EBioMedicine 3 (2016) 4–5

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

Keep Harm at Bay: Oxidative Phosphorylation Induces Nrf2-Driven Antioxidant Response Via ERK5/MEF2/miR-23a Signaling to Keap-1

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Nuclear factor E2-related factor 2 (Nrf2) is a key transcription factor which induces the expression of various cellular antioxidant and detoxifying enzymes through the binding and transcriptional activation of antioxidant response elements (ARE) in the promoters of their genes. The Nrf2/ARE pathway is known to protect cells against various stress stimuli, primarily oxidative stress associated with increased production of reactive oxygen species (ROS). Nrf2 activity is tightly regulated by a cytoplasmic inhibitory protein Kelch-like ECH-associated protein-1 (Keap-1) which acts as an adaptor between Nrf2 and cullin-3 ubiquitin ligase and promotes rapid proteasomal degradation of Nrf2. Being a sensor of various exogenous and endogenous electrophilic compounds and ROS, Keap-1 undergoes conformational changes upon interaction with such agents and this causes Nrf2 release from the complex, thus allowing it to translocate to the nucleus and transactivate Nrf2-responsive genes [see (Harder et al., 2015; Tebay et al., 2015) for recent reviews].

In their study, Khan et al. (this issue) demonstrate that there is also an alternative mechanism whereby the Nrf2/ARE pathway can be activated in human leukemia cells performing oxidative phosphorylation (OXPHOS). The authors found that while OXPHOS results in increased generation of ROS, the induction of the "classical" Nrf2-responsive genes encoding heme oxygenase-1 (HO-1) and NAD(P)H:quinone oxidoreductase (NQO1) can also occur in a ROS-independent manner. This was associated with a decrease in Keap-1 mRNA levels, implying that lower protein levels of Keap-1 may facilitate stabilization of the *de novo* synthesized Nrf2 protein, thus increasing the functional activity of the Nrf2/ARE pathway. The data also show that the MAPK ERK5 is upregulated in this system. This suggests that ERK5 kinase is responsible for the downregulation of Keap-1, which may be mediated by the downstream target of ERK5, the transcription factor MEF2C. Khan et al. show that MEF2C binds to the promoter of the microRNA miR-23a–27a–24-2 cluster and that miR-23a destabilizes Keap-1 mRNA by interacting with its 3′-untranslated region (3'UTR). Taken together, the results suggest that downregulation of Keap-1 in leukemic cells performing OXPHOS is mediated by the ERK5/MEF2/miR-23a signaling and that the resulting stabilization of Nrf2 leads to the activation of the Nrf2/ARE pathway, thus protecting the cells from the deleterious effects of ROS.

The findings by Khan et al. are in line with the previously reported ability of microRNAs to downregulate Keap-1 expression by targeting the 3′-UTR of its mRNA in several types of cancer cells (Eades et al., 2011; Kabaria et al., 2015; van Jaarsveld et al., 2013). Interestingly, MEF2A and MEF2C were shown to positively regulate the expression of different microRNAs, including miR-23a, in human vascular smooth muscle cells undergoing oxidative stress-induced senescence (Zhao et al., 2015) and in cardiac myocytes from mice with myotonic dystrophy (Kalsotra et al., 2014), respectively. Therefore, the ERK5/MEF2/miR-23a/Keap-1 axis may represent a key regulatory pathway in a broad range of cell types under various pathological conditions.

The importance of microRNAs in regulation of hematopoiesis and its aberrations has been known for several years [e.g., (Schotte et al., 2012)]. For instance Gocek et al. (2011) found that the upregulation of miR-32 by 1,25-dihydroxyvitamin D_3 in human myeloid leukemia cells leads to the targeting of the pro-apoptotic protein Bim, and inhibition of cytarabine-induced apoptosis, the latter frequently the result of excess generation of intracellular ROS. The report by Khan et al. demonstrates the important connection between microRNAs, Keap-1 and the alleviation of cellular oxidative stress. As such, it may indicate one basis for the emergence of resistance to cytotoxic chemotherapy of human neoplastic diseases. The novel, ERK5/microRNA-dependent, mode of Keap-1 downregulation suggested by this study adds to the reported mechanisms related to Keap-1 promoter hypermethylation and inactivating mutations that lead to hyperactivation of Nrf2/ARE, and thus to tumorigenesis and chemoresistance [e.g., (Zhang et al., 2010)]. In this scenario, antisense oligonucleotides which block miR-23a expression can be developed as therapeutic agents to fight consequences of the loss of function of Keap-1.

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2015.11.045.
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http://dx.doi.org/10.1016/j.ebiom.2016.01.009

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