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MITOCHONDRIAL ION CHANNELS: NEW DRUG TARGETS FOR OXIDATIVE STRESS-INDUCED DISEASES

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The recent identification of the mitochondrion as the gatekeeper of the life and death of a cell and the appreciation of the role of mitochondrial dysfunction in a range of clinical disease processes has made the mitochondrion a target for drug delivery. The long-term objective of our research is to elucidate mechanisms of mitochondrial ion transport in cardiac muscle cells under both physiological and pathological conditions. In this talk, I will present experimental data to show that 1) mitochondria are able to sequester cytosolic Ca^{2+} during excitation-contraction coupling, 2) there exists a "privileged" transport of Ca^{2+} from sarcoplasmic reticulum (SR) to mitochondria due to their physical proximity, 3) in addition to Ca^{2+} uniporter, a rapid mode (RaM) of Ca^{2+} uptake and a ryanodine receptor in the inner membrane can transport Ca^{2+} rapidly into mitochondria, which may serve as transducers for excitation-metabolism coupling, 4) mitochondrial Ca^{2+} regulates critically the mitochondrial fission, ATP synthesis, reactive oxygen species (ROS) generation, and permeability transition pores, 5) three exists a non-selective cation channel in the inner membrane of mitochondria, as was recorded with patch-clamp technique in mitoplasts, and 6) strategies for the novel synthesis of small molecules for mitochondrially targeted antioxidants have been developed.

S 12-3

INVOLVEMENT OF RHOB IN CONTROLLING NCX mRNA STABILITY

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Cardiac Na^{+}/Ca^{2+} exchanger (NCX1) expression levels change under various pathophysiological conditions. However, its mechanism is poorly understood. Recently we found that fluvastatin (Flv), an HMG-CoA reductase (HMGR) inhibitor, decreased NCX1 mRNA and protein expression by inhibiting a small GTP-binding protein, RhoB in H9c2 cardiomyoblasts. Flv-induced down-regulation of NCX1 mRNA was reversed by mevalonate, farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP), suggesting an involvement of isoprenylation in activating RhoB. Conversely, lisophosphatidylcholine (LPC), an activator of Rho-GTPase, increased NCX1 mRNA and protein. RhoB requires isoprenylation for its activation by either GGPP or FPP. Therefore we investigated which isoprenoid is involved in NCX1 increase by LPC. Incubation of H9c2 cells with Flv for 24 hours decreased NCX1 mRNA to about 60% of control. Under this condition, addition of GGPP or FPP restored NCX1 mRNA to the control level within 24 hours. No significant difference was observed between GGPP and FPP. On the other hand, when LPC was applied with Flv, NCX1 mRNA decreased by Flv did not change. However, when LPC and GGPP were applied simultaneously, NCX1 mRNA was increased to a level significantly higher than the control. Unlike GGPP, FPP did not induce this increase. These results suggest that geranylgeranylation of RhoB is involved in the effect of LPC increasing the NCX1 mRNA. This pathway might underlie some of the upregulation of cardiac NCX1 expression.