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Thrombospondin-1-induced smooth muscle cell chemotaxis and proliferation are dependent on transforming growth factor-β2 and hyaluronic acid synthase

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Abstract Angioplasty causes local vascular injury, leading to the release of thrombospondin-1 (TSP-1), which stimulates vascular smooth muscle cell (VSMC) migration and proliferation, important steps in the development of intimal hyperplasia. Transforming growth factor beta 2 (TGF-β2) and hyaluronic acid synthase (HAS) are two pro-stenotic genes upregulated in VSMCs by TSP-1. We hypothesized that inhibition of TGF-β2 or HAS would inhibit TSP-1-induced VSMC migration, proliferation, and TSP-1 signaling. Our data demonstrate that Inhibition of either TGF-β2 or HAS inhibited TSP-1-induced VSMC migration and proliferation. Activation of ERK 1 was decreased by TGF-β2 inhibition and unaffected by HAS inhibition. TGF-β2 and HAS are not implicated in TSP-1-induced *thbs1* expression, while they are each implicated in TSP-1-induced expression of their own gene. In summary, TSP-1-induced VSMC migration and proliferation rely on intact TGF-β2 signaling and HAS function. TSP-1 activation of ERK 1 is dependent on TGF-β2. These data further expand our understanding of the complexity of TSP-1 cellular signaling and the involvement of TGF-β2 and HAS.

Keywords Thrombospondin · TGF-β · Hyaluronan · Migration · Proliferation

Introduction

Balloon angioplasty for arterial stenosis is a prevalent procedure in the treatment of peripheral arterial disease (PAD). However, angioplasty causes local vascular injury, leading to a cascade of events including adherence of inflammatory cells and platelet degranulation which releases thrombospondin-1 (TSP-1), an initiating factor in the development of intimal hyperplasia (IH) and restenosis. TSP-1, a matricellular glycoprotein, is known to induce proliferation and chemotaxis in vascular smooth muscle cell (VSMC) processes which contribute to IH formation [1–4]. We previously showed that TSP-1 upregulates several pro-stenotic genes, including the genes for transforming growth factor beta 2 (TGF-β2) and hyaluronic acid synthase 2 (HAS 2), and exerts a positive feedback effect on TSP-1's own gene expression (*thbs1*) [5].

The TGF-β family of proteins are believed to be important in IH development. Supporting data to this concept are that TGF-β1 mRNA is increased in restenotic lesions compared to primary atherosclerotic lesions [6] and TGF-β activation is upregulated after endovascular interventions [7]. Most of the current research addresses TGF-β1; however, we recently found that the gene expression of TGF-β2 is increased in VSMCs stimulated by TSP-1[5]; therefore, the relationship between TSP-1 and TGF-β2, and their effects on VSMC function warrant further study.

Kristopher G. Maier and Vivian Gahtan have contributed equally to this study.

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