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Meeting abstract

Molecular dissection of cardiac hypertrophy induced by interleukin-18

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Background

Cardiac hypertrophy represents a primary mechanism by which heart is remodeled in response to a variety of intrinsic and extrinsic stimuli. The underlying role of inflammation in the molecular mechanisms of cardiac hypertrophy remains incompletely elucidated. We are investigating the role of epigenetic mechanisms in the regulation of cardiac hypertrophy induced by interleukin 18 (IL-18) using in vivo and in vitro models. Daily intra-peritoneal administration of interleukin 18 for one week in Balb/c mice induced cardiac hypertrophy as judged by increased ratios of their heart and lung weights to total body weights, and enhanced thickness of their ventricular walls. The hearts of IL-18-treated mice also elicited an increased expression of atrial naturetic factor, desmin and skeletal α-actin genes and a concomitant switch in the rate of expression of α- and β-myosin heavy chain genes. Both the gross histological manifestations of cardiac hypertrophy and altered gene expression were greatly normalized by co-administration of histone deacetylase (HDAC) inhibitors, m-carboxycinnamic acid bis-hydroxamide (CBHA) or trichostatin A (TSA). Evidently, IL-18 and HDAC inhibitors modulated the signal transduction pathways that elicit the program of hypertrophy-specific gene expression. Our data revealed that chromatin remodeling and expression of PTEN (phosphatase and tensin homolog) by CBHA and TSA was mechanistically related to amelioration of cardiac hypertrophy. A brisk induction of PTEN by inhibitors of HDACs led to attenuation of IL-18-induced PI3K-Akt/protein kinase B signal transduction pathway.

To extend these observations, we also undertook genome-wide comparisons of the transcriptomes of murine hearts treated with IL-18 in the presence and absence of HDAC inhibitors. We observed that a cohort of genes that regulate cell signaling, inflammatory response, proteasome degradation and apoptosis were differentially regulated in response to IL-18, TSA and CBHA. We will discuss mechanistic implications of these data for epigenetic regulation of cardiac hypertrophy and its reversal by HDAC inhibitors.