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Commentary

A Novel Isoform of COL4A1 in the Regulation of Vascular Intercellular Communication

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Vascular interventions have transformed the outlook towards improved patient-outcomes following atherosclerotic lesions [1]. These interventions, although revolutionizing the surgical management of such conditions, often present with a hefty clinical burden – that of restenosis. Such an end-state can be conceptualized by the fact that more than 20% of all vascular interventions result in restenosis [2];. Although anti-proliferative drug-eluting stents offer somewhat promising abilities of reducing the possibility of restenosis, the risk of late stent thrombosis still cannot be ignored, with <60% of the maximum achievable luminal diameter being achieved post-procedure [3]. Therefore, there is an urgent unmet clinical need for the better understanding of the pathogenesis and identification of therapeutic targets.

Vascular smooth muscle cells (VSMCs) in tunica media are key players in vascular remodelling after intimal injury due to their remarkable phenotypic plasticity [4]. However, this concept has recently been challenged by a discovery that adventitial stem/progenitor cells contribute to restenosis through stem cell renewal and differentiation into new VSMCs, which are stimulated by the intimal injury cascades [5]. VSMCs are derived from multiple origins including neural crest and local mesenchymal stem/progenitor cells during embryonic development [6]. Postnatally, VSMCs are derived from resident vascular wall progenitor cells [7,8]. In response to vascular injury, VSMCs undergo profound switching from a contractile to a synthetic phenotype, in which autocrine platelet derived growth factor (PDGF) signalling plays an important role [9]. In addition to dedifferentiation and proliferation of existing VSMCs, our studies and reports from other groups indicate that local resident vascular progenitor cells(VPCs) can differentiate into VSMCs and contribute to neointima formation [5,10-13]. However, the interaction between the existing activated VSMCs and VPCs recruitment remains obscure.

The work of Angbohang *et al.* seeks to bridge this incomplete understanding, by exploring the role of a novel soluble isoform of type IV collagen A1(COL4A1s) secretion mediated by X-binding Box Protein 1 splicing isoform (XBP1s), in contributing to vascular injury repair and neointima formation (14). Here, the authors described such an XBP1s-mediated COL4A1s secretion as being capable of activating VSMCs to recruit stem cell antigen 1-positive ($Sca1^+$) [14]. In the context of vascular injury, this results in the recruitment of $Sca1^+$-VPCs to the site of injury, whereby promoting the development of re-stenosis following cardiovascular interventions. In this manner, the authors stress an intercellular communication between SMCs and VPCs in the adventitia after vascular injury [14].

In addition to functioning as a mechanical scaffold and barrier, type IV collagen can support stem/progenitor cell differentiation toward vascular cell lineages [15,16]. Previous work showed that collagen IV plays a crucial role in the early stage of VSMCs differentiation from $Sca1^+$ VPC and that integrin and PDGF receptor signalling pathways can be involved in the differentiation process [17]. Like most of the genes, type IV collagen genes also undergo alternative splicing [18]. Of paramount also in the discovery, is the identification of the novel protein isomer COL4A1s, as being the mediating factor in facilitating the identified intercellular communication between VSMCs and VPCs. This COL4A1s isoform largely resembles the main structural features of the COL4A1 protein but has its internal helix domain shortened [14]. In terms of cellular function, the COL4A1s isoform may utilise its NC-domain to bind to integrins, but interaction with other cell surface components may be facilitated via the longer N-terminal [14]. Once translated however, the novel isoform of COL4A1 protein functions as a paracrine cytokine, encouraging the migration of VPCs into the site of injury. Here, they may differentiate into VSMCs and continue with their debilitating role in the

facilitation of adverse vascular outcomes in patients with cardiovascular interventions – characterised by neointima formation. The exact cellular functions of this novel isoform require further studies to comprehend its functions.

The study of Angbohang et al., delves deeper also, into the mechanism facilitating the development of the novel isomer COL4A1s, whereby increasing its clinical relevance. As such, the authors have proposed two possible mechanisms by which this COL4A1s isomer could be introduced: that of the intron by-pass mechanism, and that of the unconventional splicing mechanism. Both proposed mechanisms rely heavily on the action of the active form of XBP1s to facilitate the development of the COL4A1s isomer. As such, we demonstrate knockout of the XBP1 gene in the VSMC of mice as resulting in decreased COL4A1 in the vessel wall [14]. XBP1 therefore remains as an essential transcription factor for the COL4A1 gene transcription. In terms of the mechanism of action, we demonstrate that XBP1 does not exert its action by directly binding to the promoter region, as the overexpression of XBP1s had no effect on *pGL3-127bp-luc* reporter gene expression. We proposed therefore, there may be an enhancer element involved and have also identified this enhancer element in the study – as existing as nearly identical sequences in exon 4 and exon 42 [14].

