Vascular Pharmacology 63 (2014) 97–104

Contents lists available at ScienceDirect

Vascular Pharmacology

journal homepage: www.elsevier.com/locate/vph

Review

Notch signal integration in the vasculature during remodeling

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ARTICLE INFO

Article history:
Received 9 September 2014
Received in revised form 6 October 2014
Accepted 10 October 2014
Available online 18 October 2014

Keywords:
Notch signaling
Endothelial cell
Smooth muscle cell
MicroRNA
Metabolism

ABSTRACT

Notch signaling plays many important roles in homeostasis and remodeling in the vessel wall, and serves a critical role in the communication between endothelial cells and smooth muscle cells. Within blood vessels, Notch signaling integrates with multiple pathways by mechanisms including direct protein–protein interaction, cooperative or synergistic regulation of signal cascades, and co-regulation of transcriptional targets. After establishment of the mature blood vessel, the spectrum and intensity of Notch signaling change during phases of active remodeling or disease progression. These changes can be mediated by regulation via microRNAs and protein stability or signaling, and corresponding changes in complementary signaling pathways. Notch also affects endothelial cells on a system level by regulating key metabolic components. This review will outline the most recent findings of Notch activity in blood vessels, with a focus on how Notch signals integrate with other molecular signaling pathways controlling vascular phenotype.

Contents

1. Introduction

Notch signaling is a primary mediator of cell fate, differentiation, and intercellular communication in virtually all tissues. In this issue of *Vascular Pharmacology*, work from the Lilly lab expands upon the concept of Notch-mediated communication between vascular endothelial cells and smooth muscle cells, which is critical during vascular development and the pathogenesis of vascular disease. This work continues to expand our knowledge of endothelial and smooth muscle cell communication. This review will focus on recent concepts of Notch signal integration in the postnatal blood vasculature. We refer the reader to recent reviews on the related topics of Notch signaling in embryonic vascular development [1,2], differentiation and function of vascular cells [3,4], and an excellent comprehensive book on Notch signaling [5].

DOI of original article: http://dx.doi.org/10.1016/j.vph.2014.09.004.

Abbreviations: AngII, angiotensin II; AVM, arteriovenous malformation; BMP, bone morphogenetic protein; CADASIL, Cerebral Autosomal Dominant Arteriopathy with Sub-cortical Infarcts and Leukoencephalopathy; DLL, delta-like; EGFL7, EGF-like domain 7; MGP, matrix Gla protein; PGC1α, peroxisome proliferator activated receptor gamma coactivator 1 alpha; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase3; RBPJ, recombination signal sequence-binding protein Jκ; Synj2bp, synaptojanin-2 binding protein; TGFβ, transforming growth factor beta.

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http://dx.doi.org/10.1016/j.vph.2014.10.003
1537-1891/

2. Vascular quiescence to activation—overview

Most blood vessels in adult organisms have a very low rate of cellular proliferation. Quiescent endothelium expresses Delta-like1 (DLL1), DLL4, Jagged1, Notch1 and Notch4. Vascular smooth muscle cells in the homeostatic condition express primarily Jagged1 and Notch3. Once the vasculature achieves its mature conformation and function, constant communication between vascular cells is required to maintain homeostasis, and to respond to external stimuli such as cytokines, hormones, changes in blood flow or shear stress, inflammation, and mechanical trauma. In particular, endothelial cell communication with vascular smooth muscle cells is mediated via Notch signaling on adjacent cells; however, unique mechanisms including paracrine signaling via exosomes are emerging, and will be discussed.

The endothelium is a primary mediator of homeostasis, forming a contact-inhibited monolayer with tight cellular junctions. DLL4 is highly expressed in arterial endothelial cells, and plays a critical role in maintaining endothelial cell quiescence. One tissue-specific exception to DLL4/Notch-mediated endothelial quiescence was recently reported in postnatal long bones, where Notch activity promoted endothelial proliferation in columnar and arched vessels in metaphyseal growth plates, and was responsible for osteoblast maturation and bone deposition in a paracrine manner [6]. Circulating bone morphogenetic proteins (BMP), BMP9 and BMP10 are additional quiescence signals that promote homeostasis in endothelial cells (Fig. 1). Integration of Notch signaling with BMP signaling will be detailed below. With an intact endothelium, the smooth muscle cells also remain in a quiescent, contractile state, with high expression of smooth muscle cell markers. Highlights of the interaction between endothelium and smooth muscle cells via Notch signaling will be described.

The levels and expression patterns of Notch proteins and their ligands drastically change upon injury or pathological disease progression. These changes support the concept that Notch signaling is requisitioned during vascular remodeling, and also underscore the non-redundant roles of Notch ligands and receptors. Cardiovascular diseases are associated with dysregulation of Notch signaling, and specific genetic mutations have been mapped to *JAG1* or *NOTCH2* (Alagille syndrome, pulmonary artery stenoses, tetralogy of Fallot, cardiac septal defects, and coarctation of the aorta). In addition, mutations in *NOTCH1* are associated with tetralogy of Fallot and aortic valve abnormalities. These mutations have been comprehensively reviewed [7]. Recently, mutations in *NOTCH1* have also been linked to Adams–Oliver Syndrome, characterized by scalp aplasia cutis and terminal transverse limb defects, secondary to vasculopathy [8].

