P11

The Z-disc protein syndecan-4 activates pro-hypertrophic calcineurin-NFAT signaling in the myocardium

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Introduction: The signaling mechanisms involved in myocardial hypertrophy are not well understood. We have previously linked syndecan-4, a transmembrane proteoglycan localized to the Z-discs in cardiomyocytes, to myocardial hypertrophy. Mice lacking syndecan-4 do not develop concentric hypertrophy after aortic banding (AB). Here we demonstrate that syndecan-4 anchors and activates the pro-hypertrophic calcineurin A-Nuclear Factor of Activated T-cells (CnA-NFAT) signaling pathway.

Results: In syndecan-4 KO AB, NFATc4 activation and expression of NFAT-target genes BNP and RCAN1-4 were significantly lower than in WT AB. Conversely, overexpression of syndecan-4 in HEK293 cells or introduction of a partial syndecan-4 protein into cardiomyocytes activated NFATc4. Immunoprecipitations showed increased association between CnA, its co-activator calmodulin and syndecan-4 in AB hearts compared to sham-operated controls. Peptide array experiments showed that CnA binds to the cytoplasmic V-C2 region of syndecan-4 through its autoinhibitory domain. Cell permeable V- or C2-region peptides inactivated or activated NFATc4, respectively, while a C1-derived peptide had no effect, suggesting that syndecan-4 both anchors (V-region) and activates (C2-region) CnA. Moreover, we show that phosphorylation of serine 179 (pS179) is reduced in aortic stenosis patients and in AB murine hearts compared to controls. More CnA was immunoprecipitated with non-phosphorylated syndecan-4 than with the phosphorylated form, indicating that reduced pS179 in syndecan-4 is involved in the hypertrophic response. Accordingly, pull-down with pS179 resulted in reduced binding of CnA. Activation of NFATc4 occurred in HEK293 cells transfected with a mutant mimicking minimally phosphorylated S179 (S179A), whereas a mutant mimicking constitutive phosphorylation (S179E) did not. Finally, overexpression of CnA in HEK293 reduces pS179, indicating that CnA regulates its own binding and activation by syndecan-4.

Conclusion: Our data indicate that in a pressure-overloaded heart, syndecan-4 activates pro-hypertrophic CnA-NFATc4 signaling, and suggest a crucial role for phosphorylation of syndecan-4 and the syndecan-4-CnA interaction in development of myocardial hypertrophy.

8th Annual CHFR Symposium
September 31 – October 01, 2010
Holmenkollen Park Hotel Rica
Oslo, Norway