Mitochondrial Complex I activity signals antioxidant response through ERK5

The vast majority of eukaryotic cells perform oxidative phosphorylation (OXPHOS), which uses the energy released by the mitochondrial oxidation of certain metabolites, i.e. glucose, to produce adenosine triphosphate (ATP). OXPHOS is highly efficient in energy production but it produces reactive oxygen species (ROS) as a byproduct. Although, ROS are involved in normal cell signaling and homeostasis, under stress conditions levels may rapidly increase resulting in oxidative stress hence, cells using mitochondria as first energy source must regulate ROS levels. In fact, ROS and mitochondria are functionally linked in several ways including mitochondrial morphology. ROS lead to Kelch-like ECH-associated protein 1 (KEAP-1) degradation, thereby activating nuclear factor (erythroid-derived 2)-like 2 (NFE2L2 or NRF2), which also regulates expression of mitochondrial genes. NRF2 is a prime regulator of cellular anti-oxidant response. Under stress condition, NRF2 dissociates from the repressor protein KEAP1, translocate to the nucleus and binds to anti-oxidant response elements (ARE) in gene promoters of more than 250 genes, consequently, regulating oxidative stress. Restraining OXPHOS in vivo in liver strongly decreases Nrf2 levels. Moreover, tumor cells forced to perform OXPHOS generate a NRF2-mediated anti-ROS response. There are alternative pathways leading to *de novo* production of NRF2, thus KEAP-1 inhibition only partially accounts for OXPHOS-induced antioxidant response.

Graphical Abstract

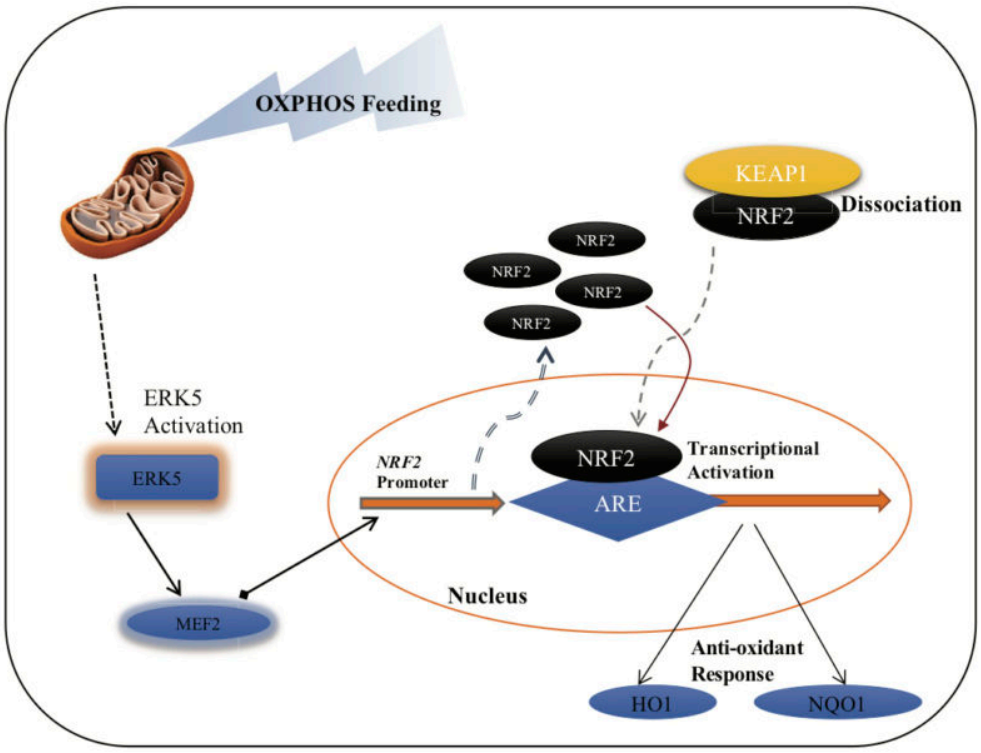

Fig. 1.

In hematopoietic cells, the MAPK extracellular signal-regulated kinase-5 (ERK5), through the transcription factor MEF2, induces expression of miR-23 that inhibits KEAP-1 mRNA leading to NRF2 activation. Several types of oxidative stress activate ERK5 in leukemic cells and ERK5 is considered a redox MAPK. The promoter of NRF2 contains numerous MEF2 binding sites. Hence, ERK5 could transcriptionally induce NRF2 expression through MEF2, a transcription factor that mediates some of the metabolic effects of ERK5. We hypothesize that mitochondrial activity triggers the ERK5 pathway that, through MEF2, induces NRF2 expression leading to antioxidant response.