Several human vascular pathologies are associated with alterations in Notch signaling activity. Here we provide a few examples that include novel signaling interactions (Fig. 1). It is well known that Notch signaling regulates the processes of angiogenesis and arteriogenesis following ischemic injury or during tumorigenesis. Recent insight has linked cellular metabolism with angiogenesis, and exciting developments in this area will be discussed. In addition, interacting proteins such as synaptojanin-2 binding protein have the potential to regulate Notch signaling during angiogenesis via direct protein–protein interaction, and specific microRNAs are being discovered as regulatory factors affecting the Notch pathway.

Notch dysregulation also occurs during the pathogenesis of pulmonary arterial hypertension. Pulmonary arterial hypertension involves hyperproliferation of smooth muscle cells of the pulmonary arterioles that leads to decreased vessel lumen size and vessel elasticity, and increased pulmonary vascular resistance. Notch3 levels are increased under hypoxic conditions leading to pulmonary hypertension [9], suggesting a role in disease progression. Indeed, mice homozygous for Notch3 deletion are resistant to pulmonary hypertension, and inhibition of Notch by gamma secretase inhibitor can reverse the hypertensive phenotype in wild type mice [10]. Disease progression in pulmonary arterial hypertension is also associated with impaired BMP signaling and the activation of miR-145. It is interesting to consider the possibility that mutations leading to loss of BMP signals could lead to compensatory increases in Notch signaling. In addition, we previously showed that miR-145 is a transcriptional target of Notch in smooth muscle cells, and

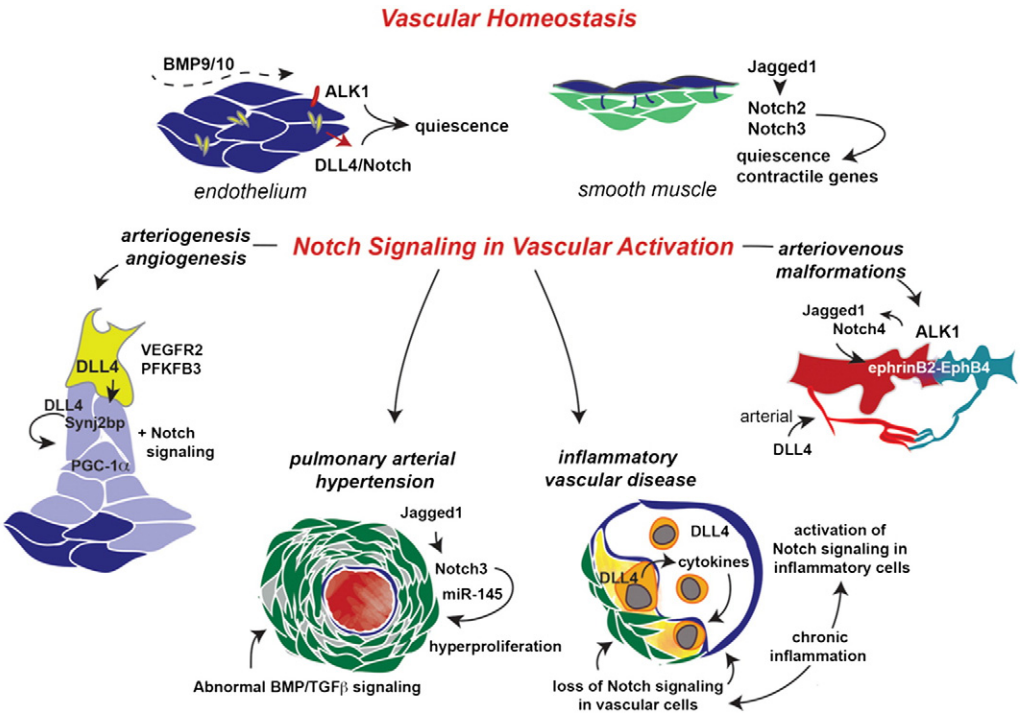

Fig. 1. Notch signaling in vascular homeostasis and remodeling. In the mature vasculature, the endothelium is a quiescent monolayer with extensive cell adhesions that extend to underlying smooth muscle cells. Quiescence signals include BMP9/BMP10 activation of ALK1, and DLL4 activation of Notch. Normal expression of endothelial cell Jagged1 activates Notch3 in smooth muscle cells to maintain their differentiated, contractile phenotype. Vascular activation under conditions of stress, injury, or disease progression is accompanied by changes in Notch ligand and receptor expression in the vessel wall. These changes regulate cellular proliferation, cell identity, cell function, and overall phenotype.