Examining the Effect of HIF and Notch in Endothelial Cell Migration and Sprouting

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Purpose: Vessels, lined by endothelial cells (ECs), supply oxygen (O2) to our bodies. When tissues are devoid of enough O2, Hypoxia Inducible Factor (HIF) is stimulated to induce >200 genes including Vascular Endothelial Growth Factor (VEGF), important for the growth of new vessels, angiogenesis. Sprouting angiogenesis is controlled by specialized 'tip' ECs through Notch and VEGF signals and inhibiting Notch leads to increased tip cells and vessel numbers. Since HIF stabilizes Notch promoting it transcriptional activity, we hypothesized that loss of HIF affects the migration and transcription of ECs in response to hypoxia and Notch stimulation. Methods: To examine the molecular interplay between HIF and Notch pathways, ECs were treated with Notch ligands (Jag1 versus Dll4) to stimulate Notch receptors or with a Notch inhibitor (DAPT). Migration and transcriptional activity were evaluated in wild-type and HIF deficient ECs after 18 hours under conditions of normoxia (21% O2) and hypoxia (2% O2). Results: We observed that HIF deficient ECs migrate slower, hypoxia stimulates the migration of controls, and Notch inhibition increases the migration of both. Hypoxic amplification of Notch target gene is not observed in mutant ECs. Analyses also show Jag1 and Dll4 ligands uniquely regulate genes in ECs. Furthermore, loss of HIF transcription downregulates all Notch genes. Conclusion: HIF and Notch differentially regulate the migration of ECs and the expression of genes involved in sprouting angiogenesis. The crosstalk between Notch and HIF signals has an important impact on vessels which could help control tumor growth and wound healing, for example.