β2 adrenergic signaling of cardiac fibroblasts induces cardiac hypertrophy through paracrine system

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【Background】
Isoprenaline (ISO), a β adrenergic receptor (βAR) agonist, activates the β2AR signal of cardiac fibroblasts (CFs) and induces cardiac hypertrophy. The purpose of this study is to elucidate this mechanism.
【Methods & Results】
Since ISO activated PKA, a downstream signal of β2AR, in CF, we generated mice with fibroblast-specific overexpression of the PKA catalytic subunit (PKA-OE mice) and found that PKA-OE mice exhibited cardiac hypertrophy. CFs were prepared from wild-type or PKA-OE mice, designated as WT-CFs or PKA-OE-CFs, respectively. The stimulation of neonatal rat cardiomyocytes (NRCMs) with the culture medium from PKA-OE-CFs resulted in cardiomyocyte hypertrophy, suggesting that CFs produce hypertrophic paracrine factors. In response to ISO, IL-6 increased through the PKA-pathway in WT-CFs, while TNF-α and IL-1β to lesser extent. We stimulated NRCMs with the culture medium of WT-CFs or IL-6KO-CFs. Importantly, the culture medium of ISO-stimulated WT-CFs induced cardiomyocyte hypertrophy, while not that of IL-6KO-CFs, suggesting that IL-6 directly or indirectly is involved in the hypertrophic response of NRCMs to ISO.
【Conclusion】
The β2AR stimulation in CFs causes cardiac hypertrophy by producing hypertrophic factors, such as IL-6, as a paracrine mechanism. IL-6 may be a therapeutic target of cardiac hypertrophy.