

Phosphorylation of syndecan-4 regulates myocardial hypertrophy through the calcineurin-NFAT signalling pathway

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Myocardial hypertrophy and subsequent heart failure develop in response to pressure overload, however the signalling processes involved are poorly understood. We here demonstrate a crucial role for phosphorylation of syndecan-4, a transmembrane proteoglycan localized to costameres and Z-discs in cardiomyocytes, in regulating the calcineurin-Nuclear Factor of Activated T-cell (NFAT) signalling which is involved in development of concentric hypertrophy. More specifically, we have investigated the interaction between syndecan-4 and the calcineurin-NFAT signalling pathway in a pressure-overload aorta-banding model of cardiac hypertrophy in mice.

In vitro results showed that recombinant calcineurin was pulled down with syndecan-4 and to a lesser extent with syndecan-2. The association between endogenous calcineurin, its activator calmodulin and syndecan-4 was increased in left ventricular lysates isolated from pressure-overloaded hearts compared to sham-operated controls. The cytoplasmic part of syndecan-4 is 28 amino acids long and composed of three regions, C1, V and C2. C1 and C2 are conserved between the four syndecans, while the V-region is specific for each of them. *In vitro* pull-down and peptide array experiments showed that calcineurin interacts with the V-region of syndecan-4 through its auto inhibitory domain. Previous results have shown that phosphorylation of serine 179 (S179) in the C1-region is important for PKC α -binding and activation. We here show that the level of phosphorylation of S179 was reduced in pressure-overloaded hearts compared to sham controls and that more calcineurin was immunoprecipitated and pulled-down with non-phosphorylated syndecan-4 than with the phosphorylated version.

In summary, in a pressure-overloaded heart, serine 179 in syndecan-4 is dephosphorylated and calcineurin binds to the intracellular V-region through its auto inhibitory domain. Binding of calcineurin to syndecan-4 results in increased activation of NFATc4, a well-known pro-hypertrophic transcription factor. Conclusively, these data indicate a crucial role for the syndecan-4-calcineurin interaction in development of concentric hypertrophy.