S10-3 Model mice for tissue-specific deletion of the manganese superoxide dismutase (Mn-SOD) gene

◯Takahiko SHIMIZU[1,2], Takuji SHIRASAWA[3]

[1]Tokyo Metro, Inst. of Gerontol., [2]Tokyo Univ. of Agri. & Tech., [3]Juntendo Univ. Grad. Sch. of Med.

Manganese superoxide dismutase (Mn-SOD) is a mitochondrial enzyme that converts toxic O_2^- to H_2O_2. Previous studies have reported that a systemic deficiency in Mn-SOD causes neonatal lethality in mice. Therefore, no mouse model is available for the analysis of the pathological role of O_2^- injuries in adult tissues. To explore an adult-type mouse model, we generated tissue-specific Mn-SOD conditional knockout mice using a Cre-loxp system. First, we generated liver-specific Mn-SOD-deficient mice by crossbreeding with albumin-Cre transgenic mice. Mn-SOD proteins were significantly downregulated in the liver of liver-specific Mn-SOD knockout mice. Interestingly, the mutant mice showed no obvious morphological abnormalities or biochemical alterations in the liver, suggesting a redundant or less important physiological role for Mn-SOD in the liver than previously thought. Next, we generated heart/muscle-specific Mn-SOD-deficient mice by crossbreeding muscle creatine kinase-Cre transgenic mice. The mutant mice developed progressive dilated cardiomyopathy with specific molecular defects in mitochondrial respiration. Furthermore, skeletal muscle-specific Mn-SOD-deficient mice that had been generated by crossbreeding with human skeletal actin-Cre transgenic mice developed a severe physical disturbance associated with impaired cellular ATP metabolism. These results imply that the superoxide generated in mitochondria plays a pivotal role in the development and progression of pathologies in the heart and skeletal muscle, but not in the liver. In conclusion, we successfully generated various tissue-specific Mn-SOD conditional knockout mice that provide useful tools for the analysis of various oxidative stress-associated diseases.