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Role of the calcium/calmodulin-dependent protein kinase II splicing variant δA in cardiac remodeling

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Heart failure (HF) is a common and life-threatening disease all over the world. A better understanding of the underlying pathological remodeling process may lead to new therapeutic approaches. The protein kinase CaMKII has been suggested as a promising therapeutic target. However, CaMKII consists of different splicing variants, and the specific and relative roles of the different splice variants are incompletely understood. The splicing variants CaMKIIδA, δB and δC were suggested to be involved in cardiac remodeling.
In this project, we set up an in vivo methodology to investigate the specific functions of these splicing variants. We used inducible knockout mice to delete CaMKIIδ and its redundant isoform CaMKIIγ. We then used adeno-associated viruses to re-express the three splicing variants δA, δB and δC, allowing us to evaluate their specific functions in a model of pressure overload-induced pathological remodeling.
Surprisingly, CaMKIIδ_A seemed to be partly involved in the induction of cardiac remodeling whereas CaMKIIδ_B and δ_C on their own could not affect pathological remodeling. But re-expression of CaMKIIδ_A could not induce the entire process of pathological remodeling that was prevented by the deletion of CaMKIIδ and CaMKIIγ, It was suggested that CaMKIIδ regulates cardiac remodeling through the HDAC4-MEF2 signaling pathway but the contribution of the different splicing variants remained unclear. Now, we show that CaMKIIδ_A like CaMKIIδ_B and CaMKIIδ_C bind and phosphorylate HDAC4, resulting in cytosolic accumulation of HDAC4. But other than CaMKδ_C, CaMKIIδ_A does not phosphorylate phospholamban at Thr17, indicating that CaMKIIδ_A is specifically involved in transcriptional control mechanisms. Based on the observation that CaMKIIδ_A, δ_B and δ_C are sufficient to regulate HDAC4 but not pathological remodeling, we conclude that HDAC4 phosphorylation is not sufficient to drive pathological remodeling and that other CaMKII-dependent processes must contribute to pathological remodeling. We further conclude that the variety of CaMKIIδ splicing variants and possibly the holoenzyme structure is required for the full process of pathological remodeling because a single splice variant has only moderate effects on cardiac remodeling in the absence of the other splice variants. Thus, the interplay of all CaMKII splice variants in the holoenzyme structure may be important for the development of pathological remodeling and heart failure.