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CD98 regulates vascular smooth muscle cell proliferation in atherosclerosis

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ABSTRACT

Background and aims: Vascular smooth muscle cells (VSMC) migrate and proliferate to form a stabilizing fibrous cap that encapsulates atherosclerotic plaques. CD98 is a transmembrane protein made of two subunits, CD98 heavy chain (CD98hc) and one of six light chains, and is known to be involved in cell proliferation and survival. Because the influence of CD98hc on atherosclerosis development is unknown, our aim was to determine if CD98hc expressed on VSMC plays a role in shaping the morphology of atherosclerotic plaques by regulating VSMC function.

Methods: In addition to determining the role of CD98hc in VSMC proliferation and apoptosis, we utilized mice with SMC-specific deletion of CD98hc ($CD98hc^{fl/fl}SM22\alpha Cre^{+}$) to determine the effects of CD98hc deficiency on VSMC function in atherosclerotic plaque.

Results: After culturing for 5 days *in vitro*, $CD98hc^{-/-}$ VSMC displayed dramatically reduced cell counts, reduced proliferation, as well as reduced migration compared to control VSMC. Analysis of aortic VSCM after 8 weeks of HFD showed a reduction in $CD98hc^{-/-}$ VSMC proliferation as well as increased apoptosis compared to controls. A long-term atherosclerosis study using $SMC\text{-}CD98hc^{-/-}/ldlr^{-/-}$ mice was performed. Although total plaque area was unchanged, $CD98hc^{-/-}$ mice showed reduced presence of VSMC within the plaque (2.1 ± 0.4% *vs.* 4.3 ± 0.4% SM22α-positive area per plaque area, $p < 0.05$), decreased collagen content, as well as increased necrotic core area (25.8 ± 1.9% *vs.* 10.9 ± 1.6%, $p < 0.05$) compared to control $ldlr^{-/-}$ mice.

Conclusions: We conclude that CD98hc is required for VSMC proliferation, and that its deficiency leads to significantly reduced presence of VSMC in the neointima. Thus, CD98hc expression in VSMC contributes to the formation of plaques that are morphologically more stable, and thereby protects against atherothrombosis.

1. Introduction

During progression of atherosclerosis, transformation of vascular smooth muscle cells (VSMC) from the quiescent contractile phenotype towards the proliferative migratory phenotype into the plaque area to form a fibrous cap is believed to be an essential step in the formation of stable plaques [1]. The two major phenotypes of VSMC include fully differentiated, contractile cells responsible for vasodilation and vasoconstriction, and migratory, proliferative cells that are activated during growth or injury [2]. During atherosclerosis development, VSMC respond to mediators such as platelet derived growth factor (PDGF)–BB, endothelin-1, thrombin, IFN-γ and IL-1 secreted by endothelial cells [3] and

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