Rescue of biosynthesis of nicotinamide adenine dinucleotide (NAD+) protects the heart in cardiomyopathy caused by lamin A/C gene mutation.

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Abstract
Cardiomyopathy caused by lamin A/C gene (LMNA) mutations (hereafter referred as LMNA cardiomyopathy) is an anatomic and pathologic condition associated with muscle and electrical dysfunction of the heart, often leading to heart failure-related disability. There is currently no specific therapy available for patients that target the molecular pathophysiology of LMNA cardiomyopathy. Recent studies suggested that nicotinamide adenine dinucleotide (NAD+) cellular content could be a critical determinant for heart function. Biosynthesis of NAD+ from vitamin B3 (known as salvage pathways) is the primary source of NAD+. We showed here that NAD+ salvage pathway was altered in the heart of mouse and human carrying LMNA mutation, leading to an alteration of one of NAD+ co-substrate enzymes, PARP-1. Oral administration of nicotinamide riboside, a natural NAD+ precursor and a pyridine-nucleoside form of vitamin B3, leads to a marked improvement of the NAD+ cellular content, an increase of PARylation of cardiac proteins, and an improvement of left ventricular structure and function in a model of LMNA cardiomyopathy. Collectively, our results provide mechanistic and therapeutic insights into dilated cardiomyopathy caused by LMNA mutations.

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