E487K MUTATION IN THE ALDEHYDE DEHYDROGENASE 2 GENE COUNTERACTS MYOCARDIAL INFARCTION-INDUCED CARDIAC MITOCHONDRIAL DYSFUNCTION IN MICE

Vanessa Morais Lima; Silva, I.B.; Ueta, C.B.; Ferreira, J.C.B.
Institute of Biomedical Sciences - University of Sao Paulo, Brazil

Introduction: The aldehyde dehydrogenase 2 (ALDH2) located in the mitochondrial matrix is crucial for the maintenance of cellular redox balance. Its main role is to metabolize reactive aldehydes produced during oxidative stress. We recently demonstrated that pharmacological inhibition of ALDH2 results in accumulation of cytotoxic aldehydes and increased myocardial damage during ischemic stress. Currently, it is estimated that 14% of the world population have a point mutation in the ALDH2 gene (E487K) which reduces its enzymatic activity by 95%. Objective: To assess the impact of the E487K variant of ALDH2 on cardiac mitochondrial metabolism in myocardial infarction-induced heart failure in wild-type (WT), heterozygous and homozygous ALDH2 E487K knock-in mice. Material and methods: We evaluated the oxygen consumption and H2O2 release of isolated cardiac mitochondria. We also evaluated whether ALDH2 E487K knock-in mice were more prone to develop cardiac dysfunction after myocardial infarction. Results: Our results indicate that both ALDH2 hetero- and homozygous mice display reduced basal oxygen consumption compared to WT. These differences are followed by decreased cardiac mitochondrial oxygen consumption and increased mitochondrial hydrogen peroxide release in ALDH2 knock-in mice compared to WT, highlighting a scenario of mitochondrial dysfunction during baseline conditions. However, when these animals develop myocardial infarction-induced heart failure, they present increased survival rate compared to WT littermates. Of interest, the E487K variant of ALDH2 induces better mitochondrial function during heart failure, characterized by higher oxygen consumption and lower mitochondrial H2O2 release in both ALDH2 hetero- and homozygous mice compared to WT. Conclusion: Our findings suggest that the E487K variant of ALDH2 induces a compensatory metabolic remodeling capable of protecting mitochondria dysfunction against myocardial infarction-induced heart failure.

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Key Words: ALDH2, Myocardial infarction, Cardiac mitochondria.