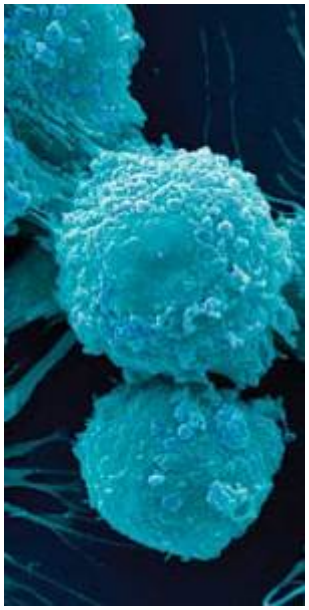


Cancer As a Metabolic Disease and Iron

The theory of cancer as a metabolic disease states that metabolic aberrations, not gene mutations, cause cancer. (Previously discussed here.) In this article I'll discuss how iron can plausibly be an initiator and enabler of cancer in accordance with the metabolic theory of cancer.

Background

In another article, we saw that there are good grounds for thinking that iron causes cancer. In brief, those grounds are:

- iron reduction via phlebotomy lowers cancer rates
- iron chelators (substances that bind and remove iron) fight cancer
- body iron stores are associated with cancer
- iron causes hypercoagulation, which is associated with cancer
- carcinogenicity of iron has been unequivocally demonstrated in animal experiments
- iron is associated with the carcinogenicity of asbestos and tobacco smoke

Iron causes cancer. But how does it do this?

Cancer as a metabolic disease

If the theory of cancer as a metabolic disease is true, then the main defect that causes a normal cell to become cancerous is metabolic injury, specifically a switch from mitochondrial aerobic respiration to aerobic

glycolysis. In his article on cancer as a metabolic disease, Thomas Seyfried discusses how this happens, or could happen.

In brief, cells require a certain level of energy to remain viable. If something injures mitochondria, where respiration (burning of fuel for energy) takes place, then the cell falls back on the much more inefficient process of glycolysis to provide energy. It has no choice but to do this to remain alive. If mitochondria are damaged beyond repair, then glycolysis continues, and the hallmarks of a cancerous cell appear as a consequence.

This sequence can explain how many different factors can cause cancer: radiation, chemicals, viruses, and inflammation. And iron.

Iron and mitochondria

Iron is intimately involved in mitochondrial function. Mitochondria play a key role in synthesizing various iron-containing proteins, such as heme and iron-sulfur proteins.

Friedrich's ataxia is a neurological disease that results from a defective or deleted gene that controls iron metabolism in mitochondria, leading to 10 times the mitochondrial iron as normal.

Perhaps most importantly, excess iron damages mitochondrial DNA.

The accumulation of iron and damage to mitochondria are both characteristic of aging, and aging leads to far greater rates of cancer. Cancer rates among those aged 65 and up are about 10 times those of younger people.

Quality control of mitochondria has a crucial role in counteracting the aging process.

Iron accumulation damages mitochondria:

> Iron is an essential mineral for normal cellular physiology, but an excess can result in cell injury. Iron in low-molecular-weight forms may play a catalytic role in the initiation of free radical reactions. **The resulting oxyradicals have the potential to damage cellular lipids, nucleic acids, proteins, and carbohydrates; the result is wide-ranging impairment in cellular function and integrity…** There is substantial evidence that iron overload in experimental animals can result in oxidative damage to lipids in vivo, once the concentration of iron exceeds a threshold level. In the liver, this **lipid peroxidation is associated with impairment of membrane-dependent functions of mitochondria and lysosomes. Iron overload impairs hepatic mitochondrial respiration** primarily through a decrease in cytochrome C oxidase activity, and hepatocellular calcium homeostasis may be compromised through damage to mitochondrial and microsomal calcium sequestration. DNA has also been reported to be a target of iron-induced damage, and this may have consequences in regard to malignant transformation.

> **Mitochondrial respiratory enzymes…** may be key targets of damage by non-transferrin-bound iron in cardiac myocytes. Levels of some antioxidants are decreased during iron overload, a finding suggestive of ongoing oxidative stress. Reduced cellular levels of ATP, lysosomal fragility, impaired cellular calcium homeostasis, and damage to DNA all may contribute to cellular injury in iron overload.

