ABSTRACT

Cardiovascular diseases are one of the leading causes of mortality. A common denominator across most of the cardiovascular diseases like diabetic cardiomyopathy, hypertrophic cardiomyopathy, myocardial infarction and dilated cardiomyopathy is the pathological remodelling of heart leading to fibrosis. Cardiac fibrosis is characterized by the excessive production and deposition of extracellular matrix components due to unwarranted proliferation of fibroblasts. Under normal conditions, following cardiac remodelling, myofibroblasts undergo programmed cell death. However, this does not happen under pathological conditions ultimately leading to fibrosis. Although the molecular events and signalling pathways that contribute to the development of cardiac fibrosis is well established, there are limited studies which try to understand the mechanisms by which fibroblasts persist and resist programmed cell death. Here we demonstrate that SIRT6, one of the members of sirtuin family of histone deacetylases, plays an important role in regulating myofibroblast cell death.

When we analysed the mice hearts and isolated fibroblasts deficient in SIRT6, we observed increased expression of myofibroblast markers, suggesting that SIRT6 deficient hearts might have a high proportion of resident myofibroblasts. Also, when SIRT6 deficient fibroblasts were subjected to genotoxic stress, they showed reduced cell death and impaired mitochondrial to nuclear AIF translocation as compared to WT controls. An important regulator of AIF mediated cell death is the protein PARP-1. When we checked the expression levels of this protein under SIRT6 deficient conditions, it was found to be low. PARP-1 was also found to degrade faster under SIRT6 deficient conditions. Further qPCR analysis revealed that the transcript levels of PARP-1 were unaffected by SIRT6 suggesting that the regulation might not be at the transcriptional level. When we studied the acetylation of PARP-1 under SIRT6 deficient conditions we found the protein to be hypo-acetylated indicating a more complex mechanism of regulation.