15-Lipoxygenase: a promising therapeutic target, to block Ferroptosis cell death in Parkinson's disease

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Résumé

We aim to determine in a cell model neuroprotective effects of targeting lipoxygenases (LOXs), central players in Ferroptosis, a novel regulated iron-dependent cell death pathway implicated in Parkinson's disease (PD).
Ferroptosis is a form of regulated cell death characterized by the iron-dependent accumulation of lipid hydroperoxides to lethal levels, which is a key marker of this pathway. Recently, we demonstrated that ferroptosis is prevalent in pro-oxidant models of PD. Notably, a unique administration of Liproxstatin-1, a ferroptosis inhibitor targeting specifically lipid peroxides, strongly attenuate MPTP-induced neurotoxicity in mice. Furthermore, several reports have characterized LOXs as key drivers of lipid peroxidation during ferroptosis. 15-LOX could therefore be an interesting therapeutic target in PD.

By quantitative PCR we examined the expression pattern of LOXs in LUHMES cells, a human neuronal precursor derived cell line, which can be differentiated into mature dopaminergic neurons. To determine whether the inhibition of LOXs confer resistance to ferroptosis, we treated LUHMES cells with selective lipoxygenases inhibitors or silenced genes of LOXs using siRNA. We then induced ferroptosis with two inducers, different by their mechanism of action - RSL3 and Erastin. Cell death was measured after 24 hours of treatment by rezasurin assay and levels of lipid peroxidation were detected by flow cytometry using a lipophilic reactive oxygen species sensor (BODIPY C11).

We have observed that selective 15-LOX inhibitors conferred a high neuroprotection against RSL3 and Erastin-induced ferroptotic cell death. Interestingly, 15-LOX inhibitors showed a stronger protective effect than Liproxstatin-1, a specific ferroptosis inhibitor. Similar results were obtained by decreasing the expression levels of genes detected by qPCR (15-LOX, 15B-LOX). Levels of lipid peroxidation in response of RSL3 or Erastin were equally reduced by pharmacologic or genetic inhibition of LOXs.

The implication of ferroptosis in the neurodegeneration of PD offers wide possibilities of neuroprotective strategies and targeting lipoxygenases, in particular 15-LOX, seems a promising strategy.

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Mots-Clés: Ferroptosis, Parkinson's disease, 15, lipoxygenase, lipid peroxidation, neuroprotection, cell death, neurodegeneration