In his paper and book, Seyfried emphasizes the role of damage to cardiolipin, a phospholipid important to the mitochondrial membrane.

> Alterations in mitochondrial membrane lipids and especially the inner membrane enriched lipid, cardiolipin, disrupt the mitochondrial proton motive gradient ($\Delta\Psi_m$) thus inducing protein-independent uncoupling with concomitant reduction in respiratory energy production. Cancer cells contain abnormalities in cardiolipin content or composition, which are associated with electron transport abnormalities. Cardiolipin is the only lipid synthesized almost exclusively in the mitochondria. Proteins of the electron transport chain evolved to function in close association with cardiolipin…
>
> Cardiolipin abnormalities in cancer cells can arise from any number of unspecific influences to include damage from mutagens and carcinogens, radiation, low level hypoxia, inflammation, ROS, or from inherited mutations that alter mitochondrial energy homeostasis. Considering the dynamic behavior of mitochondria involving regular fusions and fissions, abnormalities in mitochondrial lipid composition and especially of cardiolipin could be rapidly disseminated throughout the cellular mitochondrial network and could even be passed along to daughter cells somatically, through cytoplasmic inheritance.

To summarize these above two points:

- iron can damage mitochondrial membranes
- damage to those membranes, especially of the easily damaged membrane component cardiolipin, could lead to cancer.

Iron could be the proximate cause of many or most cases of mitochondrial damage, such that other causes of cancer, such as chemicals, radiation, viruses, inflammation, etc., work by causing the release of free iron from ferritin and heme. In normal circumstances, iron is tightly controlled, locked away inside ferritin, transferrin, and other molecules. Damage to ferritin, for example, could lead to free, reactive iron being released, which in turn damages mitochondrial membranes, leading to cancer.

Consider that radiation, including solar radiation, causes cancer. Radiation damage to skin is dependent upon iron.

> By adding or chelating iron, UVA radiation-dependent oxidation of sulphydryl groups of bovine serum albumin and human γ-globulin was shown to be iron-dependent.

Topical iron chelators dramatically delay the onset of UVB photodamage in mice. Kojic acid, a cosmetic ingredient, prevents skin wrinkling from photodamage by chelating iron.

Consider that anthracycline, an anti-cancer drug, produces significant toxicity in cardiac tissue by damaging cardiolipin, the mitochondrial membrane constituent whose importance in cancer Seyfried emphasizes. Anthracycline toxicity can be prevented by treatment with iron chelators *in vitro*.

Inflammation induced by endotoxins causes the release of free iron which then damages mitochondria.

Tobacco smoke, another carcinogen, not only contains high amounts of iron but alters iron homeostasis.

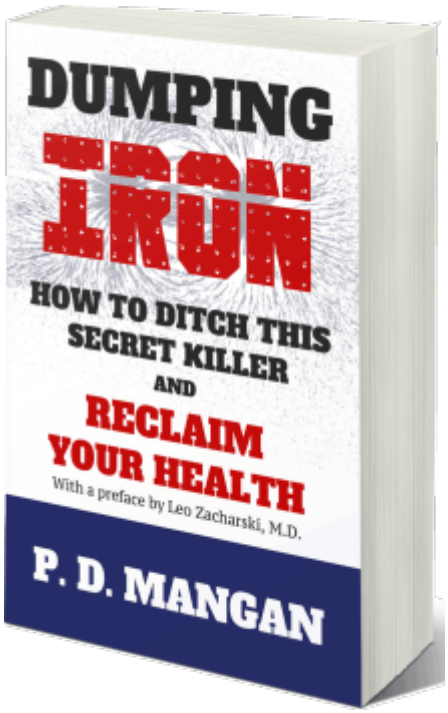
Is it iron all the way down?

We've seen that not only is iron a carcinogen, and that iron is intimately involved in the mechanisms of many other carcinogens, but that iron specifically damages mitochondria and its membrane constituent, cardiolipin.

Therefore, damage by iron is not only compatible with the theory of cancer as a metabolic disease, but may be all but essential to it.

Iron may be the proximate cause of many or all cases of cancer.

PS: More on iron and disease in my book, Dumping Iron.



PPS: Check out my Supplements Buying Guide for Men.