As for the exact proposed mechanism, both pathways share a common origin – as that of endothelial denudation triggering thrombosis and the subsequent release of the platelet derived growth factor (PDGF). PDGF plays a dual role in VSMC differentiation and proliferation. It triggers VSMC differentiation in stem/progenitor cells, while it induces dedifferentiation and proliferation of mature VSMCs [16,17,19]. Our recent study has uncovered that PDGF activated XBP1 mRNA unconventional splicing in VSMCs, which contributed to VSMC proliferation [20]. XBP1 is an endoplasmic reticulum stress responsive transcription factor [21]. Our previous studies indicate that XBP1 plays multiple roles in endothelial cells [22-25]. In the present study, if the unconventional splicing mechanism is to be considered, the XBP1s can be said to bind to the previously outlined enhancer element in exon 4 and exon 42, whereby increasing the transcription of the COL4A1. Upon binding to the COL4A1 mRNA, the XBP1s protein can direct the COL4A1 mRNA to IRE1α, which can lead to the formation of the novel COL4A1s (spliced isoform). The subsequent unconventional splicing between exon 4 and 42 is said to be a key mediator in this unconventional splicing pathway. Alternatively, if the intron-bypass mechanism is to be considered, it can be said that the dimerization of exon 4 and 42-bound XBP1s leads to close proximity between exon 4 and 42, facilitating RNA polymerase transcription directly from exon 4 to exon 42. Consequently, a short transcript variant, COL4A1s, is produced. The development of this variant is characterised by the bypassing of the internal sequences. Theoretically, this mechanism will apply for gene transcription with large introns more efficiently and energy-saving. The phenomenon of transcription bypass was first described in transcriptional mutagenesis in cancer cells evolution [26,27]. As for COL4A1, the coding sequence region between exon 4 and exon 42 corresponds to its internal triple-helical domain, which corresponds to the mechanical support function but may not be necessary to perform intercellular communication. Regardless of the molecular biological process being considered, the end fates of such mechanisms are the same – that of soluble COL4A1s protein production, which once secreted into extracellular matrix, functions as chemoattractant to recruit VPCs.

An important element of the research of Angbohang et al. also, is the assertion of the influential relationship between the COL4A1s' stimulation and the activation and differentiation of VPCs. However, the pathophysiological mechanisms underlying such a relationship remain unclear; future research could also focus on exploring the mechanism of migration of the COL4A1s-stimulated VPCs, to possibly investigate pharmacological interventions to inhibit this migration. Furthermore, future areas of research could focus on the identification of the transmembrane receptors interacting with COL4A1s in VPCs, to possibly determine whether pharmacological inhibition of these transmembrane receptors would prove fruitful in limiting the progression of restenosis. Additionally, albeit the structural make-up of COL4A1 mRNA renders it as possibly also being another unconventional splicing target of IRE1α (as its exon 4 and exon 42 elements resemble the stem-loop structure observed in *XBP1* mRNA, the well-known splicing target of IRE1α), there remains limited understanding of the exact role of IRE1α in influencing the molecular properties of the COL4A1s mRNA. Exploring this in future studies could perhaps lead to breakthroughs in the treatment/prevention of restenosis following cardiovascular interventions, should the influence of IRE1α on COL4A1 mRNA be established – similar to the findings of Jiang et al., who demonstrate the anthracycline antibiotic, doxorubicin, as being capable of inhibiting the IRE1α – XBP1 axis that's incorporated in the unfolded protein response. They assert also, that doxorubicin may be utilized clinically to target IRE1α–XBP1-dependent tumours [28] – the clinical extrapolation may prove it as a useful therapeutic mechanism to target IRE1α–XBP1-dependent COL4A1s mRNA-induced VSMCs and VPCs communication.

Overall, the study of Angbohang et al. is useful in establishing the intercellular communication between VSMCs and VPCs in adventitia after vascular injury; and in highlighting a novel protein isomer COL4A1s as being capable of medicating this intercellular communication. Furthermore, they also propose that the mechanism of this protein production is relatively special and put forward two hypotheses: the "bypass transcription" at a transcriptional level, and "unconventional splicing" at a translational level. Their study also highlights areas of potential future research, such as other substrates of action for the IRE1α, as well as investigating possible transmembrane receptors that could interact with COL4A1s in VPCs, to serve as targeting inhibition points in the treatment/prevention of restenosis. Should these areas be explored, targeting the XBP1–mediated COL4A1s secretion and the pathophysiological mechanisms involved, could provide breakthroughs in lowering the risk of developing restenosis, following cardiovascular injuries.

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