Abstract: Dual Regulation of SUMO2 and STAT1 by HectD3 Protects Heart from Hypertrophy and Inflammation

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Background:

We recently identified SUMO2 as a sumoylation independent inducer of cardiomyocyte hypertrophy through activation of Calcineurin-NFAT signaling via direct interaction and increased nuclear localization of calcineurin.

Purpose:

In this study, we aimed at identifying cardiac-specific interactome of SUMO2 to decipher its cardiac function in depth.

Methods and results:

Using Yeast two-hybrid screen, we identified HECT domain-containing E3 ubiquitin ligase 3 (HectD3) as one of the cardiac SUMO2-interacting protein. Adenovirus-mediated HectD3 overexpression significantly increased polyubiquitination and reduced protein levels of SUMO2 and its sumoylation targets in neonatal rat ventricular cardiomyocytes (NRVCMs). Presence of a proteasome inhibitor MG132, however, prevented this reduction. Moreover, inverse correlation of SUMO2 and HectD3 expression was observed in human hearts with hypertrophic cardiomyopathy. Interestingly, several proteins from interferon signaling, including signal transducer and activator of transcription-1 (Stat1), were found downregulated by HectD3 overexpression in mass-spectrometry based proteomics. Also a known SUMO2/3 target, Stat1 we found as a bona fide cardiac target of HectD3, overexpression of latter strongly attenuated LPS or interferon-mediated activation of Stat1 and downstream inflammatory signaling. Importantly, AAV9-mediated overexpression of HectD3 not only reduced cardiac SUMO2/Stat1 levels, but also significantly dissipated pathological hypertrophy, inflammation, and fibrosis induced by transverse aortic constriction or Angiotensin-II treatment.

Conclusion:

In conclusion, we report here a novel mechanism of regulation of cardiac hypertrophy and inflammation by HectD3 via dual regulation of SUMO2 and one of its sumoylation targets, Stat1, establishing an important crosstalk between sumoylation and ubiquitination via a common substrate.
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