Gerald W. Dorn, II, MD

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Gerald Dorn II discovered fundamental mechanisms regulating mitochondrial homeostasis, programmed elimination, and metabolic remodeling in cardiac and neurological disease. His early studies showing that neurohormonal signaling promotes myocardial transcription of mitochondrial Bcl2 family death proteins were among the first to mechanistically link cardiac hypertrophy with apoptotic heart failure. Using conditional gene manipulation Dorn uncovered multiple pathological roles for Nix and Bnip3 in cardiac decompensation: activating the intrinsic (mitochondrial) apoptotic pathway, promoting mitophagy, and stimulating mitochondrial calcium import from endo/sarcoplasmic reticulum (ER/SR).

Dorn demonstrated the central role for a mitochondrial fusion protein, mitofusin (Mfn) 2, in tethering cardiomyocyte ER/SR to mitochondria, enabling mitochondrial calcium uptake that leads to mitochondrial permeability transition pore opening and dilated cardiomyopathy. In embryonic hearts he showed how mitofusins regulate embryonic heart development by modulating calcium-sensitive transcriptional signaling.

Dorn's interrogation of mitochondrial tethering and fusion revised fundamental concepts of mitochondrial quality control and metabolic transitioning. He discovered dual, mutually exclusive functioning of Mfn2 as mitochondrial fusion protein and mitochondrial receptor for Parkin, establishing Mfn2 phosphorylation as a critical determinant of individual mitochondrial fate. Dorn then demonstrated that this mechanism also mediates generalized mitochondrial turnover essential to the normal perinatal cardiac switch in metabolic substrate use from carbohydrates to fatty acids.

Dorn recently established that mitofusins transition between fusion-constrained and fusion-permissive conformations. He engineered cell-permeable peptides and small molecule peptidomimetics that destabilize the fusion-constrained conformation, thus promoting mitochondrial fusion. As Mfn2 mutations impair mitochondrial fusion in the neurodegenerative disorder, Charcot-Marie-Tooth disease (CMT2A), Dorn is using these first-in-class mitofusin agonists to correct mitochondrial abnormalities caused by CMT2A and ALS mutations.