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Mini Review

CRP3/MLP as a New Target to Prevent Vein Graft Failure

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Introduction

Coronary artery bypass graft surgery is the most frequently performed surgical intervention for relieving consequences associated with myocardial infarction. Despite its efficiency and advances in the methodology of collection, preservation and early onset antithrombotic treatment, vein graft failure is estimated between 15 and 30% during the first year. After 10 years of surgery, only 50% of these grafts are free of significant stenosis. Thrombosis, intimalhyperplasia, and accelerated atherosclerosis are the primary events pathophysiological of vein graft [1,2]. Successful vein graft adaptation is a complex process. In the vein graft procedure, a vein segment is submitted to arterial haemodynamic condition and thus genes associated with venous and arterial identities can be modulated as triggers to the adaptive response. Biomechanical factors, such as shear stress and stretch, are responsible for disturbed flow patterns which make the vein susceptible to remodeling within timal thickening which reduces grafts patency [3]. The adaptations of the vein require reorganization of the vascular architecture and reprogramming of gene expression [4]. Although the morphological changes are well characterized, the molecular mechanisms of vascular remodeling are still unclear. Several markers for arteries and veins have been described and well characterized in vascular beds [5]. In the past, the molecular and structural differences observed between arteries and veins were often attributed only to physiological factors. More recently, evidence supports the idea that during embryonic development there is a genetic program specifying artery and vein identities, even before the onset of circulation [6]. In the adult vascular system, arterial and venous endothelial cells have different phenotypic markers, as well as differences in their ability to adapt to haemodynamic changes [7]. A reorganization of the venous architecture with the acquisition of an artery-like structure has been demonstrated and there is evidence for the loss of the venous phenotypemarker, Eph-B4, during the adaptative process, but without induction of the arterial phenotypemarker, Ephrin-B2 [8].

Wang et al. [9], showed that a member of the cysteine-richprotein (CRP) family of LIM domain proteins - cysteine and glycine-richprotein 3 (Crp3) is associated with vascular remodelling after balloon angioplasty injury in rats and mice. This was the first evidence of CRP3/MLP in vascular smooth muscle raising the possibility that, similar to observations in cardiacmuscle, it participates in the vascular response to increased tension. CRP3/MLP was originally identified in cardiac and striated muscle [10]. It is described to be present exclusively in nucleio fearly differentiated muscle cells and to later accumulate in the cytoplasm [11]. Nuclear CRP3/MLP seems to interact with transcription factors and positively regulate myogenesis, while cytoplasmic CRP3/MLP is associated with the actin-based cytoskeleton and maybe important for the maintenance of the contractile apparatus [12].

Later, in 2008, we have demonstrated that CRP3/MLP is modulated during the vein graft adaptation in response to the increased stretch of smooth muscle cells (SMC). The CRP3/MLP expression is present mainly in arteries and virtually absent in veins. Interestingly, during vein adaptation process, CRP3/MLP is up-regulated in a stretch-dependent manner *in vitro* and *in vivo*. Furthermore, the activation of CRP3/MLP expression in veins is secondary to the effect of increased stretch on SMCs, rather than increased shear stress on ECs [13]. This data indicated that the CRP3/MLP protein maybe considered as a new arterial SMC marker.

Flick and Konieczny [11] proposed an indirect link between CRP3/MLP with act infilaments through the interaction of its domain LIM1 with actin in and LIM2 with spectrin in cardiac and skeletal muscle tissue. It maybe assumed that a similar organization could occur in vascular smooth muscle tissue. This arrangement of the cellular cytoskeleton enables the cell to support physical forces, such as stretching in the SMCs. Veins normally exposed to low haemodynamic load may not require high levels of CRP3/MLP, but when exposed to high haemodynamic stress, such as during vein grafting, the induction of CRP3/MLP may contribute to strengthen

the connections of the cytoskeleton and prepare them to support the new haemodynamic condition.

Remodelling of the vascular wall in response to injury involves alterations in cell proliferation and migration, differentiation, programmed cell death and changes in production and/or degradation of the extracellular matrix components [14]. Evidences suggest that the CRP3/MLP protein can regulate these process by controlling gene transcription processes and celular signalling [9]. In this context, recently [15] we developed a CRP3/MLP-KO rat and showed that CRP3/MLP acts as a key modifier of the vein arterialization remodeling through its ability to sensitize stretched SMC to apoptosist hrough a decrease in the integr in-mediated signaling pathway. Our data demontrated for the first time that upon arterialization of rat jugular vein for 28 days, the CRP3/MLP-KO rats displayed a three-fold increase in the intima layer compared with wild-type animals, indicating that lack of CRP3/MLP sensitizes vein remodeling in response to arterialization. We then used CRP3/MLP-KO SMC model system to show that CRP3/MLP interacts with Fakto sensitize stretched vein SMC to apoptosis. This response is due to a decrease in integrin-mediated down stream signaling, followed by a decrease in Fak (Y397) and Akt (S473) phosphorylation, with the subsequent increase in Bax expression andactivation of effect or caspase-3. Notably, these findings under score the potential role of Crp3 as a modulator of vascular remodeling during the vein graft arterialization and other vascular remodeling processes. Thus, it is tempting to speculate that CRP3/MLP gene variants may influence vascular remodeling outcomes and that this pathway maybe explored to prevent neo intimal growth leading to pathological remodeling or to predict vascular therapeutic outcomes.

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