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Mini Review

Challenges in Battling with Iron Deficiency by Ferritin

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Abstract

Iron deficiency is still a public health problem all over the world. Ferritin as a member of the superfamily of iron storage and detoxification proteins is being explored as a novel and natural strategy for iron supplementation. For some reasons, the bioavailability of ferritin iron has not been fully understood. This article discusses about the possibility of ferritin iron to combating iron deficiency and the confused questions encountered during the research. To study the digestive stability of ferritin *in vivo* and explore appropriate evaluation methods can help solve the questions. The putative receptors for ferritin uptake are the focus of this research as well. However, there is little knowledge on the receptor characterization and purification. Developing related receptor screening methods is essential for exploring ferritin as an efficient functional factor for iron supplement.

Keywords: Iron deficiency; Ferritin; Receptors; Endocytosis

Abbreviations

TfR1: Transferrin Receptor 1; IDA: Iron Deficiency Anemia; Tf: Transferrin; DMT1: Divalent Metal Transporter 1

Introduction

Iron is an essential micronutrient for the growth, development and functioning of the plants, animals and human. Under physiological conditions, there is a balance between iron absorption, iron transport and iron storage in human body [1]. Iron deficiency anemia (IDA) is derived from increased iron requirements, limited external supply and increased blood loss, which is still a major public health problem in the world. This problem remains one of great significance in early childhood as well as in menstruating and pregnant women. Nutritional iron is generally classified as two types: heme iron of animal origin and nonheme iron of plant origin. The former is absorbed as stable porphyrin complex unaffected by other food components such as phytates and tannins. However, recent studies on heme iron from red meat indicated that higher dietary intake of heme iron is associated with an increased risk of cardiovascular disease [2]. In contrast, an iron form plant source is present in a nonheme form. Unfortunately, nonheme iron compounds with small molecular weights were found to be easily altered by dietary factors such as phytic acids and polyphenols [3]. This is mainly because these dietary factors are capable of capturing the nonheme iron from the plant sources, forming insoluble compounds in the intestinal lumen, finally resulting in inhibition of iron absorption [4]. One promising approach to fighting iron deficiency is to find new functional factors for iron supplement that overcome the above-mentioned shortcomings, e.g., ferritin. Challenges for ferritin as iron supplements are as follows: the digestive stability of ferritin, effects of food components, and the putative receptors at cell surface.

Ferritin structure and function

Ferritin is a specific class of iron storage and detoxification proteins present in all living organisms except for yeast and play important roles in controlling cellular iron homeostasis [5]. Ferritin usually has 24 subunits that arranged in 432 symmetry to form a hollow protein shell (outside diameter is 12–13 nm, inside 7–8 nm) that can store up to 4500 Fe^{3+} atoms in its inner cavity in the form of an iron oxyhydroxide-phosphate mineral [6]. The shape of the subunit is cylindrical, with a length of 5 nm and a width of 2.5 nm [6]. Each subunit is composed of a four-α-helix bundle containing two antiparallel helix pairs (A, B and C, D) that is connected by a long non-helical stretch of 18 residues (the BC-loop) between B and C helices. A fifth short helix (Eα-helix) lies at one end of the bundle at about 60^{O} to its axis. The Eα-helix exists around the four-fold intersubunit symmetry axes of the protein shell and forms a hydrophobic pore. These hydrophobic and hydrophilic pores are main pathways for iron deposition into ferritin cavity and iron release from ferritin cavity [7]. Ferritin plays a crucial role in keeping the iron balance *in vivo*, through controlling the rate of both iron oxidative deposition into the protein with the help of oxygen/hydrogen peroxide and iron release from the protein induced by reductants [8]. Generally, iron oxidation/mineralization in human ferritin occurs by at least three reaction pathways [9]. During this process, ferritin was found to have protective function against oxidative stress by attenuating the toxicity of both Fe^{2+} and H_2O_2, thereby inhibiting the production of hydroxyl radical [10]. More importantly, since phytoferritin from legume seeds stores the majority of the total iron (~90%), it represents an alternative iron source for iron supplements [4].

Recently, the digestive stability of ferritin has been studied by simulating the human gastrointestinal conditions *in vitro* [11]. Generally, the pH value of the human stomach has traditionally been considered as low as pH 2.0. However, recent studies have shown that the pH after a meal often is considerably higher than 2.0, and is around pH 4-5 [12,13]. What's more, previous studies have not taken the effect of other food components into consideration. Thus, there is a need to study the digestive stability of ferritin in the presence of other food components *in vitro* and *in vivo* at a higher pH value.

