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Abstracts

S5 Mitochondria, Reactive Oxygen Species and Ageing

Lectures

5L.1 Substrate-dependence of mitochondrial reactive oxygen species generation

Vera Adam-Vizi[1,2], Zsofia Komary[1,2], Laszlo Tretter[1,2]
[1]*Semmelweis University, Department of Medical Biochemistry, Hungary*
[2]*Hungarian Academy of Sciences, Neurobiochemical Group, Hungary*
E-mail: veronika.adam@eok.sote.hu

Production of reactive oxygen species (ROS) is inherent to mitochondrial oxidative metabolism and numerous sources of ROS have been revealed in mitochondria. ROS production capacity is controlled by factors affecting and reflecting the metabolic state of intact mitochondria; among them the chemical nature of the substrates fuelling the respiratory chain and the amplitude of the membrane potential of mitochondria. In the presence of FAD-reducing substrates electrons reduce coenzyme Q and when the mitochondrial membrane potential is high, electrons can flow back to complex I (reverse electron transport; RET) and reduce NAD^+ to NADH. RET is associated with high rate of ROS generation. In mitochondria supported by NAD^+-linked substrates, NADH/NAD^+ ratio is critical for ROS generation by both complex I and α-ketoglutarate dehydrogenase. A common conception is that calcium overload leads to stimulated ROS generation in mitochondria. However, data in the literature are controversial; some supporting, others arguing against this. For the effect of calcium on ROS generation in isolated mitochondria the choice of substrate and the metabolic state of mitochondria are critical. In succinate-supported well-coupled mitochondria ROS emission is decreased by calcium due to the depolarization-related elimination of RET. With NAD^+-linked substrates, in the absence of induction of permeability transition pore (PTP), highly polarized mitochondria exhibiting high rate of ROS generation respond to a calcium load with a decreased ROS generation, whereas in depolarized mitochondria actively synthesizing ATP, the effect of calcium depends on the amount of calcium load and could result in either no change or stimulation of ROS generation reflecting the membrane-potential-dependent character of ROS formation. In mitochondria favoring calcium-induced PTP, ROS emission from mitochondria is dominated by PTP-related permeability increase of the inner membrane.

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5L.2 Control of ROS production and T-cell turnover by the p13 protein of HTLV-1

Micol Silic-Benussi[1], Ilaria Cavallari[1], Luigi Chieco-Bianchi[1], Fabio di Lisa[2], Donna M. D'Agostino[1], Vincenzo Ciminale[1]
[1]*Department of Oncology and Surgical Sciences, University of Padova, I-35128 Padova, Italy*
[2]*Consiglio Nazionale delle Ricerche Institute of Neuroscience at the Department of Biomedical Sciences, University of Padova, I-35121 Padova, Italy*
E-mail: v.ciminale@unipd.it

The present study was aimed at gaining insight into the function of p13, an 87-amino acid mitochondrial protein expressed by HTLV-1. Although necessary for viral propagation in vivo, the mechanism of p13 function is incompletely understood. In previous studies we showed that p13 exerts antitumor effects in experimental transformation models. More recently, using synthetic p13 and isolated mitochondria, we showed that the protein triggers an inward K^+ current that leads to mitochondrial depolarization, increased activity of the respiratory chain, and reactive oxygen species (ROS) production. These findings prompted us to test the effects of p13 on ROS in living cells, including T-cells, the main targets of HTLV-1 infection in vivo. Expression of p13 in primary T-cells resulted in cell activation, measured using the CD38 surface marker. p13-induced activation was blocked in the presence of ROS scavengers and was not observed using a p13 mutant that was inactive in the in vitro assays, indicating a connection between the effects on ROS those on mitochondrial K^+ influx. In the context of the transformed cell line Jurkat, p13 did not affect ROS levels unless the cells were subjected to glucose deprivation, which led to a p13-dependent increase in ROS and cell death. Using RNA interference we confirmed that expression of p13 also influences glucose starvation-induced cell death in HTLV-1-infected cells. Taken together, our findings indicate that in the context of the HTLV-1 propagation strategy, p13 could increase the pool of "normal" infected cells while culling cells acquiring a transformed phenotype, thus favoring life-long persistence of the virus in the host.

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5L.3 Redox signaling (cross-talk) from and to mitochondria involves mitochondrial pores and reactive oxygen species

Andreas Daiber
Universitätsmedizin der Johannes Gutenberg Universität Mainz, II. Medizinische Klinik - Molekulare Kardiologie, 55101 Mainz, Germany
E-mail: daiber@uni-mainz.de

This review highlights the important role of redox signaling between mitochondria and NADPH oxidases. Besides the definition and general importance of redox signaling, the cross-talk between mitochondrial and Nox-derived reactive oxygen species (ROS) is discussed on the basis of 4 different examples. In the first model, angiotensin-II is discussed as a trigger for NADPH oxidase activation with subsequent ROS-dependent opening of mitochondrial ATP-

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