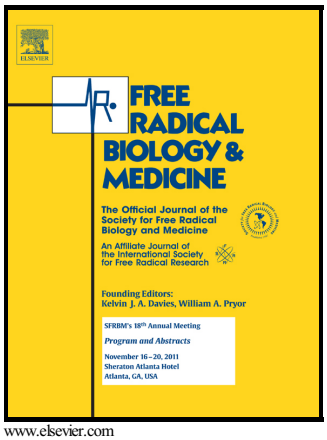

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Electrophilic nitro-fatty acids prevent astrocyte-mediated toxicity to motor neurons in a cell model of familial amyotrophic lateral sclerosis via nuclear factor erythroid 2-related factor activation

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Running title: *Nrf2 activation by nitro-fatty acids in ALS*

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ABSTRACT:

Nitro-fatty acids (NO_2-FA) are electrophilic signaling mediators formed in tissues during inflammation, which are able to induce pleiotropic cytoprotective and antioxidant pathways including up regulation of Nuclear factor erythroid 2-related factor 2 (Nrf2) responsive genes. Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease characterized by the loss of motor neurons associated to an inflammatory process that usually aggravates the disease progression. In ALS animal models, the activation of the transcription factor Nrf2 in astrocytes confers protection to neighboring neurons. It is currently unknown whether NO_2-FA can exert protective activity in ALS through Nrf2 activation. Herein we demonstrate that nitro-arachidonic acid (NO_2-AA) or nitro-oleic acid (NO_2-OA) administrated to astrocytes expressing the ALS-linked $hSOD1^{G93A}$ induce antioxidant phase II enzyme expression through Nrf2 activation concomitant with increasing intracellular glutathione levels. Furthermore, treatment of $hSOD1^{G93A}$-expressing astrocytes with NO_2-FA