Ferritin: Structure, Mechanism, Neuroferritinopathy in Human Body

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ABSTRACT

When functioning well, ferritin plays a significant role in human body functioning as it helps to store and release iron ions to maintain human body stability. Otherwise, ferritin may fail in storing or release extra highly oxidative iron ions at different brain tissues, resulting in diseases such as neuroferritinopathy. Neuroferritinopathy is caused by gene mutations through two kinds of FTL genes. It can be inherited through genes and is autosomal dominant. Without paying efforts in tackling this diseases, more and more patients will suffer from its symptoms within generations. These symptoms will affect their daily physical movement and even personalities. Because neuroferritinopathy is caused by oxidative damage, anti-oxidation method therefore might be effective. Inheritance can be prevented by utilizing DNA polymerase or mismatch excision prepare enzymes for eggs and sperms.

Background

Even though the brain contains just 30-40 mg of iron, less than 1% of the total amount of iron stored in the human body (LEVI et al., 2005), iron continues to function in a variety of critical activities. It is involved in a variety of processes, including oxygen transport, dative phosphorylation, myelin formation, and neurotransmitter synthesis and metabolism (Ward et al., 2014). Iron is mostly preserved in ferritin. However, if the iron metabolic mechanism is disturbed, for example, if the ferritin's capacity to store iron is degraded, a large amount of free ferrous iron (Fe^{2+}) is released, resulting in the production of toxic free radicals that can harm a variety of bodily functions, most notably the nervous system (Crompton et al., 2002). Additionally, the ferritin level is controlled in vivo by the iron content in cellular circumstances, a process mediated by iron regulatory proteins (IREs) and iron-responsive elements. Even if the protein itself is not physically or functionally damaged, a breakdown in this self-regulatory mechanism might jeopardize ferritin's function and that of the human body. As a result, ensuring that ferritin functions properly is critical for maintaining the human body in a condition of homeostasis.

Mechanism of Ferritin

Storage of Iron

Ferritin is composed of 24 four-helix bundle subunits that are cylindrical in form (about 5 nm long and 2.5 nm wide). Each pair of subunits forms an anti-parallel dimer, resulting in a rhomboid dodecahedron structure with 432 points of

symmetry and a hollow structure capable of harboring up to a few thousand iron cations in their various forms. There are 12 two-fold symmetric channels, 8 three-fold symmetric channels, and 6 four-fold symmetric channels on the dodecahedron, respectively, along the two-fold, three-fold, and four-fold (Figure 1) rotation axes (BAI et al, 2012). The triaxial channel serves as a conduit for material exchange between ferritin and the surrounding environment

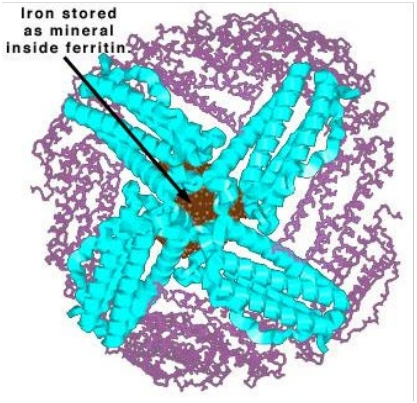

Figure 1. *Ferritin Structure*

Release of Iron

Ferritin is responsible for a variety of important activities in the human body. Dynamic homeostasis serves as the human body's iron reserve; the capacity to reserve ferric ions and ferroxidase sites capable of converting the soluble ferrous element into relatively stable ferric cations is critical for bodily function. Additionally, a ferritin reserve serves as a store of extra iron. Due to the fact that humans lack the ability to eliminate excess iron, this function is critical to the regular functioning of the human body. With iron regulatory proteins (IRPs) regulating its translation, this store of extra iron may adjust dynamically to the serum iron content (Cairo & Recalcati, 2007). Additionally, suchprotein may operate as a regulator of human immunological function;however its role as an active pathogenic mediator is still debatable and is now under intense scrutiny (epelak et al., 2020).