ROS generation is inherent to the activity of the electron transport chain and Complex I is one of the main sites for ROS production. Once produced, ROS is going to initiate many biochemical reactions that could potentially damage cell structures. Hence, it is on the cell's own benefit to create the antioxidant response when ROS production is going to occur. We show here that complex I activity induce transcriptional expression of ERK5, which through MEF2 induces NRF2 *de novo* expression. Therefore, mitochondrial activity is directly linked to the most important antioxidant response in the absence of *de novo* increase in ROS levels. This implies that eukaryotic cells have evolved a genetic programing to prevent oxidative stress directly linked to OXPHOS.

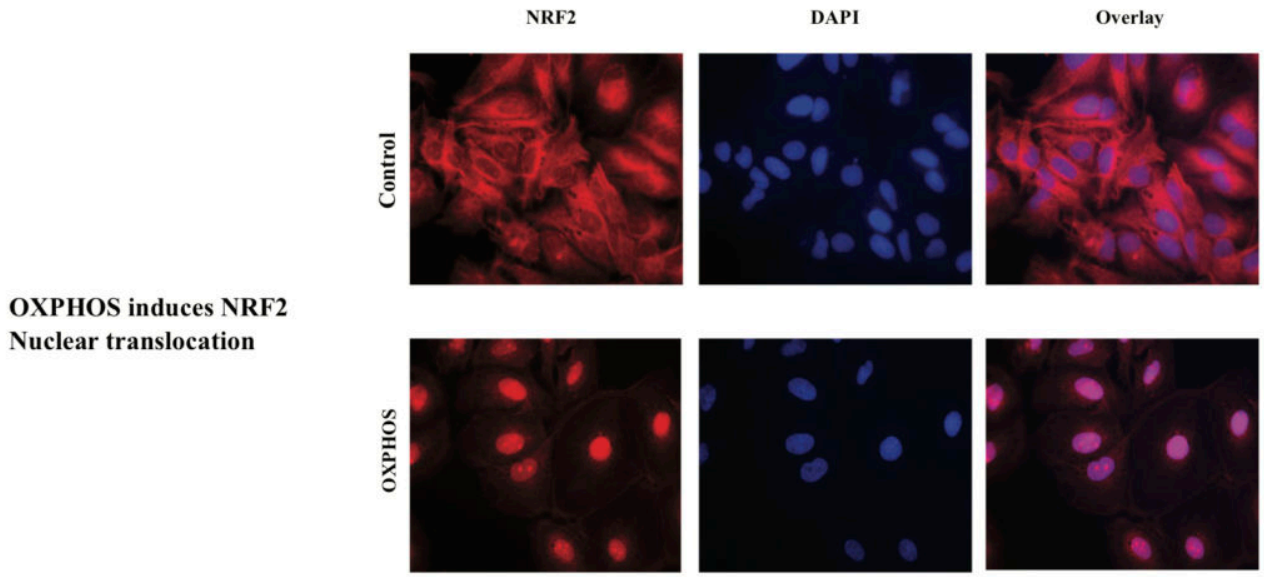

Fig. 2.

We have examined several possibilities that could account for our observation: i) ROS can activate several signaling pathways; however, in our experiments, ROS do not mediate OXPHOS-induced

ERK5 expression; ii) Fatty acid oxidation (FAO) could be another mechanism involved, but etomoxir decreases basal ERK5 expression. Moreover, if this is the case, complex II inhibition should decrease it, but we observed the opposite; iii) pharmacological and genetic approaches also suggest that AMPK is not involved on ERK5 expression during OXPHOS; iv) Strong mitochondrial complex I activity could decrease electron transport through complex II and subsequent accumulation of succinate or reduced fumarate be responsible for ERK5 expression. Our results support this possibility. On one hand, fumarate can covalently modify cysteine residues by an uncatalyzed process termed succination, which occurs on KEAP1 and results in constitutive NRF2 activation. On the other hand, fumarate blocks CII thereby increasing complex I activity and this triggers ERK5 expression. ERK5 triggers NRF2-mediated antioxidant response by at least 3 ROS-independent mechanisms: i) direct transcription through MEF2 and/or NF-?B and upregulation of miR-23 and downregulation of KEAP1 mRNA. This emphasizes the central role of ERK5 in the antioxidant response.

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Publication

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