Hypoxia signalling by reactive oxygen species. What can be the relation of celular sodium movements with redox signalling?

IST1-10

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Oxygen is fundamental for eukaryotic life, and at the same time is the source for reactive oxygen species, which can act as signalling molecules in what we call redox signalling. Cells and organisms have developed specialized mechanisms to sense and trigger different adaptive responses to the reduced availability of oxygen (hypoxia). In our research group we have been interested in studying what are the redox signalling pathways that mediate these hypoxic responses in mammalian cells in different pathophysiological scenarios.

Once upon a time in the lab we established that different cell types produce a superoxide burst from mitochondrial origin in response to acute hypoxia that could be used as a redox signal. Searching for the mitochondrial mechanisms producing this superoxide signal, we uncovered an unexpected role of mitochondrial Na^+ import as a key signal transducer in this process, mediated by the mitochondrial $Na^+/Ca^{2+}/Li^+$ exchanger NCLX and exerted by a biophysical mechanism of Na^+ binding to the inner mitochondrial membrane that regulates electron transport chain behaviour.

We have explored the implications of this redox signalling mechanism triggered by mitochondrial Na^+ import in different physiological responses to hypoxia, such as acute hypoxic pulmonary vasoconstriction and the activation of the hypoxia-inducible factors (HIF) pathway regulating hypoxic gene expression signatures. We have also found that NCLX activity is also important in non-hypoxic processes such as activation of the NLRP3 inflammasome, probably by a redox signalling mechanism. Using novel pharmacological candidates developed in our Institute, we have searched for possible therapeutic benefits of inhibiting this NCLX-dependent redox pathway in situations of oxidative stress linked to ischemia and reperfusion such as in cellular and animal models of ischemic stroke.