The role of 15-lipoxygenase/PE-binding protein 1 complex in the ferroptotic cell death program

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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 and Parkinson disease, acute brain injury, kidney damage, and asthma. Active research shows that ferroptosis may become a new strategy in the treatment of cancers. Its characteristic feature is the enhanced lipid peroxidation where abstraction of H-atoms from polyunsaturated phospholipids drives the entire peroxidation process causing membrane damage. We demonstrated that a protein complex composed of 15-lipoxygenase and PEBP1[1], is a master promoter of ferroptotic cell-death signaling regulated by several enzymatic mechanisms occurring independently or concertedly. Our objective is to unearth the enzymatic mechanisms underlying the ferroptosis process at the molecular level. Using molecular dynamics simulations, elastic network models, and bioinformatic tools together with the experimental verification, we explained the previously unknown mechanisms and factors that affect ferroptosis, thus providing molecular insights of the catalytic processes involved[2-4]. Our recent studies also revealed a critical role of iNOS/nitric oxide [5, 6] and phospholipase $iPLA_2\beta$[7] in the regulation of ferroptosis. We also resolved an apparent paradox related to the most common ferroptosis inhibitor, Ferrostatin 1. We demonstrated that its anti-ferroptotic action is not limited to radical scavenging but also includes suppression of peroxidation of arachidonoyl-phosphatidylethanolamine catalyzed by the 15-lipoxygenase/PEBP1 complex[8].

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