Role of the mitochondrial sodium/calcium exchanger NCLX in the activation by redox signaling of the NLRP3 inflammasome.

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The NLRP3 inflammasome is a cytosolic multiprotein complex which activates the pro-inflammatory caspase-1, triggering the maturation and secretion of the pro-inflammatory cytokines IL-1β and IL-18, as well as inducing pyroptosis, a form of cell death. This response is necessary to end the inflammation, however, an exacerbated activation of the inflammasome can become harmful.

NLRP3 activation requires two processed that can be achieved in two phases responding to different stimuli. A priming stimulus induces gene expression of its components while an activation stimulus drives the catalytic activity of the assembled complex. There is a great range of stimuli triggering these processes, and in some of them an implication of the mitochondria in the catalytic activation of NLRP3 has been acknowledged.

We have previously described a mechanism by which the mitochondrial sodium/calcium exchanger NCLX activity is needed for a redox signal mediated by mitochondrial superoxide production in the response to acute hypoxia. We wondered if this mitochondrial redox signal driven by NCLX activity could take part in other cellular processes such as the NLRP3 inflammasome activation.

We have observed that selective NCLX inhibition by ITH12575 impairs NLRP3 activation after treatment with lipopolysaccharide (LPS) and ATP, inhibiting the activation signal and not the priming signal. At the same time, NCLX inhibition abolishes the increase in mitochondrial superoxide produced by LPS+ATP.

Thus, we want to confirm the role of NCLX and mitochondrial ROS production in NLRP3 activation, with the working hypothesis that upon priming, NLRP3 inflammasome components are recruited to the proximity of or interact with mitochondria, and that upon receiving certain activation signals, mitochondria produce ROS that constitute a redox signal that is transduced in the nearby inflammasome complexes into caspase-1 activation.