Targeting mitochondria to prevent ferroptosis: A focus on cAMP signaling

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Since their discovery, exchange proteins directly activated by cAMP (EPAC) proteins, have been implicated in a wide range of cellular functions, including oxidative stress and cell survival. Mitochondrial-dependent oxidative stress has been associated with the progressive neuronal death underlying the pathology of many neurodegenerative diseases, such as Alzheimer's and Parkinson's disease. In many cases, these cellular functions have been shown to be coordinated by scaffolding proteins known as A-kinase anchoring proteins (AKAPs). One AKAP family member, mitochondrial AKAP1 is associated with EPAC proteins and it contributes to oxidative stress responses by preventing cell death via mitochondrial dynamics.

Aims:

In this study, the cellular distribution of EPAC proteins in neuronal cells i.e. immortalized hippocampal (HT22) cells was investigated and in addition the differential expression in the mitochondrial fraction was also investigated. Furthermore, the role of EPAC proteins and AKAP1 in oxidative stress were investigated by pharmacological targeting of EPAC in HT22 cells, and over expression of AKAP1 respectively. Finally, mitochondrial respiratory chain activity in the presence of various EPAC modulators was also examined in HT22 cells.

Methods:

mRNA and protein expression of EPAC in HT22 cells was determined by qPCR and western blot analysis respectively. One type of cell death was represented by erastin-induced ferroptosis, in which the oxidative stress was initiated by a reduction of glutathione levels and a dysfunction of the iron metabolism. Mitochondrial respiratory chain activity was determined by high-resolution respirometry.

Results/Conclusions:

It was showed upon specific pharmacological modulation of the two forms of EPAC proteins, EPAC1 and EPAC2, that these isoforms exert opposing effects on a diverse subset of oxidative stress. EPAC1 inhibition prevented cell stress linked to glutathione loss, while EPAC2 inhibition had limited effects during impairment of cellular thioreductase enzymes. These results support previous findings demonstrating that overexpression of AKAP1 offers protection against oxidative stress. Taken together, this data indicates that EPAC1 and EPAC2 have different cellular localization and functions within the cells and may thus be involved in different oxidative stress pathways.

References:

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