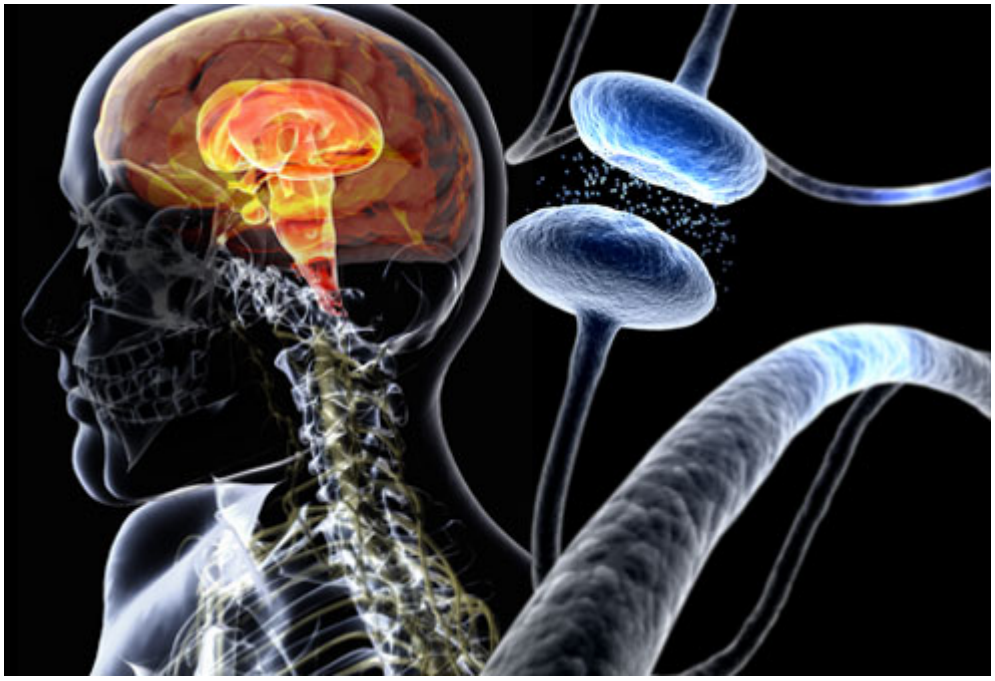


Iron-Induced Cell Death: Ferroptosis

As I wrote about in my book Dumping Iron, excess body iron stores are implicated in many diseases, including heart disease, diabetes, and cancer, as well as in aging itself. Among the other diseases that excess body iron is implicated in are Alzheimer's and Parkinson's diseases, which are characterized by (among other things) neuronal cell death. A process that causes cell death has recently been elucidated and this is iron-induced cell death, ferroptosis.

Programmed cell death

Programmed cell death occurs when cells initiate actions that lead to cell suicide, or apoptosis. This is thought to be done as a safety measure that ensures the integrity of the organism. When cells die in a non-programmed way, necrosis occurs, which presents problems for the organism, so cells have ways of killing themselves in the face of certain stimuli.

Programmed cell death is also essential in embryogenesis, tissue homeostasis, and immune response.

Ferroptosis is a newly discovered mechanism of programmed cell death, and as its name makes evident, iron is involved.

Much research has gone into elucidating the specific biochemical reactions that take place in ferroptosis, but for now, I'll stick to basics. Three different chemical entities are involved in ferroptosis:

1. iron
2. polyunsaturated fatty acids
3. glutathione.

Polyunsaturated fatty acids are necessary components of cell membranes, but they are readily oxidized. Free iron, that is, iron that is not bound by proteins such as ferritin or transferrin, react with the polyunsaturated components of the cell membranes to form highly toxic lipid peroxides.

Glutathione, the cell's most important and abundant internal antioxidant, is used to detoxify these lipid peroxides. If enough glutathione is not present, then lipid peroxides accumulate to critical levels, at which point the cell executes its cell death program, ferroptosis. Schematic illustration, below. (Source.)

Cystine, the dimerized form of the conditionally essential amino acid cysteine, enters the cell to be used in the production of glutathione. When it's blocked, or when enough isn't available, glutathione decreases, lipid peroxides cannot be detoxified and therefore accumulate, at which point ferroptosis occurs.

There are a few important points here as this process relates to health – this isn't just a bunch of dry biochemistry, and in any case, I've greatly simplified it.

Iron chelators – molecules that bind and remove iron – prevent ferroptosis. This is important because it shows that free and not bound iron initiates the process. If the iron were bound – to ferritin, transferrin, hemoglobin, or any of a number of other iron containing molecules – iron chelators would be powerless to stop it.

Adding iron to the cell culture medium increases ferroptosis. Again, free iron is the cuplrit

Autophagy, specifically ferritinophagy, the breakdown of ferritin, is required for ferroptosis. That's where the free iron comes from, the breakdown of ferritin.

Polyunsaturated fatty acids in cell membranes come from the diet. The membrane phospholipids that become peroxidized are composed of arachidonic acid, which is made from dietary linoleic acid, the most abundant fatty acid in seed oils. Since polyunsaturated fatty acids (PUFAs) compete for enzymatic conversion and subsequent space in cell membranes, excessive consumption of seed oils means a greater fraction of peroxide-capable arachidonic acid compounds in the cell membrane. Thus, diet can be linked to ferroptosis. One study says that the lipid peroxidation is specific for two omega-6 fatty acids only, arachidonic and adrenyl derivatives.

Lack of glutathione is also critical in ferroptosis, and this can also be linked to diet. Cysteine, the rate-limiting amino acid in glutathione synthesis, is found in all protein-containing foods; whey protein is

especially abundant in cysteine. Diabetics and others suffering from oxidative stress have low levels of glutathione, and it's said that aging could be (in part) a cysteine deficiency syndrome.

It appears that the high iron content of cancer cells can be exploited by making them enter ferroptosis, for example with the drug artemisinin or with vitamin C.

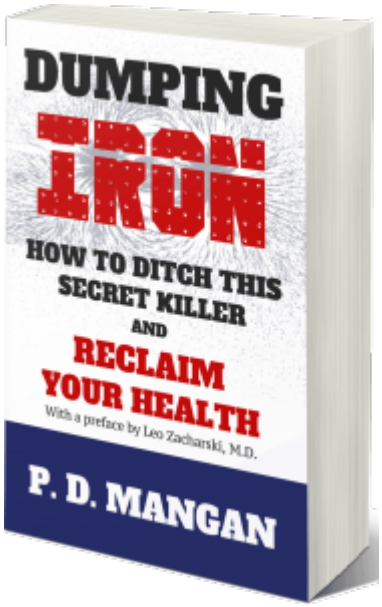
The process of ferroptosis provides another mechanism by which excess body iron, polyunsaturated fats in seed oils, and the absence of sufficient protein, can harm health.

Excess body iron in the form of high ferritin means that abundant ferritin is available to be broken down via ferritinophagy, leading to free iron inside cells. As I wrote in my book, ferritin is like stored dynamite: in theory, it's safe, but you don't want a bunch of it lying around your house. The more you have, the more likely an accident can happen.

Consumption of seed oils leads to a high proportion of the kind of membrane lipids that lead to ferroptosis.

Low dietary protein, or oxidative stress brought on by diabetes or other conditions, leads to low glutathione, which promotes ferroptosis.

PS: For more on iron and health, see my book, Dumping Iron.



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