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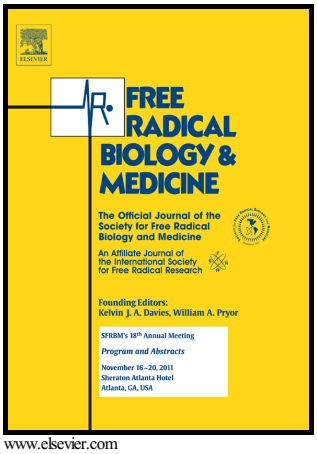

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Intracellular labile iron determines H_2O_2-induced apoptotic signaling via sustained activation of ASK1/JNK-p38 axis

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Short title: Implication of labile iron in H_2O_2-induced apoptosis

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ABSTRACT

Hydrogen peroxide (H_2O_2) acts as a second messenger in signal transduction participating in several redox regulated pathways, including cytokine and growth factor stimulated signals. However, the exact molecular mechanisms underlying these processes remain poorly understood and require further investigation. In this work, using Jurkat T lymphoma cells and primary human umbilical vein endothelial cells, it was observed that changes in intracellular "labile iron" were able to modulate signal transduction in H_2O_2–induced apoptosis. Chelation of intracellular labile iron by desferrioxamine rendered cells resistant to H_2O_2–induced apoptosis. In order to identify the exact points of iron action, we investigated selected steps in H_2O_2-mediated apoptotic pathway, focusing on mitogen activated protein kinases (MAPKs) JNK, p38 and ERK. It was observed that spatiotemporal changes in intracellular labile iron, induced by H_2O_2, influenced the oxidation