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An overview of Notch3 function in vascular smooth muscle cells

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Abstract

Proteins of the Notch family are cell surface receptors that transduce signals between neighbouring cells. The Notch signalling pathway is highly evolutionarily conserved and critical for cell fate determination during embryonic development, including many aspects of vascular development. The interaction of Notch receptors with ligands leads to cleavage of the Notch intracellular domain (NICD) which then translocates to the nucleus and activates the transcription factor CBF1/JBP-Jκ, regulating downstream gene expression. To date four Notch receptors have been found in mammals. Of these, Notch3 is predominantly expressed in adult arterial smooth muscle cells in human. *NOTCH3* gene mutations cause the autosomal dominant condition, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoecephelopathy (CADASIL), an inherited early stroke syndrome leading to dementia due to systemic vascular degeneration. This suggests that Notch3 plays a critical role in maintaining the phenotypic stability of vascular smooth muscle cells (VSMCs). Recent publications indicate that Notch3 is involved in vascular injury and is a determinant of VSMC survival, but its exact function is unknown. The molecular mechanisms underlying CADASIL pathology are therefore intriguing. Investigation of CADASIL mutant Notch3 shows that the majority of mutations do not change CBF1/JBP-Jκ mediated classic Notch activation, so the pathological consequences of *NOTCH3* mutations in CADASIL patients can not be simply explained by loss- or gain-of-function in the classic Notch signalling pathway. This suggests that a novel Notch3-mediated signalling pathway may be present in VSMCs, or cross-regulation of Notch3 to other signalling pathway(s) may play a critical role on VSMCs survival. Alternatively, the mutant Notch3 may gain a novel or toxic function in VSMCs. This review will focus on recent findings of Notch3 in vascular development and in regulating the VSMC behaviour and phenotype, and will use findings on investigating the molecular pathology of the single gene disorder CADASIL to understand the function of Notch3 in VSMCs.

Keywords: Notch3; Vascular smooth muscle cells; CADASIL; Notch signalling; Vascular development

Contents

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1. Introduction

Genes of the Notch family encode large single-pass transmembrane receptors that transduce signals between neighbouring cells. The Notch signalling pathway is highly evolutionarily conserved and critical for cell fate

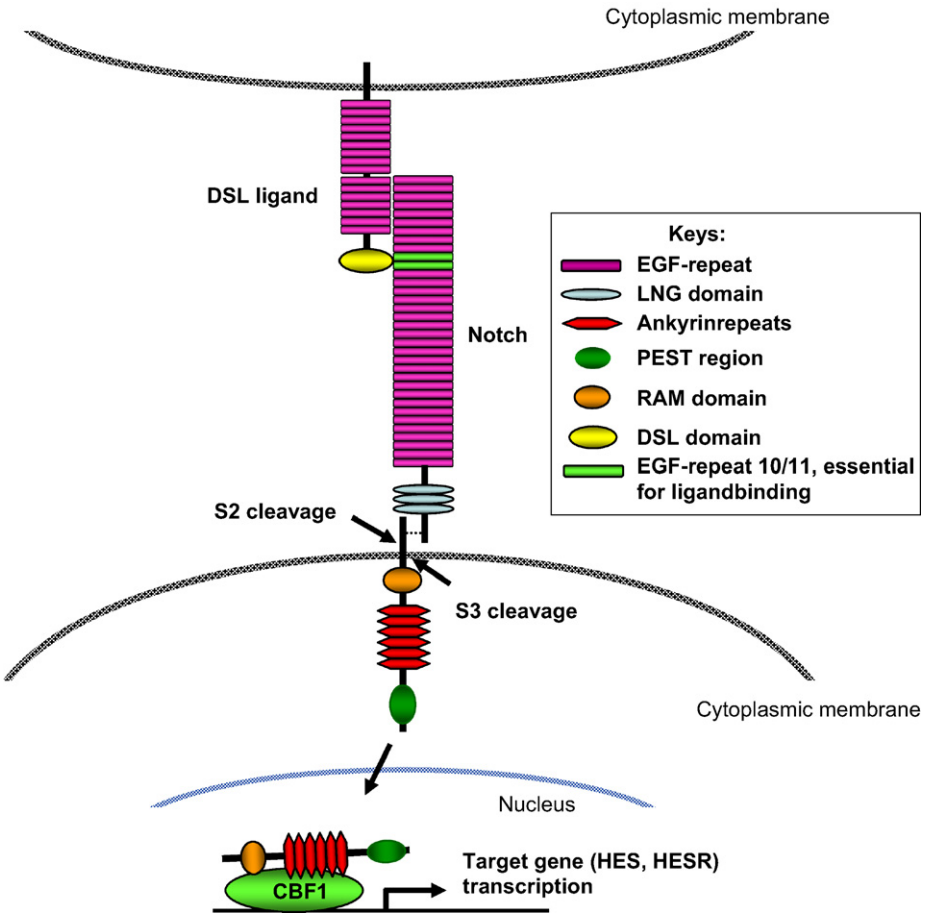

Fig. 1. The classic Notch signalling pathway. The Notch receptor locates at cell surface as a heterodimer following protease cleavage (S1 cleavage) during protein maturation. The extracellular domain (NECD) associates non-covalently with a membrane-tethered intracellular domain (NICD). The NECD contains up to 36 EGF-repeats and three cysteine-rich Notch/LIN-12 repeats (LNG domain); the NICD has a RAM domain, six tandem ankyrin repeats and a praline-, glutamate-, serine, threonine-rich sequence (PEST domain). The interaction between the DSL-ligand (Jagged, Delta) and the Notch receptor leads to two proteolytic cleavages: S2 cleavage is mediated by the ADAM metalloproteinase family protein TNFα-converting enzyme, TACE; the subsequent S3 cleavage within the transmembrane domain by presenilin-dependent γ-secretase results in the release of the NICD. The NICD then translocates to the nucleus, where it interacts with CBF1/RBP-Jκ to activate transcription of target genes HES and HESR (or HRT).