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Suppression of Matrix Metalloproteinase-3 by Doxycycline Attenuates Angiogenesis in Response to the Intracranial Venous Hypertension

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Introduction

The molecular mechanism of brain arteriovenous malformation (BAVM) is largely unknown. Intracranial venous hypertension (VH) may enhance focal angiogenesis and promote the BAVM formation and development. The present study is therefore to demonstrate the role of matrix metalloproteinase-3 (MMP-3) in the venous hypertension induced angiogenesis and the potential therapeutic target for the MMP-3 inhibition.

Methods

A venous hypertension rat was produced via common carotid artery and distal external jugular vein anastomosis. These rats then underwent a Doxycycline treatment daily up to 4 weeks. Microvessel density in the peri-sinus area, expression of MMP-3/2/9, VEGF, TIMP-1, TGF-ß and HIF-1? were further examined. In in vitro study, we overexpressed or knockdown MMP-3 in human brain microvascular endothelial cells (HBMECs). We then examined cell proliferation, migration, capillary-like tube formation in these cells, and examined wound healing test between different MMP-3 expression level HBMECs.

Results

After venous hypertension, microvessel density in the peri-sinus cortex greatly increased accompanying with elevated expression of MMP-3/2, VEGF, TGF-ß and TIMP-1 except MMP-9. Doxycycline could suppress microvessel density and inhibit MMP-3, as well as reduce VEGF, TGF-ß and TIMP-1expression compared to the controls ($p<0.05$).MMP-3 overexpression promoted HBMECs migration while knockdown MMP-3significantly attenuated HBMECs proliferation, migration, and tube formation ($p<0.05$).

Conclusions

MMP-3 plays an important role in the venous hypertension induced angiogenesis and in promoting vascular remodeling. Doxycycline could suppress MMP-3, which provides a potential target for inhibiting BAVM formation and development.

Learning Objectives

By the conclusion of this session, participants should be able to: 1) Describe the importance of MMP-3 in the venous hypertension induced angiogenesis and in promoting vascular remodeling. 2) Describe the potential therapeutical mechanism of MMP-3 inhibiton by Doxycycline. 3) Provide a potential target for inhibiting BAVM formation and development.

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