# β2-adrenergic stimulation induces Arid5a through cAMP/PKA/CREB axis to promote IL-6 upregulation

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**Background**

Cardiac inflammation is an exacerbation factor of heart failure. Cardiac fibroblasts (CFs) are involved in the inflammation by producing proinflammatory cytokines. We have revealed CFs expressed β2 and β3-adrenergic receptors (AR) and isoproterenol (ISO), a non-selective βAR agonist, mainly upregulated IL-6. However, it remains to be fully clarified how β-adrenergic stimulation induces IL-6 expression in CFs.

**Methods**

CFs were isolated from adult mice. The expression of mRNA was measured by real-time RT-PCR. The protein level was analyzed by ELISA. The activity of transcriptional factors was assessed by western blotting and ELISA-like assay.

**Results**

In CFs, the stimulation of β2AR with salbutamol (SAL) increased IL-6 but not that of β3AR. *β2AR*-null CFs suppressed the expression of IL-6 in response to ISO. Bucladesine, a cAMP precursor, also upregulated IL-6. Concomitant with IL-6, Arid5a, an IL-6 mRNA stabilizing factor, was induced with SAL and bucladesine. Moreover, *Arid5a* gene ablation downregulated IL-6 both in basal and SAL treated CFs. SAL activated CREB and the inhibition of PKA with H89 blocked CREB phosphorylation. Finally, 666-15, a CREB inhibitor, suppressed SAL-mediated Arid5a and IL-6 upregulation.

**Conclusion**

β2-adrenergic stimulation induced Arid5a through cAMP/PKA/CREB pathway and promoted IL-6 upregulation.