The physiological implication of the mitochondrial Na^+ Ca^{2+} exchanger NCLX regulation by metabolic state and kinases.

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Mitochondrial Ca^{2+} transient starts by mitochondrial Ca^{2+} permeation into the mitochondria via the mitochondrial Ca^{2+} uniporter MCU followed by Ca^{2+} efflux by the 3Na+/Ca^{2+} exchanger, NCLX .The Ca^{2+} efflux of the latter I much slower then influx by MCU thereby playing a rate limit role in mitochondrial Ca^{2+} transients Consistent with its importance, knock out of NCLX expression led to fatal heart failure. In my talk I will focus on the mode of regulation and physiological role of NCLX. I will first describe the mode of NCLX regulation by PKA and CK2 kinases and the role of this regulation in neurodegenerative and carcinogenesis. I will then show how NCLX is controlled by mitochondrial metabolic state communicated via allosteric regulation of NCLX by mitochondrial membrane potential. I will then focus on the physiological role of NCLX in thermoregulation by brown fat tissue and show how impaired thermogeneration triggered by NCLX deficiency can be rescued by blocking the mitochondrial permeability pore. Finally I will describe the essential role of NCLX in synaptic transmission, LTP thus linking a human NCLX mutation to mental retardation.