

Interface of Mitochondrial Quality Control and Immune Activation in Heart Transplant

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For heart transplant patients, primary graft dysfunction (PGD) is devastating, resulting in 35% 1-year mortality. One factor that contributes to PGD is mitochondrial damage due to ischemia-reperfusion (I/R) stress during transplant. After I/R, mitochondrial recovery must occur through mitochondrial quality control (MQC) processes. We hypothesize that a) deficits in mitochondrial damage recovery contribute to the PGD phenotype, and b) persistent mitochondrial dysfunction leads to adaptive immune activation and may contribute to graft rejection.

These hypotheses will be investigated using a syngenic abdominal heterotopic heart transplant in knockout mice with defects in MQC. In Aim 1) we will characterize the impact of impaired MQC on the PGD phenotype for knockout vs. wild type cardiac grafts. In Aim 2) we will use this model to characterize the corresponding immune phenotype, to evaluate innate and adaptive immune responses.

Identification of molecular targets that control the interface between MQC and inflammatory activation would allow improved organ survival by facilitating a) peri-operative interventions to induce MQC, and b) targeted modulation of the mitochondrial-inflammatory interface to prevent immune activation, graft rejection, and viability in the longer term.