Ferritin is found in the cytoplasm, and some research indicates that ferric reductase may be able to decrease certain ferritin iron minerals (Schröder et al., 2003). After being recognized and subjected to proteolysis, the oxidatively changed ferritin can also be absorbed via the lysosomal degradation pathway, resulting in the breakdown of a protein shell and iron returning to the cytoplasm. The protein breakdown process is thought to be the primary mechanism by which iron proteins in the body release iron. Following acute iron depletion, studies have revealed that the K562 cell line's coverage of available iron is followed by a reduction in ferritin in the cell fluid and the protease inhibitors leupeptin (Konijn et al., 1999). Chymostatin inhibits this process, highlighting the critical role of ferritin in the iron release route of enzymatic degradation in the context of physiological iron loss (Konijn et al., 1999).

The Mechanism of Fe^{2+} Oxidation and Regulation of Iron in Ferritin

The process of iron storage in ferritin consists of four steps: the entrance and oxidation of Fe^{2+}, the migration of Fe^{2+}, the mineral creation, and the mineral development. The oxidation of iron occurs within the protein shell, and the

iron is bound to a particular location in the ferroxidase site's core (Chen et al., 2020). When Fe^{2+} comes into contact with oxygen, it forms Fe $(OH)_3$. Fe^{3+} moves to the cavity's surface, where it eventually forms the nucleus.

There is an IRE that can interact with IRP, and the combination of these two proteins inhibits both ribosomal binding and translation. As a result, the creation of the IRE-IRP complex prevents ferritin from being translated. The higher the iron content, the more the complex is removed, resulting in ferritin translation and iron storage (P et al., 1998)

Disease: Neuroferritinopathy

Neuroferritinopathy (a.k.a. hereditary ferritinopathy) is a ferritin-related disease. (Medlineplus Genetics 2020: Neuroferritinopathy) The illness is caused by an accumulation of iron in the brain, most notably in nerve cells. The accumulation will result in chorea, involuntary jerking motions, and other movement problems. Tremor, a disorder characterized by rhythmic shaking, may be present in certain persons. Other illnesses, such as ataxia, in which patients struggle to coordinate their movements, or dystonia, in which patients lose control of their muscles, may also appear. The basal ganglia are the most impacted part of the brain by buildup, impairing patients' capacity to control their movements. Apart from these physical variables, it appears as though persons with neuroferritinopathy have little cognitive impacts. Their IQ is usually unaffected. However, certain individuals' thinking and cognitive abilities will decline. Increased illness severity can also result in personality changes.

Neuroferritinopathy is a condition caused by a mutation in the FTL gene, which codes for the ferritin light chain. FTL460-461lnsA is one of the FTL mutations that results in the insertion of adenine between 460 and 461 in exon 4, therefore changing the frame of the gene (LEVI et al., 2005). The final 22 amino acids of the ferritin light chain are replaced with 26 extra amino acids (figure 2).

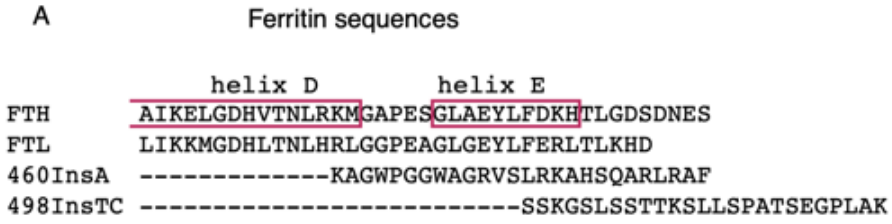

Figure 2. *Change of Ferritin Sequences in 460InsA and 498InsTC Mutation*

Another kind of FTL gene mutation is the FTL 498-499lns TC mutation (498lnsTC), which results from the insertion of two nucleotides between the ferritin light chain sites 498 and 499. (LEVI et al., 2005). Similarly, the gene's frame is changed, with the final nine amino acids replaced with an extra 25. (Figure 1). The most visible pathologic alteration is the formation of intranuclear and intracytoplasmic bodies containing ferritin and iron (LEVI et al., 2005). Except for the increased cognitive impairment caused by 498lnsTC, the disorder's phenotype is identical to that of 460lnsA. Another distinction is that serum ferritin levels are normal in the 498lnsTC, but are severely low in the

460lns A. Neuroferritinopathy is typically inherited. It is autosomal dominant, which means that just one copy of the mutant FTL gene in each cell from one parent is required to transmit the condition to the next generation (Figure 3). Additionally, neuroferritinopathy may arise as a result of novel mutations in the reproductive process (Figure 4). This may explain why some individuals develop neuroferritinopathy while having no family history of the disorder. The amount of iron in the brain rises with age. And neuroferritinopathy caused by 460lnsA typically manifests in individuals in their forties and fifties. Neuroferritinopathy symptoms begin at the age of 20 in persons with the 498lnsTC mutation and gradually worsen over the next two to four decades. (2005) (LEVI et al.).

