Notch シグナルを介した血管分岐の形成と成熟機構

Notch-mediated vascular sprouting and the maturation in health and disease

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Importance of the Notch signaling is well-recognized for lateral inhibition following to the cell fate definition during developmental stages. In the case of vascular development, Notch signaling are involving to the critical competing events for artery vs. venous fate definition. Besides the artery formations, endothelial cell (EC)s display various phenotypic heterogeneity among organs, which is mainly regulated by dynamic epigenetic status in gene transcription. Thus, we examined global mapping of EC-sprouting-mediated dynamic transcriptional events, coordinated them to enriched transcription factor profiling with MEME-ChIP. Remarkably, Notch and calcium-NFAT signaling were exclusively enriched into the sprouting ECs cluster. Subsequently, to evaluate the NFAT inhibition in EC sprouting *in vivo*, we generated EC-specific conditional Down syndrome critical region (DSCR)-1 transgenic (Tg^{EC}) mice. DSCR-1 functions as the feedback inhibitor of VEGF-NFAT signaling in ECs. Highly DSCR-1 expression resulted in embryonic lethal due to lacking the EC proliferations, whereas, conditionally reduced DSCR-1 expression rescued to the birth. Importantly, DSCR-1 stable expression resulting to the NFAT inactivation in ECs revealed the malformations of Dll4-Notch-mediated tip/stalk cell balances and the proper branch formations, therefore total maturated blood vessel densities were markedly reduced. Collectively, our studies provide new insights into mechanisms underlying angiogenesis via EC sprouting with VEGF-NFAT/DSCR-1-Notch signaling, which would be helpful for both Down syndrome and cancer patients with malignant angiogenesis in future advanced therapy.