Transcriptional regulation of Global Cellular Protein Synthesis during Heart failure

Global protein synthesis is an important paradigm in the context of cardiac hypertrophy. However, the intricate molecular networks that regulate protein synthesis are not well understood. Our findings indicate that SIRT6, a class III histone deacetylase, represses global protein synthesis by transcriptionally regulating mechanistic target of rapamycin (mTOR) signaling. Global as well as muscle specific deletion of SIRT6 increases spontaneous protein synthesis in mice, which is caused by hyperactivation of mTOR signaling. Further, in vitro analysis of protein synthesis using the SUnSET assay, polysome analysis and the cap-dependent translation reporter assay, indicate that SIRT6 negatively regulates protein synthesis independent of its deacetylase activity. Mechanistically, SIRT6 binds to and represses promoters of key mTOR signaling genes via transcription factor Sp1. SIRT6 deficiency increased the recruitment of mTOR and Rheb to the surface of lysosomes, leading to enhanced phosphorylation of mTOR and activation of mTORC1. Inhibition of either mTOR or Sp1 abrogated the increased protein synthesis observed in SIRT6 deficient cells. These findings have unraveled a new layer of regulation of global protein synthesis by SIRT6, which can be potentially targeted for combating heart failure.