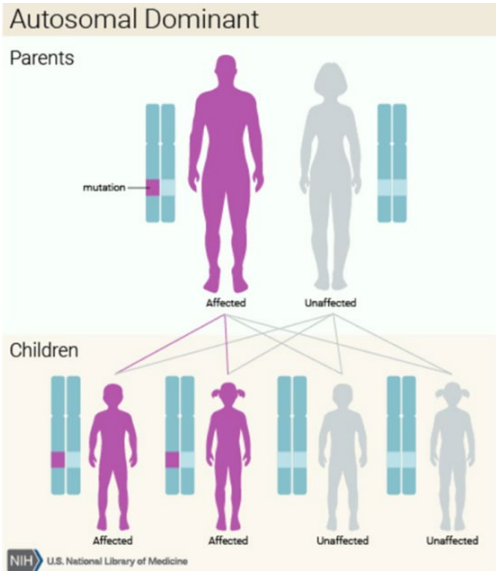

Figure 3. *Inheritance of Neuroferritinopathy through Gene Inheritance from Parents*

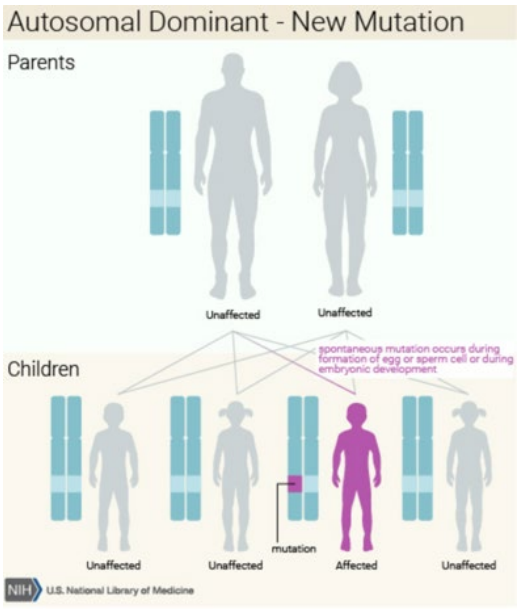

Figure 4. *New Mutation Occurrence causing Neuroferritinopathy*

The FTL gene mutation reduces ferritins' capacity to store iron atoms, leading in the release of iron atoms in nerve cells. Ferritins are generated in greater quantities to store iron in order to minimize the number of free iron atoms. However, because the mutant ferritin is an inefficient iron storage protein, this approach is not feasible. Iron and ferritin eventually build in various brain tissues, resulting in oxidative damage to the brain and, consequently, problems (Burn & Chinnery, 2006). However, it is unknown whether neuroferritinopathy is caused by an excess of free iron ions or by an excess of ferritins, which are intended to control free iron ions.

Because neuroferritinopathy is caused by oxidative damage, any drug that decreases oxidative damage may be utilized to treat the illness. The antioxidant is promising in this strategy since it has been found to aid in the treatment of various oxidative damage-related diseases, such as Friedreich ataxia and Parkinson's disease (Müller et al., 2003). Another treatment approach is to use DNA polymerase (Goldsby et al., 2002) or mismatch excision repair (MMR) enzymes (Yang, 2000), both of which are proteins. This appears to be beneficial just for eggs and sperms in terms of avoiding neuroferritinopathy in future generations.

Conclusion

In conclusion, this study discusses not only the function of ferritin as the primary iron storage protein in the human body, but also one uncommon human illnesse associated with ferritin, neuroferritinopathy.

Neuroferritinopathy is caused by two different types of FTL gene mutations: FTL 460-461lns and FTL 498-499lns TC.. As demonstrated by these diseases, iron, while less prevalent in vivo, was critical to the human body's homeostasis, and a disruption in its predominant mode of storage and release, whether due to an altered structure of the storage protein or an excessive amount of said protein, can result in a series of pathological reactions that can be extremely harmful to human life. However, further research should be performed to determine the source of the illness, as it is still unknown whether the two uncommon diseases are caused by an excess of free iron ions or by increased ferritin formation as a result of controlling the excess iron.

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