ROLE OF FIBRONECTIN EXTRA DOMAIN A (EDA) IN CARDIOVASCULAR DISEASES: EVIDENCES FROM ANIMAL MODELS OF NEOINTIMAL HYPERPLASIA AND ATHEROSCLEROSIS

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Background: Fibronectins (FN) are multifunctional glycoprotein present in the plasma and in the ECM of the tissues. The primary transcript undergoes alternative splicing to generate various iso-forms including FN-EDA whose levels are increased during a series of pathological conditions. In this study we investigated the role of FN-EDA in restenosis and atherosclerosis.

Methods and Results: Specific gene targeting allowed the generation of mice expressing fibronectin constitutively expressing EDA Neo-intima formation was studied by placing a non-obstructive collar on the right carotid artery of FN-EDA⁺⁻, FN-EDA⁺⁺ and FN-EDA⁺⁺ mice for a period of 9 weeks. The neointimal thickening (measured as intima to media ratio, IMT) was greater in mice lacking fibronectin EDA exon (FN-EDA⁻⁻) compared to FN-EDA⁺⁻ and FN-EDA⁺⁺ mice (IMT 1.42±0.21 vs 0.84±0.11 and 1.00±0.35, respectively). The remodelling index (measured as the slope of external elastic lamina area versus IMT curve, RI) was found to be lower in both FN-EDA⁻⁻ and FN-EDA⁺⁻ compared to FN-EDA⁺⁺ mice (RI: 0.83±0.11, 0.56±0.20 vs 1.20±0.27 respectively). The vascular smooth muscle cells from FN-EDA⁻⁻, FN-EDA⁺⁻ and FN-EDA⁺⁺ were isolated for the study of cell-mediated mechanisms. A preliminary analysis showed a decrease in atherosclerosis development in mice lacking FN-EDA compared to controls and liver specific knock-out models.

Conclusion: These data support a role for fibronectin extra domain-A in the process of intimal hyperplasia and atherosclerosis. Further studies are warranted to elucidate the molecular mechanisms and the pathways observed.