**Lipid metabolism in ferroptosis, an iron-dependent regulated cell death**

**: An emerging target in cancer and cardiovascular diseases**

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Ferroptosis is an iron-dependent regulated necrosis mediated by lipid peroxidation. In the normal state, polyunsaturated fatty acids (PUFAs) are frequently oxidized but immediately reduced by GPX4 and its cofactor glutathione (GSH). However, when GPX4 is inhibited or GSH is depleted, lipid peroxides accumulate in cells, leading to ferroptosis. The critical roles of ferroptosis in various human diseases including neurological disorders, ischemia-reperfusion injury, kidney damage, and blood disorders, have become widely recognized through extensive in vitro and in vivo studies. In addition, cancer cells, especially chemoresistant or persister cancer cells, are highly vulnerable to ferroptosis inducers, which suggests a strategy for anti-cancer therapy using ferroptosis. While AA and AdA are the most susceptible PUFAs to peroxidation, how these lipids are controlled in cells is largely unknown. The most abundant PUFA in serum and plasma is LA (C18:2), and a comparable amount of AA is also found in serum. However, very long-chain PUFAs (VLC-PUFAs) with more than 22 carbons, such as AdA (C22:4), are rarely present in serum and plasma. In this regard, we recently reported that cell-autonomous synthesis of AA and AdA by fatty acid desaturases (FADSs) and elongases (ELOVLs) is critical for ferroptosis, although AA can be imported when PUFA synthesis is inhibited. Nevertheless, a number of studies have suggested that AA import and AA esterification by ACSL4 play a pivotal role in ferroptosis. Although both AA synthesis and AA uptake are crucial in ferroptosis, these pathway seems to be relatively slow. Therefore, it is thought that cells may also have a metabolic mechanism that rapidly respond to environmental changes. Oure recent study suggest that cell-autonomous recycling of AA by Lp-PLA2 is rapid and crucial pathway that determines the amount of AA-containing PE and PE-p, thereby contributing ferroptosis resistance. In this talk, I will brifely introduce several factors that mediate lipid synthesis and lipid remodeling, which eventually affect ferroptosis in cancer and cardiovascular diseases. Our results will provide insights into treatment strategies for ferroptosis-related diseases.