TRPC3-Nox2 axis mediates nutritional deficiency-induced cardiomyocyte atrophy

ABSTRACT

Myocardial atrophy, characterized by the decreases in size and contractility of cardiomyocytes, is caused by severe malnutrition and/or mechanical unloading. Extracellular adenosine 5'-triphosphate (ATP), known as a danger signal, is recognized to negatively regulate cell volume. However, it is obscure whether extracellular ATP contributes to cardiomyocyte atrophy. Here, we report that ATP induces atrophy of neonatal rat cardiomyocytes (NRCMs) without cell death through P2Y2 receptors. ATP led to overproduction of reactive oxygen species (ROS) through increased amount of NADPH oxidase (Nox) 2 proteins, due to increased physical interaction between Nox2 and canonical transient receptor potential 3 (TRPC3). This ATP-mediated formation of TRPC3-Nox2 complex was also pathophysiologically involved in nutritional deficiency-induced NRCM atrophy. Strikingly, knockdown of either TRPC3 or Nox2 suppressed nutritional deficiency-induced ATP release, as well as ROS production and NRCM atrophy. Taken together, we propose that TRPC3-Nox2 axis, activated by extracellular ATP, is the key component that mediates nutritional deficiency-induced cardiomyocyte atrophy.