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Sirt1 modulates endoplasmic reticulum stress-induced autophagy in heart
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Purpose: Heart failure is a leading cause of morbidity and mortality worldwide. Disruption of Endoplasmic Reticulum (ER) homeostasis, a condition referred to as ER stress, has been implicated in many cardiovascular diseases including ischemic heart, heart failure, dilated cardiomyopathy, atherosclerosis and cardiotoxicity. In cardiomyocytes, ER stress is known to trigger autophagy, a dynamic process responsible for the degradation of cell components by the lysosomal pathway. However, it has become apparent that autophagy in the heart may have both adaptive and maladaptive consequences depending on the context. Besides, the NAD-dependent deacetylase SIRT1, the founding member of the sirtuins family, has been shown to be activated in response to different heart stresses to promote cell adaptation and survival. We thus hypothesised that SIRT1 might be involved in the regulation of ER stress-induced autophagy in the heart to provide a cardioprotective adaptation.

Methods: H9c2 cells (rat cardiomyoblasts) were treated with the well known ER stress inducer tunicamycin (TN, 10 μg/mL), which impedes N-glycosylation and provokes the accumulation of misfolded proteins in the ER lumen. The level of ER stress (GRP78, GRP94) and autophagy (LC3-II) were assessed by western blot. Autophagy was also evaluated by flow cytometry using Cyto-ID® autophagy detection probe. The role of SIRT1 was studied by using EX527, a specific pharmacological inhibitor of this deacetylase and by RNA interference. For in vivo experiments, mice were injected intraperitoneally with 2 mg/kg TN once daily and heart tissues were analyzed 48h after injection.

Results: In H9c2 cells, time course of TN treatment showed an increase of ER stress markers (GRP78, GRP94) and autophagy markers (LC3-II and Cyto-ID®), reaching a maximum after 24 hours. Following TN treatment, SIRT1 inhibition by EX527 or siRNA decreased ER stress-induced autophagy flux to a level similar to that of the well known inhibitor of autophagy initiation, 3-methyl adenine (3-MA), suggesting that SIRT1 regulates induction of autophagy in response to ER stress. In vivo, TN injection triggered a sustained ER stress response associated with exacerbated cardiac dysfunction in KO-Sirt1 inducible mice.

Conclusions: Our results demonstrate for the first time that SIRT1 is involved in the regulation of the ER stress-induced autophagy in cardiac cells. Therefore, SIRT1 could be an interesting therapeutic target to induce adaptive autophagy in ER stress-linked cardiac pathologies.