, aorta and cardinal vein. After arterial and venous ECs are specified, the complex blood vasculature is formed via extensive remodeling. At E9.5, a subset of ECs of the cardinal vein acquires lymphatic endothelial cell (LEC) fate and develops into lymphatic vessels.

Figure 2. Developmental potential of FLK1 expressing (FLK1$^+$) mesoderm. FLK1$^+$ mesoderm originates from Brachyury/T-expressing cells in the primitive streak of the developing embryo and subsequently gives rise to not only endothelial and blood cells, but also other mesodermal lineage cells including vascular smooth muscle, cardiomyocyte and skeletal muscle cells.

Figure 3. Model of mesodermal progenitor cell differentiation into endothelial cells by spatiotemporal regulation of transcription factors. ER71 and FOXC2 cooperatively activate the generation of FLK1$^+$ mesoderm. *Flk1* expression is also augmented by SCL and ID1 complex, which sequesters E2-2, a negative regulator of *Flk1* expression. ER71 directs multipotent FLK1$^+$ cells to hemangiogenic mesoderm, while inhibiting the formation of cardiogenic mesoderm. Endothelial and hematopoietic lineages are determined by various transcription factors such as *Er71, Gata2, Scl* and *Gata1*. Further differentiation of endothelial cells into arterial fate is mediated by at least both NOTCH signaling (HEY1 and HEY2) and FOX family factors (FOXC1 and FOXC2), whereas venous identity is determined by COUP-TFII-mediated suppression of NOTCH signaling in conjunction with Sox family factors (SOX7 and SOX18). PROX1, SOX18 and COUP-TFII promote lymphatic endothelial ell specification from a subpopulation of the cardinal vein endothelial cells.

Figure 4. Schematic diagram of the function of ER71 and other key transcription factors required for vessel development and endothelial cells. (**A**) Structural domains of ER71 protein. Transactivation (TA) and ETS DNA binding domain are depicted. (**B**) Transcriptional regulation of ER71. FOXC2, CREB and Nkx2.5 have been identified as direct transcriptional activators of ER71. Upon translation, ER71 interacts with FoxC2 to activate the expression of key endothelial genes *Flk1, VE-cadherin, Tie2, Scl, Notch4*, and *NFATc1* through conserved composite FOX:ETS motif. FOXC2 is also necessary for arterio-venous specification and lymphatic vessel development. (**C**) The role of SOXF family transcription factors on vessel development and specification. Functional redundancies have been found among these factors; however, only SOX18 is responsible for specification of lymphatic endothelial cells. (**D**) Specification of endothelial cells and key transcription factors responsible for the fate decision. NOTCH signaling downstream effectors HEY1/2 promote arterial differentiation, whereas an orphan nuclear receptor COUP-TFII, suppresses NOTCH signaling during vein specification. Lymphatic endothelial cells competence is obtained by SOX18, which then directly activates the transcription of lymphatic endothelial cell determinant, *Prox1*. Also, COUP-TFII cooperates with PROX1 to stimulate the expression of genes required for lymphatic differentiation.

Figure 5. Schematic illustration of directed cell fate conversion from differentiated somatic cells to other cell lineages. (**A**) Differentiated somatic cells can be induced to undifferentiated pluripotent stem cells (iPSCs) by introducing four transcription factors (OCT4, KLF4, SOX2, C-MYC). Alternatively, fully differentiated somatic cells can be directly converted to other cell lineages upon ectopic expression of lineage-specific transcription factors and/or by modulating the culture milieu, independent of the iPSC stage. (**B**) Possible mechanisms and strategies for obtaining endothelial cells from differentiated somatic cells. A certain population of somatic cells such as human amniotic cells from mid-gestation stage can be converted into endothelial cells via combination of ETS factor proteins (ER71, FLK1 and ERG1) and TGFβ inhibition.[83] Various subtypes of ECs could then be generated by overexpressing EC transcription factors crucial for promoting specification into arterial (HEY1, HEY2), venous (COUP-TFII), or lymphatic (PROX1) endothelial cells.