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Control of mitochondrial oxidative stress prevented the evolution of cardiomyopathy in chronic chagasic rodents

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Objectives: Determine the pathological importance of oxidative stress-induced injurious processes in chagasic heart dysfunction.

Background: Trypanosoma cruzi-induced inflammatory pathology and a feedback cycle of mitochondrial dysfunction and oxidative stress may contribute to Chagas disease.

Methods: Sprague Dawley rats and C57BL6 mice (wt and MnSODtg) were infected with T. cruzi. Infected rats were treated with phenyl-alpha-tert-butylnitrone (PBN-antioxidant) and/or benzonidazole (BZ-anti-parasite). We monitored myocardial parasite burden, oxidative adducts, mitochondrial complex activities, respiration and ATP synthesis rates, and inflammatory and cardiac remodeling responses during disease development. Cardiac hemodynamics was determined for all rats.

Results: BZ (not PBN) decreased the parasite persistence and immune adverse events (proinflammatory cytokine expression, NADPH oxidase and myeloperoxidase activities, and inflammatory infiltrate) in chronic hearts. PBN and BZ (not BZ alone) decreased the mtROS level, oxidative adducts (malonyldialdehyde, 4-hydroxynonenal, carbonyls), hypertrophic gene expression (ANP, BNP, αsk-Actin), and collagen deposition, and preserved the respiratory chain efficiency and energy status in chronic hearts. Subsequently, left-ventricular dysfunction was prevented in PBN/BZ-treated chagasic rats. MnSODtg mice controlled cardiac oxidative and inflammatory stress, mitochondrial damage, and collagen remodeling during chronic Chagas disease.

Conclusions: BZ treatment after acute stage decreased the parasite persistence and inflammatory pathology. Yet, oxidative adducts, mitochondrial dysfunction and remodeling responses persisted and contributed to declining cardiac function in chagasic rats and mice. Combinatorial treatment (PBN/BZ) or control of mitochondrial oxidative stress was beneficial in arresting the T. cruzi-induced inflammatory and oxidative pathology and chronic heart failure in chagasic rats.

Biography

Nisha Jain Garg, Ph.D. is currently a Professor in the Departments of Microbiology & Immunology and Pathology in School of Medicine, and serves as Robert E. Shope, MD and John S. Dunn Distinguished Chair in Global Health, Director, Global Health Policy, Epidemics, International Organization and Associate Director, Center for Tropical Diseases at the University of Texas Medical Branch at Galveston. She also serves as a member of the NIH study sections and the American Society of Microbiology International Education Board; Associate editor of the American Journal of Pathology and the Journal of Neuroparasitology; and on the Editorial Boards of several journals. Recently she served as Senior Scientific Advisor at the US Agency for International Development (USAID). She has developed a strong and successful research program in the field of tropical infectious cardiomyopathy.

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