Tenascin-C is induced by chronic hypoxia in cardiomyoblasts and exacerbates post myocardial infarction remodeling

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Aims The overexpression of Tenascin-C (TNC) following myocardial infarction (MI) is associated with adverse left ventricular (LV) remodeling and poor cardiac function. The aim of this study was to clarify 1) the contribution of TNC on impaired hemodynamic function following MI ex vivo and 2) to assess the MMP and TIMP expression as well as the impact of TNC on MMP formation in cardiomyocytes.

Materials and Methods MI was induced in TNC knockout and wildtype mice. Six weeks later hemodynamics were assessed by the isolated working heart preparation. Myocardial mRNA levels of TNC, TIMP-1, TIMP-3 and MMP-9 were determined one and six weeks post-MI. In addition, H9c2 cardiomyoblasts were subjected to 6 and 16 hours of total hypoxia and TNC mRNA expression was evaluated. Moreover, the effect of human tenascin-C (hTNC) on MMP-2 and MMP-9 mRNA expression was evaluated by RT-qPCR.

Results and Discussion Cardiac output and external heart work were improved in knockout mice six weeks after MI. Collagen ratio was reduced (p<0.05) in knockout. TIMP-1 was downregulated both one and six weeks, TIMP-3 was upregulated one week (all: p<0.01) post-MI in knockout. MMP-9 was decreased in knockout six weeks post-MI (p<0.05). TIMP-3/MMP-9 ratio was higher in knockout mice one week and six weeks post-MI (both p<0.01). In vitro data revealed oxygen and glucose deprivation as the main inducer of TNC expression on short incubation (p<0.05). Moreover, a lower concentration of hTNC revealed a higher influence on MMP-2 regulation in both short and prolonged incubation (24 and 48 h; p<0.05), while MMP-9 mRNA expression was constant regardless of hTNC concentration or incubation time.

Conclusion TNC expression was markedly increased both following MI and chronic hypoxia. This was associated with the elevation of MMP-2 expression. Collectively, our results underline the central role of TNC in adverse LV remodeling as well as show TNC as a potential therapeutic target to attenuate adverse LV remodeling following MI.