Free Radical Biology and Medicine 117 (2018) 45–57

Contents lists available at ScienceDirect

Free Radical Biology and Medicine

journal homepage: www.elsevier.com/locate/freeradbiomed

Mitochondrial rescue prevents glutathione peroxidase-dependent ferroptosis

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ARTICLE INFO

Keywords:
RSL3
Ferroptosis
HT22 cells
BID
GPX4
Mitoquinone

ABSTRACT

Research into oxidative cell death is producing exciting new mechanisms, such as ferroptosis, in the neuropathologies of cerebral ischemia and hemorrhagic brain insults. Ferroptosis is an oxidative form of regulated necrotic cell death featuring glutathione (GSH) depletion, disrupted glutathione peroxidase-4 (GPX4) redox defense and detrimental lipid reactive oxygen species (ROS) formation. Further, our recent findings identified mitochondrial damage in models of oxidative glutamate toxicity, glutathione peroxidase depletion, and ferroptosis. Despite knowledge on the signaling pathways of ferroptosis increasing, the particular role of mitochondrial damage requires more in depth investigation in order to achieve effective treatment options targeting mitochondria.

In the present study, we applied RSL3 to induce ferroptosis in neuronal HT22 cells and mouse embryonic fibroblasts. In both cell types, RSL3 mediated concentration-dependent inhibition of GPX4, lipid peroxidation, enhanced mitochondrial fragmentation, loss of mitochondrial membrane potential, and reduced mitochondrial respiration. Ferroptosis inhibitors, such as deferoxamine, ferrostatin-1 and liproxstatin-1, but also CRISPR/Cas9 Bid knockout and the BID inhibitor BI-6c9 protected against RSL3 toxicity. We found compelling new information that the mitochondria-targeted ROS scavenger mitoquinone (MitoQ) preserved mitochondrial integrity and function, and cell viability despite significant loss of GPX4 expression and associated increases in general lipid peroxidation after exposure to RSL3. Our data demonstrate that rescuing mitochondrial integrity and function through the inhibition of BID or by the mitochondria-targeted ROS scavenger MitoQ serves as a most effective strategy in the prevention of ferroptosis in different cell types. These findings expose mitochondria as promising targets for novel therapeutic intervention strategies in oxidative cell death.

1. Introduction

Cellular dysfunction and death owing to the increased accumulation of reactive oxygen species is a well-established feature in the neuropathology of neurodegenerative diseases such as Alzheimer's (AD) and Parkinson's disease (PD), and after acute brain injury caused by cerebral ischemia, hemorrhagic insults or brain trauma [1]. The underlying mechanisms driving the formation of ROS, such as lipid peroxides, hydrogen peroxide or superoxide anion, hydroxyl radical or nitric oxide radicals, and their biochemical function in oxidative programmed neural cell death, however, remain poorly defined. Increasing evidence has linked impaired calcium homeostasis to the accumulation of ROS and concomitant excessive mitochondrial damage. In particular, loss of mitochondrial integrity and function is regarded as a hallmark in oxidative neuronal death, since neuronal activity and maintenance largely depend on high metabolic turnover and functional energy metabolism. Further, beyond their role in energy metabolism through ATP production, mitochondria are key organelles involved in regulating the cellular redox balance, intracellular calcium homeostasis and apoptosis signaling, thereby determining cellular viability and function in all tissues, and particularly in the nervous system.

More recently, ferroptosis emerged as an iron-dependent form of oxidative programmed cell death in a variety of pathological conditions with particular emphasis on neurodegeneration in the brain. Death by

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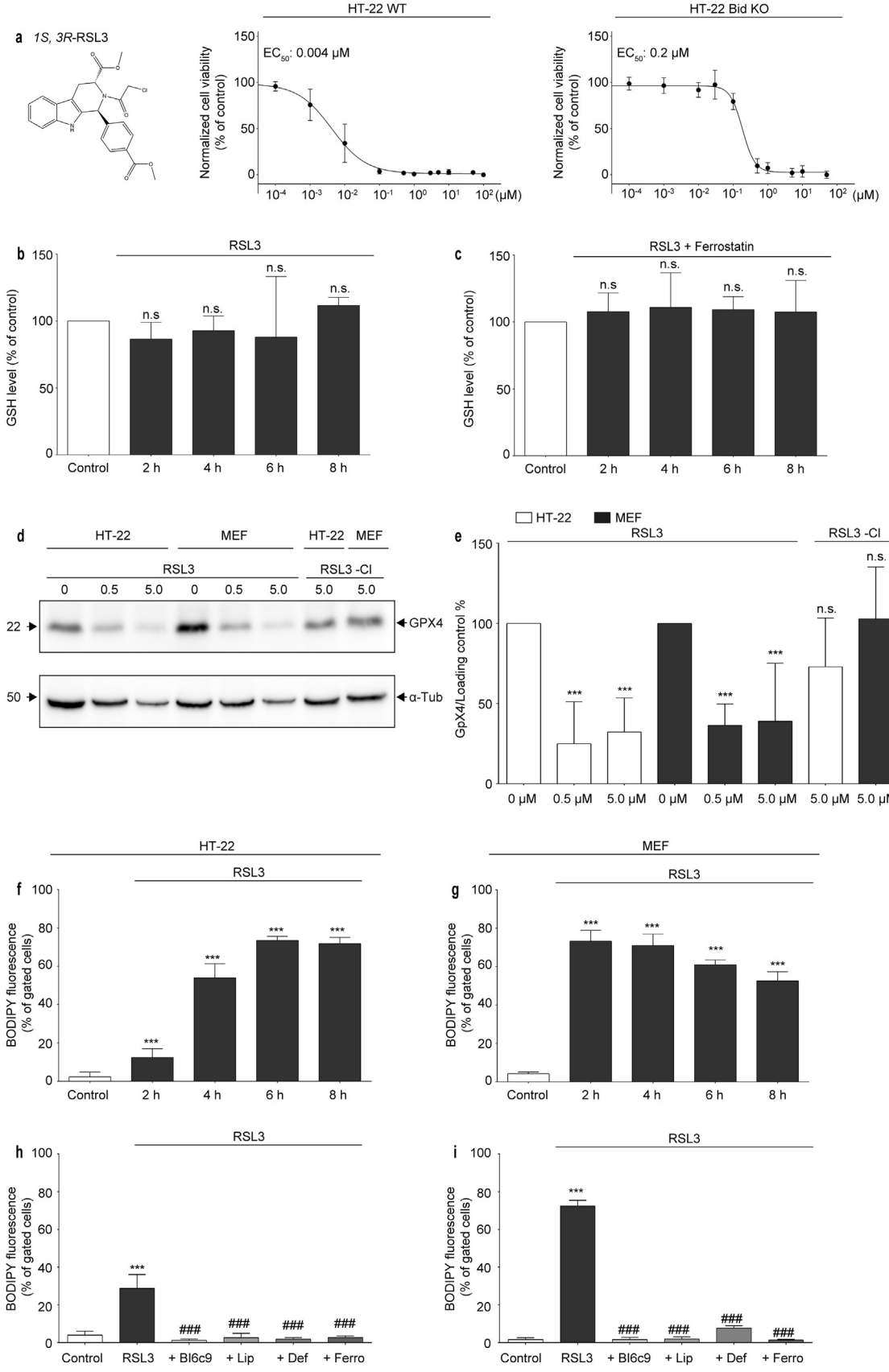
https://doi.org/10.1016/j.freeradbiomed.2018.01.019
Received 1 December 2017; Accepted 17 January 2018



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