HYDROGEN PEROXIDE-DEPENDENT ERK1/2 DEPHOSPHORYLATION MEDIATES TOXICITY VIA UPSTREAM INHIBITION OF THE SURVIVAL SIGNALLING IN U937 CELLS EXPOSED TO PEROXYNITRITE

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Sequential activation of cytosolic phospholipase A_2 ($cPLA_2$) and 5-lipoxygenase (5-LO), critically regulated by extracellular signal-regulated kinase 1 and 2 (ERK1/2)-dependent phosphorylation, mediates survival to peroxynitrite in cells belonging to the monocyte/macrophage lineage. In contrast, a limiting factor for survival is represented by the parallel mitochondrial formation of H_2O_2 leading to suppression of the survival signalling. We herein extend our previous findings by showing that the inhibitory effects of H_2O_2 are upstream to ERK1/2 phosphorylation. This leads to inhibition of $cPLA_2$, 5-LO and downstream events preventing mitochondrial permeability transition (MPT) thereby causing a rapid MPT-dependent lethal response. Finally, we also report results consistent with the notion that the mechanism whereby H_2O_2 inhibits ERK1/2 phosphorylation involves activation of orthovanadate-sensitive phosphotyrosine protein phosphatase(s).