**THE DEGRADATION SYSTEM IN CARDIOMYOCYTES**

**O. Yamaguchi1**, T. Oka1, K. Otsu2

1Osaka University Graduate School of Medicine, Suita, Osaka, Japan, 2King's College London, UK

Nuclear DNA in apoptotic cell is digested by lysosomal deoxyribonuclease II

(DNase II) in macrophages. Improper DNA digestion can lead to inflammation. Inflammation has been implicated in the pathogenesis of heart failure, however, infection with microorganisms is not involved in the development of heart failure in most cases. Mitochondria damaged by external hemodynamic stress are degraded by the autophagy/lysosome system in cardiomyocytes. We found that cardiac-specific DNase II-deficient mice (CKO) exhibited heart failure after transverse aortic constriction (TAC). DNase II activity was up-regulated in hypertrophied hearts, but not in failing hearts. Here we show that mitochondrial DNA that escapes from autophagy leads to Toll-like receptor (TLR) 9-mediated inflammatory responses in cardiomyocytes and is capable of inducing myocarditis and dilated cardiomyopathy. Early in the pathogenesis of TAC-induced cardiac dysfunction, DNase II-deficient hearts showed infiltration of inflammatory cells and increased messenger RNA expression of inflammatory cytokines, with accumulation of mitochondrial DNA deposits in autolysosomes in the myocardium. Administration of inhibitory oligodeoxynucleotides against TLR9, which is known to be activated by bacterial DNA, or ablation of Tlr9 attenuated the development of cardiomyopathy in DNase II-deficient mice. To determine the significance of TLR9 signaling pathway in the pathogenesis of heart failure, we subjected TLR9-deficient mice to TAC. They showed significant resistance to TAC-induced heart failure. TLR9-inhibitory oligodeoxynucleotides also improved the mortality in wild-type TAC-operated mice. These data indicate that mtDNA-TLR9 axis is involved in inflammatory responses in failing hearts in response to pressure overload.