Epigenetic control of inflammation by histone methylation in cardiometabolic heart failure with preserved ejection fraction

S. Costantino1, S. Ambrosini1, S.A. Mohammed1, E. Gorica1, A. Akhmedov2, F. Cosentino3, F. Ruschitzka4, F. Paneni1

1University Hospital Zurich, Center for Translational and Experimental Cardiology, Zurich, Switzerland
2University of Zurich, Center for Molecular Cardiology, Schlieren, Switzerland
3Karolinska University Hospital, Stockholm, Sweden
4University Hospital Zurich, Cardiology, Zurich, Switzerland

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Background: Obesity represents one of the most common comorbidities in patients with heart failure with preserved ejection fraction (HFpEF). Histone post-translational modifications by chromatin modifying enzymes (CMEs) are emerging as pivotal regulators of gene transcription in the heart.

Purpose: To investigate the role of chromatin remodelling in obese HFpEF (obHFpEF).

Methods: Unbiased gene expression profiling of CMEs (PCR array) was performed in left ventricular (LV) myocardial specimens from obHFpEF patients and age-matched control donors (n=8/group). Among myocardial CMEs, the methyltransferase SETD7 showed the highest variation in gene expression. Hence, we investigated the role of SETD7 and its chromatin mark H3K4me1 in a murine model of obHFpEF. Mice with cardiomyocyte-specific deletion of SETD7 (c-SETD7-/-) and control littermates (SETD7fl/fl) were generated and subjected to high fat diet feeding and L-NAME treatment for 15 weeks to induce obHFpEF. Echocardiography and Treadmill exhaustion test were performed. ChIP-Seq datasets were employed to determine the biological pathways regulated by SETD7, whereas chromatin immunoprecipitation assays (ChIP) were performed to investigate SETD7/H3k4me1 enrichment on target gene promoters. SETD7 gain- and loss-of-function experiments were performed in cultured neonatal rat ventricular myocytes (NRVMs) exposed to palmitic acid (200µM) for 48h. Selective inhibition of SETD7 by (R)-PFI-2 was performed in skinned cardiomyocytes isolated from left ventricular specimens of obHFpEF patients. Passive stiffness, a main feature of HFpEF, was assessed before and after RPFI-2 treatment.

Results: CMEs profiling showed SETD7 as the top-ranking transcript (fold change, 7.36, P < 0.01) in myocardial specimens from obHFpEF patients as compared to controls. ChIP-Seq in CMs showed a strong enrichment of SETD7 and H3k4me1 on the promoter of NF-kB p65 gene, a master regulator of inflammation. SETD7 and H3k4me1 were upregulated in HFpEF vs. control mouse hearts, showed enrichment on NF-kB p65 promoter and were associated with IL-1β and IL-6 upregulation. In HFpEF mice, cardiomyocyte-specific deletion of SETD7 protected against LV hypertrophy, diastolic dysfunction (assessed by E/E’ ratio) and lung congestion while improving exercise tolerance. At the molecular level, SETD7 deletion blunted H3K4me1 enrichment on p65 promoter thus preventing the upregulation of inflammatory genes and myocardial apoptosis. In cultured CMs exposed to PA, SETD7 inhibition by (R)-PFI-2 prevented H3k4me1-driven p65 upregulation, whereas SETD7 overexpression mimicked HFpEF features. Moreover, knockdown of NF-kB p65 prevented IL-1β/IL-6 transcription in SETD7-overexpressing CMs. Of clinical relevance, (R)-PFI-2 reduced passive stiffness in skinned CMs isolated from obHFpEF patients.

Conclusions: Pharmacological targeting of SETD7 may represent a new strategy to prevent myocardial inflammation in cardiometabolic HFpEF.