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Commentary: Ferritins: Furnishing proteins with iron

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Text

Numerous diseases in humans are connected with the metabolism of iron. Indeed, on some estimates diseases related to iron affect more of the World's population than any other disease. This is because iron deficiency affects over 30% of the world's population[1] and this can lead to anemia[2]. Often the lack of iron results from poor diet, though there are genetic defects that lead to iron deficiency, such as the rare disease iron-refractory iron deficiency anemia[3]. Too much iron can lead to iron-overload diseases[4], which are often called hemochromatosis[4]. Again, such diseases can have a dietary origin as well as a genetic origin. Central to the problem of humans attaining the right levels of iron are some of its chemical properties. Importantly, iron can exist in different oxidation states. The most common ones in biology are the ferrous state (Fe^{2+}) and the ferric state (Fe^{3+}). The ability of iron to cycle between these states is an important feature of many of the biochemical pathways that require iron for their normal function but such cycling can also be detrimental if not controlled properly. The conversion of Fe^{2+} to Fe^{3+} requires an oxidant and the most common one in biology is dioxygen, O_2, although hydrogen peroxide (H_2O_2), a natural by-product of aerobic respiration, can also oxidize iron efficiently. The propensity of Fe^{2+} to react with these species underpins many of the problems with too much iron. Unlike the majority of normal biochemical pathways, uncontrolled reactions of Fe^{2+} with O_2 can produce so-called 'reactive oxygen species' (ROS). ROS are much more reactive than O_2 and lead readily to tissue damage by reacting with components of cells, such as proteins and membranes. While many tissues have mechanisms for eliminating ROS before they can do harm, these mechanisms can be overwhelmed by the amount of ROS produced in cases of iron-overload. Another potential problem with iron is that while Fe^{2+} is relatively soluble in water under physiological conditions, Fe^{3+} is highly insoluble. This leads to iron-containing particles being deposited in tissues where iron-overload is present.

The database maintained by the National Organization for Rare Diseases (NORD)[5] lists four rare diseases involving iron-overload. These are: African iron overload, Neonatal hemochromatosis, Infantile neuroaxonal dystrophy, and Pantothenate linase-associated neurodegeneration. The first two have, at least in part, a genetic component that directly affects iron metabolism, whilst the genetic defects causing the latter two concern enzymes that have organic substrates but whose misbehavior leads to iron particles accumulating in the brain. It seems probable that there are other rare diseases involving iron not yet in the database as NORD state

that their database is not comprehensive. And as an illustration of this, iron-refractory iron deficiency anemia[3] is not in the NORD database.

Because of the twin problems with iron of solubility and the formation of ROS, organisms throughout the animal, plant and microbial kingdoms have evolved an elegant means of storing iron that is not needed for immediate biochemical use in a soluble and non-toxic form. What they do is to deposit the iron within a protein shell[6-9]. The protein is ferritin, and this was the subject of our review[9]. Each molecule of ferritin can hold as many as 4,300 Fe^{3+} ions; it was the high iron content that led Laufberger[10], who first described ferritin, to coin the name ferritin from the Latin ferratus, which means shod or furnished with iron. Since Laufberger's publication[10] there have been numerous original research papers and many excellent reviews published about it, such as references[6-8]. Our article[9] took a different approach to many of these. Two widely held views in the ferritin field are that ferritins in the animal, plant and microbial kingdoms share a common evolutionary origin[11], and that their primary function is as iron stores to protect the organism. However, it is clear that not all ferritins behave the same in *in vitro* assays and that many differ in the nature of the genetic control of their production. These observations underpinned our proposal that different ferritins have different primary functions[9]. An example of one such alternative function is the rapid removal of O_2, in which ferritin acts as an antioxidant since deposition of Fe^{3+} within ferritin starts with Fe^{2+}, which is used to reduce O_2 to H_2O at catalytic sites within the protein. A ferritin whose primary function is to rapidly remove O_2 may experience different evolutionary pressures to one whose function is to rapidly sequester iron in a non-toxic form, or to rapidly release iron from its mineralized store.

A major topic in our review[9] was how ferritin handles iron. This has been intensively studied for more than 70 years but, as we noted[9], it is not known precisely how any ferritin accumulates iron, let alone releases it, and both are still major areas of activity. Whilst most in vitro studies of iron release do not involve damage to the protein component, in humans an intracellular degradative process, ferritinophagy[12-14], directs ferritin to lysosomes where it is degraded, releasing iron to the cell. Whether there is a non-destructive release mechanism in humans as well is not certain but it is clear that in bacteria iron release from some ferritins occurs without damage to the protein component[15,16]. The elegant work of Theil and her colleagues[17] with frog ferritin has provided a picture of iron uptake by this protein, but it is not clear how much of this holds for other ferritins. This mechanistic area is one of continuing debate, with a common view that we set out in our review[9], that different ferritins accumulate iron by different mechanisms. However, a counter view is that there is a single mechanism that holds for all ferritins[18].

Our review[9] did not address directly the human health issues connected with iron metabolism but we did describe some studies[19,20] on ferritins from patients suffering with beta-thalassemia and hemochromatosis. We noted[9] that it was unclear whether the results of these studies can be extrapolated to ferritins from humans not suffering from such diseases since the flow of iron into ferritin is likely to be different under normal and iron-overload conditions. It is probable for the rare diseases in the NORD database[5] referred to above, and for the more common cases of severe iron-overload, that it is not the absolute amount of iron in a tissue that is the key factor, but the amount relative to the available storage capacity of ferritin.

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