Abstract

Approximately half of the damage done to the heart by a myocardial infarction occurs during reperfusion of the ischemic region, while the patient is in the care of the treatment team. While many different adjuvant treatments have been explored in an attempt to attenuate this ischemia-reperfusion (I/R) injury, little progress has been made in translating novel therapies to the clinic. Recently, it was discovered that pan-inhibition of histone deacetylase enzymes (HDACs) before I/R injury or during reperfusion promotes improved recovery of the heart from injury, but little is known about the exact mechanism by which this improvement occurs. Here, we hypothesized that class I selective HDAC inhibition, administered before ischemia or during reperfusion alone, is sufficient to attenuate I/R injury in the heart. To examine this, we utilized ex vivo and in vitro models of I/R injury to interrogate the effects of class I HDAC inhibition on I/R injury. We discovered that class I histone deacetylase (HDACs) activity acutely exacerbates I/R injury, and that inhibition of class I HDACs with MS-275 (entinostat) preserves left-ventricular (LV) function and substantially reduces the area of infarcted tissue in isolated rat hearts subjected to ischemia-reperfusion (IR) injury. Notably, this protective effect occurs whether MS-275 is given as a pretreatment or during the reperfusion phase alone. When class I HDAC inhibition was administered as a pretreatment, it increased transcription of superoxide dismutase and catalase, priming the heart to withstand I/R injury. When class I HDAC inhibition was administered during reperfusion alone, it modified the metabolic response of the heart to injury, reducing ROS release. These observations led us to the discovery that HDAC1 localizes to the mitochondria in adult ventricular cardiac myocytes, the first known observation of HDAC1 mitochondrial localization in mammalian tissue. We then synthesized a mitochondrion-specific class I HDAC inhibitor, which demonstrated identical effects on I/R injury as the whole cell class I HDAC inhibitor. We further utilized mass spectrometry analysis to identify putative HDAC1 targets within the mitochondria. From these data, we conclude that mitochondrial HDAC1 activity is deleterious in very early reperfusion and constitutes an exciting new target for the treatment of cardiac I/R injury.