**MITOPHAGY PLAYS A PROTECTIVE ROLE IN THE DIABETIC MOUSE HEART**

**F. Zhao**, S. Kobayashi, T. Kobayashi, Y. Huang, Y. Zhang, Q. Liang

New York Institute of Technology, New York, NY, USA

**Objective:**To investigate the role of mitophagy in streptozotocin (STZ)-induced diabetic mouse heart.

**Background:**Cardiac dysfunction in diabetes mellitus is closely related to mitochondrial injury and increased reactive oxygen species (ROS) generation. However, several clinical antioxidant therapies have failed to reduce heart failure in diabetic patients, suggesting the insufficiency of scavenging existing ROS for managing diabetic cardiac complications. New therapeutic strategies are clearly needed. Mitophagy degrades dysfunctional mitochondria and is believed a major mechanism that maintains mitochondrial quality and limits ROS production. The E3 ubiquitin ligase Parkin is a positive regulator of mitophagy, but its functional role in the diabetic heart remains unclear.

**Methods:**Transgenic mice expressing Parkin in the heart and mice deficient in Parkin (knockout) were used in the study. Diabetes was induced by ip injections of STZ, and cardiac mitophagy flux was determined by the difference in LC3-II protein levels and a novel reporter transgenic mouse line in the absence and presence of the lysosome inhibitors. Cardiac function was determined 9 weeks after STZ injection by echocardiography and hemodynamic measurements. Western blot analysis and histochemical staining were used to examine mitochondrial related proteins, cardiac fibrosis, oxidative damage and apoptosis.

**Results:**Mitophagy flux was reduced in the diabetic heart as indicated by western blot analysis and the novel mitophagy reporter. Overexpression of Parkin accelerated mitophagy flux in diabetic heart, improved cardiac function, reduced fibrosis (Picrosirius red staining) and attenuated oxidative cardiac injuries, as shown by oxidative DNA damage, oxidized proteins and apoptosis. In contrast, inactivation of Parkin gene increased diabetic cardiac injury as determined by the same parameters.

**Conclusions**These results demonstrate that Parkin-mediated mitophagy plays an important role in mitochondrial quality control and cardiac homeostasis in diabetes. Manipulating Parkin pathway may represent a promising therapeutic strategy for the treatment of diabetic cardiac complications.