Abstract

Introduction

Obesity, particularly when induced by chronic consumption of a high-fat diet, is closely associated with adverse cardiac remodeling and increased cardiovascular risk. In this study, we explored the role of Bone Morphogenetic Protein 4 (BMP4), a mechano-sensitive cytokine in the hearts of mice with diet-induced obesity (DIO) and its possible association to the IL-33/sST2 signaling axis a well-known mechanisms involved in maladaptive heart remodeling.

Methods

Twelve six-week-old male C57BL/6N DIO-mice (Charles River Laboratories, Calco, Italy) were divided into two groups and fed for 20 weeks as follows: (1) normal chow diet (10% fat, CTR) and (2) high-fat (HF) diet (60% fat). At the age of 26 weeks (human beings age matched of 20-30 years) the mice were sacrificed through exposure to atmosphere saturation of carbon dioxide for 15 min. Heart were collected, subdivided in two parts: 1) half heart is immediately snap-frozen in liquid nitrogen, and stored at −80° until genomic analysis and proteomic analysis.The Italian Ministry of Health approved all animal procedures (Number 5AD83.N.G1Q).

Results

Our results revealed a significant upregulation of BMP4 gene in the myocardium of DIO mice. Elevated BMP4 levels were associated with increased expression of hypertrophic markers (ANP, BNP) and pro-fibrotic genes (TGF-β1, collagen I). Interesting, BMP4 expression directly correlates with IL1RL1 gene, which transduce for sST2, a cardiac maker of maladaptive remodeling. In parallel, we observed an imbalance in the IL-33/sST2 axis: IL-33 expression was markedly decreased, while levels of soluble ST2 (sST2), a decoy receptor that neutralizes IL-33, were significantly elevated. This dysregulation was accompanied by enhanced myocardial fibrosis and infiltration of inflammatory cells, as evidenced by increased gene expression of MCP-1 and IL-6.

Conclusions

These findings suggest that obesity-induced mechanical and metabolic stress enhances BMP4 signaling and disrupts the IL-33/sST2 cardioprotective pathway, promoting inflammation and structural remodeling of the heart. Understanding these mechanisms may offer novel targets for therapeutic intervention in obesity-related cardiac dysfunction.