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The Cellular Interplay Between CD44 and Na+/H+ Exchanger1 in Cardiac Remodeling

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Background: Extracellular matrix (ECM) remodeling is a characteristic feature of cardiac remodeling which, if left untreated, progresses to heart failure. Cardiac fibroblasts, the major cellular component of the myocardium, are responsible for maintaining the ECM integrity. Upon cardiac injury, such as myocardial infarction (MI), pressure or volume overload, cardiac fibroblasts transdifferentiate into cardiac myofibroblasts. Cardiac myofibroblasts are capable, of secreting proinflammatory cytokines and collagen; initiating tissue repair mechanisms (i.e., cardiac fibrosis). Hyaluronan (HA), a major component of the ECM, which is synthesized by hyaluronan synthase enzyme-2 (HAS-2), was shown to contribute in ECM remodeling and myocardial fibrosis by interacting with its cell surface receptor; CD44. CD44 is a transmembrane glycoprotein involved in multiple physiological and pathological conditions. Na /H exchanger isoform-1 (NHE-1) a cardiac specific intracellular pH regulator, which is triggered by neurohormonal stimulation of Angiotensin II (ANG II), phenylephrine (PE), endothelin-1 (ET-1) or inflammatory mediators has also been implicated in cardiac remodeling. A previous study has shown that HA-CD44 interaction enhanced ECM remodeling in a non-cardiac model through activation of NHE-1 and hyaluronidase-2 (HYAL-2), a low pH-dependent enzyme which degrades hyaluronan polymers into lower molecular weight fragments. Yet, the link between NHE-1 and CD44 interaction in cardiac setting has not been addressed.Methods: CD44 expression was measured by qPCR and immunohistochemistry in transgenic mice expressing cardiac specific NHE-1. In vitro, normal human ventricular cardiac fibroblasts (NHCF-V) were treated with either 0.1 or 1 μM ANG II for 6, 24 or 48 hours to induce myofibroblast

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phenotype. Cell lysates and culture media were collected and analyzed by immunoblotting. Standard CD44 (CD44s), soluble CD44 (solCD44), unmodified CD44, HYAL-2 and HAS-2 protein expression were measured following ANG II treatment.Results: mRNA expression and immunohistochemistry data demonstrated that CD44 expressions were significantly elevated in heart tissues from transgenic mice expressing cardiac specific NHE-1 compared to wild type. Immunoblotting analysis of NHCF-V cell lysates showed a significant increase of CD44s protein expression, appearing at 75 KDa, following 0.1 μM ANG II treatment for 24 hours (131.14 ± 3.18 % ANG II vs. 100% control; $P \leq 0.01$). CD44s protein expression did not show a change at 6-hour or 48-hour time point. Unmodified CD44, appearing at 37 kDa, HAYL-2 and HAS-2 protein expressions did not change following stimulation with various concentrations of ANG II at various time points. However, a trend towards increase was observed with solCD44 protein expression, appearing at 75 kDa, in NHCF-V conditioned media (CM) following 24-hour treatment with both 0.1 and 1 μM ANG II. A similar trend was observed with HYAL-2 protein expression in NHCF-V CM following 24-hour treatment with 1 μM ANG II, whereas there was no observed protein expression for HAS-2 and the unmodified form of CD44. Conclusion: ANG II, a well-established stimulator of NHE-1, is able stimulate the CD44s in NHCF-V cell lysates. Similarly, a trend towards increase of solCD44 expression was demonstrated in NHCF-V CM when treated with ANG II. This maybe due to the expression of CD44 in the extracellular space. HYAL-2 protein was also expressed in NHCF-V CM, while no change was detected in cell lysates. The protein and gene expressions of CD44, HYAL-2 and HAS-2 in the presence and absence of a NHE-1 inhibitor and ANG II type 1 receptor (AT-1) inhibitor remain unknown and need to be addressed to further understand the cellular interplay of NHE1 and CD44 in cardiac remodeling. It is of a significant importance to identify the signaling pathways leading to CD44 activation for better understanding of etiologies behind cardiac remodeling; and to find new potential targets that would suppress or regress the progression to myocardial dysfunction and heart failure.