ROLE OF ADAM-12/SYNDECAN-4 SIGNALLING PATHWAY IN VENTRICULAR REMODELLING IN RATS WITH ALCOHOLIC CARDIOMYOPATHY

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Objectives Chronic excessive consumption of alcohol causes cardiac remodelling and eventually leads to alcoholic cardiomyopathy (ACM). A disintegrin and metalloproteinase-12 (ADAM-12) is involved in degradation of extracellular matrix using syndecan-4 as a primary cell surface receptor. This study aimed to investigate the role of ADAM-12/syndecan-4 signalling pathway in ventricular remodelling of ACM.

Methods Fifty healthy Wistar rats were randomly divided into a control group (n=20) and an ACM group (n=30). Animals in the ACM group were given 10% alcohol ad libitum as the drinking water and 60% alcohol (5 ml kg\(^{-1}\) once per day) by intragastric administration in the first week; 10% alcohol ad libitum as the drinking water and 60% alcohol (10 ml kg\(^{-1}\) twice per day) by intragastric administration in the second week; 20% alcohol ad libitum as the drinking water and 60% alcohol (15 ml kg\(^{-1}\) twice per day) by intragastric administration from week 3 to week 16; and 30% alcohol ad libitum as the drinking water and 60% alcohol (15 ml kg\(^{-1}\) twice per day) by intragastric administration from week 17 to month 6. Animals in the control group received purified drinking water in the same regimen with alcohol treatment. Before and 6 months after initiating the study, left ventricular end diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF), and fractional shortening (FS) were assessed by echocardiography. Histopathology and ultrastructure of myocardium were examined with light and electron microscopy; mRNA expressions of ADAM-12 and syndecan-4 were evaluated by real-time PCR; and protein expressions of ADAM-12 and syndecan-4 were analysed using immunohistochemistry and western blot, respectively. The expression of TIMP-3, an endogenous inhibitor of ADAM-12, was also tested.
Results  Following 6 months of alcohol feeding, LVEF and FS were reduced $p<0.05$ for both), while LVEDD was augmented in the ACM group $p<0.05$), as compared with the control group. In addition, severe changes in cardiac structure were seen in the ACM group. The mRNA and protein expressions of ADAM-12 and syndecan-4 were up-regulated in the ACM group in comparison with the control group $p<0.05$ for all), while those of TIMP-3 were down-regulated. In both groups, the protein expression of ADAM-12 positively correlated with that of syndecan-4 and LVEDD $p<0.05$ for both), whereas it negatively correlated with LVEF $p<0.05$).

Conclusions  Along with decreased expression of TIMP-3, ADAM-12 and syndecan-4 are over-expressed and are associated with ventricular remodelling in ACM. Therefore, the ADAM-12/syndecan-4 signalling pathway may represent a new therapeutic target in the prevention and treatment of ventricular remodelling in ACM.
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