Towards Understanding the Molecular Mechanism of Inhibiting Ferroptotic Cell Death by Targeting Lipoxygenases

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Recent years have brought attention to ferroptosis, an iron- and lipid peroxidation-dependent form of regulated cell death implicated in a broad range of diseases, including Alzheimer's and Parkinson's disease, acute brain injury, sepsis, or asthma. Ferroptosis characteristic feature is the enhanced lipid peroxidation where abstraction of H-atoms from polyunsaturated phospholipids drives the entire peroxidation process causing a membrane damage. We demonstrated that a protein complex composed of 15-lipoxygenase and PE-binding protein 1 (Cell 2017) is a master promoter of ferroptotic cell-death signaling regulated by several enzymatic mechanisms.

Our objective is to block the enzymatic mechanisms underlying the ferroptosis process at the molecular level. Using computational molecular approaches such as molecular dynamics simulations, elastic network models, and bioinformatics together with the experimental verification, we explained the previously unknown mechanisms and factors that affect or block ferroptosis, thus providing molecular insights of the catalytic processes involved (JACS 2018, J Clin Invest 2018, JCIM 2019).

Our recent studies revealed a critical role of iNOS/nitric oxide (Nature Chem Biol 2020, IJMS 2021) and phospholipase iPLA2β (Nature Chem Biol 2021) in the regulation of ferroptosis. We also resolved a paradox related to the most common ferroptosis inhibitor, Ferrostatin 1 (Redox Biol 2021), and we proposed new inhibitors of the human complex which can effectively block the ferroptotic cell death signal (PNAS 2023). Our studies showed that computational studies could be effectively applied to explain and block fundamental biological processes.

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