The bioavailability of ferritin iron

Since ferritin iron is masked by a protein coat, it is less sensitive

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to dietary chelators [14,15]. Previous human studies show that iron is equally well absorbed from ferritin and ferrous sulfate independent of the phosphate content of the ferritin iron mineral, suggesting that dietary ferritin iron is likely to be a good source of iron [16]. Whereas, the bioavailability of iron from ferritin has been a matter of controversy [17]. Largely, the controversy appears to relate to the isotope labeling techniques used, and, to some extent, how the ferritin was produced. And extrinsic labeling by adding radio iron directly to ferritin was used in some studies, but this added isotope does not equilibrate with the insoluble iron inside the ferritin core. There is another problem that stimulants of ferritin synthesis, such as inflammation and stress, can also cause changes in the ferritin protein and iron contents [17]. Therefore, seeking for appropriate evaluation methods is imperative. Meanwhile, although the protein cage can protect iron from dietary chelators, other dietary factors may also affect the ferritin uptake mediated by receptors. Recent *in vitro* studies indicated that dietary factors can affect absorption of ferritin to an extent depending on the degree of digestion, the impact of them will be less than those affecting Fe uptake from $FeSO_4$ [18]. However, another animal study on the effect of proanthocyanidins (PAs) on iron uptake from soybean seed ferritin (SSF) crude showed that PAs inhibited iron uptake of rats from SSF, and are toxic for rats with IDA [19]. The reason for this observation is unclear, which needs to be further investigated.

Receptors responsible for ferritin iron absorption

Increasing attentions have been paid to elucidate possible ferritin receptors recently. Generally, there are three pathways for ferritin iron absorption. The first one is the normal pathway, as previously proposed for divalent ions. The iron core was released from ferritin by pepsin and the low pH (2.0) in the stomach, and then it was reduced to Fe^{2+} under the action of reducing agents, such as ascorbate, followed by absorption in the gut via the only protein responsible for ferrous iron uptake divalent metal transporter 1 (DMT1) [5,20,21]. The second one is the pathway for iron core. There may be putative transporters at the cell surface responsible for intact iron core uptake [20]. The third one is the pathway for undigested ferritin iron or partially digested ferritin iron. So far, the receptors related to ferritin iron uptake have been studied by several researchers. For example, Tim-2 expressed in mice kidney and liver cells (all splenic B cells, bile duct epithelial cells, and renal tubule cells) is considered as a receptor for H-ferritin rather than L-ferritin, but no human analog has been found [22]. Meanwhile, research on developing kidney cells of mice indicated that the Scara5 is a ferritin receptor mediating non-transferrin iron delivery. Scara5 bound serum ferritin and then stimulated its endocytosis from the cell surface with consequent iron delivery [23]. Afterwards, the other study on soybean ferritin absorption by Caco-2 intestinal epithelial cells indicated that ferritin is usually absorbed by receptor-mediated endocytosis and AP2 as adapters may play significant roles during this process [24,25]. Moreover, TfR1 has been identified as the receptor for human H-ferritin uptake by endocytosis for most cell types [26]. It was observed that TfR-1 is specific for H ferritin but not for L ferritin. Interestingly, transferrin only partially inhibited H ferritin binding to TfR-1, indicating the ferritin and transferrin-binding sites do not overlap and raising the possibility that this dual receptor function may coordinate the processing. However, the exact receptors at Caco-2 cell surface responsible for ferritin uptake have not been identified yet. Research on the bioavailability of plant and animal ferritin iron indicated that the interaction between ferritin and putative receptors depended on the subunit composition of ferritin (not published).

Conclusion

In summary, although ferritin iron is a potential candidate for iron supplement in the future to combating iron deficiency, there are still some limitations for its application. Firstly: the digestive stability of ferritin *in vivo*. Whether ferritin can pass through the gastrointestinal tract completely is crucial for the bioavailability. To date, there have been significant differences between *in vivo* and in *vitro* conditions, which need to be addressed. Secondly, the effect of other dietary components on ferritin should be also further elucidated. Finally, the mechanism by which ferritin is absorbed by Caco-2 remains unclear, but screening out the putative receptors at the intestinal cells can help us figure it out.

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