Targeting the methyltransferase SETD7 prevents myocardial ischemic injury: a translational study

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Introduction

Despite significant advances in coronary revascularization, acute myocardial infarction remains the leading cause of heart failure and death worldwide. Upon cellular stress, the Hippo pathway is activated leading to cytosolic retention and degradation of the pro-survival transcription factor YAP. Post-translational modifications, namely methylation, have been shown to regulate YAP activity. The protein SET domain-containing lysine methyltransferase 7 (SETD7) - which induces a specific mono-methylation of both histone and non-histone proteins - is emerging as a pivotal modulator of protein functionality and gene expression.

Hypothesis

The present study investigates the role of SETD7 in modulating the Hippo pathway during myocardial ischemia.

Results

Figure 2: Pharmacological inhibition of SETD7 restores YAP nuclear localization under glucose deprivation conditions. Representative images of NRVMs exposed to control and glucose deprivation conditions for 15 h, in the presence or in the absence of the SETD7 pharmacological inhibitor (R)-PF2 or its inactive enantiomer (S)-PF2 (10 μM). Cardiomyocytes were stained for YAP (red), SETD7 (green) and DAPI (blue). All images were acquired by confocal microscopy. C: control, GD: glucose deprivation.

Figure 3: Pharmacological inhibition of SETD7 increases YAP binding to the promoter of anti-oxidant genes. A) YAP binding to the promoter of anti-apoptotic genes was assessed by chromatin immunoprecipitation in NRVMs exposed to control and glucose deprivation conditions for 15 h, in the presence of the SETD7 pharmacological inhibitor (R)-PF2 or its inactive enantiomer (S)-PF2 (10 μM). B) Western blot quantification of anti-oxidant genes expression following treatment.

Figure 4: Genetic deletion of SETD7 protects against ischemia-reperfusion injury. A) Quantification of area at risk (AAR) per ventricle surface (V). B) Quantification of infarct size (I) per AAR. C) Quantification of infarct size (I) per ventricle surface (V). D) Representative images of TTC-stained middle heart sections of wild type and SETD7 knockout mice following myocardial infarction. Blue: continuously perfused tissue, red: stained ischemic viable tissue, white: unstained necrotic tissue. Data are expressed as mean ± standard deviation. A p-value <0.05 vs control by t-test was considered as statistically significant.

Discussion

Our findings suggest that - in conditions of myocardial ischemia - SETD7 triggers cardiomyocyte apoptosis via increased YAP methylation and subsequent reduction of YAP-dependent anti-oxidant genes. Pharmacological modulation of the Hippo pathway by SETD7 may represent a novel therapeutic approach to prevent myocardial damage in patients with ischemic heart disease.

Disclosures: none

References
