CDB SEMINAR

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Foxc transcription factors in arterial endothelial cell specification

Summary

Compelling evidence demonstrates that arterial and venous endothelial cells are defined by genetic mechanisms involving the vascular endothelial growth factor (VEGF) and Notch signaling pathways before circulation begins. In arterial endothelial progenitors, VEGF signaling initially activates the Notch-Delta like 4 (Dll4) pathway and also induces expression of *Neuropilin 1 (Nrp1)*, a co-receptor for VEGF, as a positive feedback loop to promote the arterial program. Notch signaling subsequently upregulates downstream effector genes, Hey transcription factors, leading to the determination of an arterial cell fate. Thus, the VEGF-VEGF receptor 2/Nrp1-Notch-Hey-cascade is required for arterial specification/differentiation. By contrast, the COUP-TFII nuclear receptor, which is expressed in venous endothelial progenitors, suppresses an arterial cell fate by inhibiting the expression of *Nrp1*. However, transcriptional regulation during arterial-venous specification remains to be elucidated.

We have recently shown that Foxc1 and Foxc2, two closely related forkhead/Fox transcription factors, are key players for arterial specification that act upstream of Notch signaling. Compound mutants for *Foxc1* and *Foxc2* exhibit abnormal fusion of arteries and veins and lack the induction of arterial-specific genes such as *Nrp1, Dll4* and *Hey2*. Venous-specific genes such as *COUP-TFII* are normally expressed in compound *Foxc1*; *Foxc2* mutants, suggesting a failure to acquire an arterial cell fate. Moreover, our recent data demonstrate the importance of Foxc1 and Foxc2 in arterial cell specification: (1) Foxc proteins directly transactivate the *Dll4* and *Hey2* promoters via Fox-binding elements (FBEs); (2) COUP-TFII does not suppress Foxc-mediated induction of *Dll4* and *Hey2*; and (3) Foxc's transcriptional activity to induce *Dll4* and *Hey2* expression is modulated by VEGF-activated phosphatidylinositol-3 kinase (PI3K) and ERK (p42/44 MAP kinase) pathways. Taken together, our findings suggest that Foxc1 and Foxc2 are key components of VEGF-mediated arterial cell determination during vascular development.

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