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Soluble Jagged-1 inhibits restenosis of vein graft by attenuating Notch signaling

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ABSTRACT

The excessive proliferation of vascular smooth muscle cells was key factor in the restenosis of vein graft. And the Notch signaling was demonstrated to regulate vSMC proliferation and differentiation. Soluble Jagged-1 (sJag1) can inhibit Notch signaling *in vitro* and *in vivo*; however, its capacity to suppress restenosis of vein graft remains unknown. Under the microscope, the left jugular vein of these rats was interposed into the left common carotid artery, followed without any treatment (control), or with Ad-Jag1 (treatment) or placebo (DMSO) post operation. We showed that Ad-Jag1 can attenuate restenosis of vein graft by inducing decreased proliferation and increased apoptosis *in vivo*. Notch1–Hey2 signaling is critical for the development of intima thickening by controlling vSMC-fate determination. By blocking Notch signaling, Ad-Jag1 can significantly inhibit intima thickening. These studies identify that Ad-Jag1 can restore the vSMC phenotype and inhibit the vSMC proliferation by suppression of Notch1 signaling, and thus open a new avenue for the treatment of restenosis in vein graft.

Introduction

The vein is used most as surgical revascularization for vascular stenosis disease, such as coronary and peripheral artery arteriosclerosis (Campeau et al., 1984; Conte et al., 2006). However, autologous veins are especially prone to failure, and about 30–50% of grafts result in restenosis and pathologic vascular wall thickening within 10 years (Motwani and Topol, 1998). Venous grafts become occluded when abnormal cell proliferation in the smooth muscle layer produces extra tissue in the inner lining of the vessel, a process called intimal hyperplasia (Sabik, 2011). The pathogenesis of this disease is poorly understood, and no successful clinical interventions have been identified. Most authorities consider such restenosis and intimal hyperplastic lesions as a result of excessive vascular smooth muscle cell (vSMC) proliferation and migration (Muto et al., 2010; Pintucci et al., 2006). Furthermore, vSMCs of vein graft are highly plastic and capable of modulating the transition from the contractile phenotype to pro-proliferative and anti-apoptotic phenotype in response to extracellular cues (Owens et al., 2004). However, little is known regarding the genetic pathways that regulate proliferation and plasticity of vSMCs in vein graft *in vivo*.

The Notch signaling is an evolutionarily conserved regulatory system that can regulate differentiation, proliferation, and cell survival depending on organ and tissue type. The effect of Notch signaling on cell-fate decisions is based on the expression of certain genes in cell-type specific manner (Artavanis-Tsakonas et al., 1999). Notch member proteins are expressed on the cell's surface that are activated by five Notch ligands, including Jagged-1 and -2 and Delta-1, -2, and -3. Of the Notch receptors, only Notch1, 2, and 3 are expressed on vasculature and critical in regulation of vascular morphogenesis and function during development and disease (Rehman and Wang, 2006). Ligand binding triggers a conformational change in proteolytic cleavage and release of the intracellular domain of Notch (NICD), which translocates into the nucleus and interacts with the DNA-binding protein. This transcriptional activator complex induces transcription of target genes, most notably the Hey and Herp genes, which regulate cell fate (Roca and Adams, 2007).

Recently, Notch members were demonstrated the capacity to mediate vSMC proliferation and neointimal formation following vascular injury through CHF/Hey (Jarriault et al., 1995). And overexpression of Notch1 increased proliferation and inhibited apoptosis of vSMCs (X. Li et al., 2009). Furthermore, members of the Notch family have been fundamentally extended to regulate vSMC plasticity (Sweeney et al., 2004). Consistently, Jagged1 increased the expression of smooth muscle–myosin heavy chain, whereas the Notch downstream transcription factors HERP1

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and HERP2 were able to stimulate vSMC proliferation, and differentiation (Tang et al., 2008; Wang et al., 2003; Doi et al., 2005). This study has suggested that Notch signaling may be important in regulating vSMC proliferation and differentiation. As proliferation of vSMCs is a prerequisite for intimal hyperplasia of vein graft, blockage of Notch signaling could inhibit formation and development of restenosis in