Cancer treatment by Ferroptosis

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Abstract

Background: There are many considerable advances in the treatment of cancer, but cancer is still the second major cause of death globally. The principle approach to kill cancer cells is to trigger cell death by apoptosis by anti-cancer chemicals. But cancer cells become resistant to induced apoptosis so the effectiveness of induced apoptosis by anti-cancer chemicals is not effective. To kill cancer cells and to limit the survival of clones which are drug resistant, non-apoptotic cell death allows to open new therapeutic opportunities. Last two decades of cell research has shown the existence of various regulated processes including necrosis, ferroptosis and necroptosis. Ferroptosis is being explored as alternative ways to eliminate cancer cells with apoptotic resistance. There are various compounds and anti-cancer chemicals have been reported to induce the process of necroptosis and ferroptosis.

Introduction: The key challenge in cancer research is to kill cancer cells effectively without affecting the normal cells of the body. There are many defects in cancer cells including resistance to cell death or apoptosis. In order to grow, cancer cells need increased demand of iron as compared to the normal cells (Non-cancerous cells) of the body. Dependency on iron makes the cancer cells more susceptible to iron catalyzed necrosis, which is known as ferroptosis. Ferroptosis is actually an iron catalyzed biochemical reaction of regulated necrosis which occurs through the extreme peroxidation of poly-unsaturated fatty acids.

In the recent years, ferroptosis has earned a lot of interest as in the view of gene silencing and downregulation of genes which are involved in the induction of necroptosis in the cancer cells. In this abstract, we briefly described about the induction and execution of ferroptosis and its modulation and also future perspective of this evolving field. Ferroptosis was actually recognized as a process involving cell death caused by small molecules, including RSL3 and erastin, causes the over expression of oncogenic mutant H Ras gene. Morphologically, cancer cells undergoing the process of ferroptosis have dysfunctional mitochondria with decreased size of crista and ruptured inner and outer mitochondrial membrane. Moreover, cells undergoing the process of ferroptosis do not show any marks of apoptosis. Even the knockdown of some important necroptosis mediators which includes RIPK3 and RIPK1 do not protect cells from the process of ferroptosis. Iron catalyzed extreme peroxidation of poly unsaturated fatty acids containing phospholipids which are present in excess in cell membranes causes the execution of feroptosis. Supplementation of polyunsaturated fatty acids in cell membranes promotes the process of ferroptosis. While exchanging the polyunsaturated fatty acids with other molecules that are less resistant to peroxidation or the mutation in the genes which are required for the process of ferroptosis by incorporation of polyunsaturated fatty acids into phospholipids in the cell membranes retards ferroptosis. Mechanically, double bonds which are next to to methylene groups in polyunsaturated fatty acids, decrease the energy of hydrogen bonds of the bisallylic groups of methylene which result in the increased vulnerability of abstraction of hydrogen and subsequent oxygenation, that can be examined through approaches of oxidative lipidomics. Some iron chelating agents like as deferoxamine, and a vast variety of lipid soluble compounds like vitamin E, liprox-statin as well as ferrostatin are used to neutralize the damaging effects of peroxidation of polyunsaturated fatty acids in ferroptosis. The exact mechanism that leads to cell death by ferroptosis involves the formation of lipid pore like structure which are similar to pores formed in pyroptosis and necroptosis. Continuous depletion of poly unsaturated fatty acids by peroxidation and the increased permeability of cell membrane, eventually causing the loss of integrity of cell membrane. Ferroptosis causes the thinning and destabilizing of membrane ultimately leads to the development of more pores in the membrane. Ferroptosis is the result of dysfunction metabolism involving polyunsaturated fatty acids, variety of genes and various pathways which are related to metabolism of iron lipogenesis and oxidative stress. These are the modulators of ferroptosis. Significantly, inhibition of some nuclear factor like erythroid related factor 2 (NRF2) and quieting of NRF2 genes increases sensitivity of cancer cells to the process of ferroptosis.

Ferroptosis is the result of dysfunction metabolism involving polyunsaturated fatty acids, variety of genes and various pathways which are related to metabolism of iron lipogenesis and oxidative stress. These are the modulators of ferroptosis. Nano medicine is also used to induce ferroptosis because this strategy is highly effective and more safe to use. Nanoparticles containing iron oxide increase the level of iron in cancer cells. Hydrolysis of nanoparticles containing iron oxide releases iron in cancer cells that triggers the process of ferroptosis.

Conclusion and future perspectives: This paper explained that how ferroptosis is an iron-catalyzed form of cell death non apoptotically and a significant target for further studies. Discovery of ferroptosis opens discovery new therapeutic drugs and some small molecules to induce the process of ferroptosis through peroxidation of polyunsaturated fatty acids and through targeting the metabolism of iron. The compounds that induce ferroptosis are highly specific with minimum side effects. However, there are many questions still need further clarification. How effective is the process of ferroptosis as compared to immunotherapy? In this regard, the use of Nano medicine can provide various opportunities for the development of therapeutics in ferroptosis with higher efficacy with less toxicity. In short, an enhanced understanding of mechanism of ferroptosis and also the role of ferroptosis in cancer treatment will open new opportunities for the diagnosis of cancer rapidly and therapeutic invention.

Keywords: Apoptosis, ferroptosis, nano medicine, peroxidation, iron metabolism, mitochondria, toxicity.