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Review

The significance of ferritin in cancer: Anti-oxidation, inflammation and tumorigenesis

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ABSTRACT

The iron storage protein ferritin has been continuously studied for over 70 years and its function as the primary iron storage protein in cells is well established. Although the intracellular functions of ferritin are for the most part well-characterized, the significance of serum (extracellular) ferritin in human biology is poorly understood. Recently, several lines of evidence have demonstrated that ferritin is a multi-functional protein with possible roles in proliferation, angiogenesis, immunosuppression, and iron delivery. In the context of cancer, ferritin is detected at higher levels in the sera of many cancer patients, and the higher levels correlate with aggressive disease and poor clinical outcome. Furthermore, ferritin is highly expressed in tumor-associated macrophages which have been recently recognized as having critical roles in tumor progression and therapy resistance. These characteristics suggest ferritin could be an attractive target for cancer therapy because its down-regulation could disrupt the supportive tumor microenvironment, kill cancer cells, and increase sensitivity to chemotherapy. In this review, we provide an overview of the current knowledge on the function and regulation of ferritin. Moreover, we examine the literature on ferritin's contributions to tumor progression and therapy resistance, in addition to its therapeutic potential.

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1. Introduction

Ferritin is the oldest known protein involved in iron metabolism. It was first described in 1894 by the German pharmacologist Oswald Schmiedeberg who noted an iron-rich component in horse livers [1]. However, it was not until 1937 that ferritin was purified from horse spleen by the Czech biologist Vilém Laufberger who proposed that it "must be a substance which serves as a depot for iron in the organism" [1,2]. The early isolation of ferritin was facilitated by several distinct biochemical characteristics: its stability at high temperatures (>80 °C), relative insolubility in ammonium sulfate solutions, and its crystallization with cadmium salts.

Ferritin is a 450 kDa hollow nano-cage (outside diameter 12–13 nm; inside diameter 8 nm) capable of incorporating up to 4500 iron atoms in a non-toxic but bioavailable form [3,4]. In mammals, each ferritin complex is composed of 24 subunits that form a spherical symmetrical protein shell. Each ferritin subunit folds into a 4-helix bundle with a fifth short helix in close proximity to the C-terminus [5,6]. In its assembled form, the ferritin complex has eight hydrophilic channels which have been proposed to serve as entry ports for ferrous iron [7,8]. Iron is stored within the ferritin cavity as mineralized ferrihydrite ($Fe_2O_3 \cdot 9H_2O$) with traces of phosphorus and nitrogen [9].

Two functionally and genetically distinct ferritin subunits exist: L-ferritin and H-ferritin (also known as light chain and heavy chain ferritin). In humans, but not all species, their molecular masses are 19 and 21 kDa respectively [10,11]. Although the two subunits share approximately 55% of their sequence as well as their multi-helical three dimensional structures, they are functionally distinct [11–13]. The H subunit possesses enzymatic activity and can oxidize ferrous iron into ferric iron. The ferroxidase center in H-ferritin is composed of several residues (mainly glutamic acid) which are buried within the H-ferritin helical bundle and serve as metal ligands [5,14]. The ferroxidase activity of H-ferritin is not dependent on the assembly of the full-ferritin complex and can be detected in the monomeric form [15]. The presence of a ferroxidase center within the ferritin subunit is essential and sufficient for rapid iron uptake [13,14,16]. A mutant of H-ferritin generated by mutating two residues within the ferroxidase center (Glu62 and His65) was capable of forming stable ferritin complexes but lacked detectable ferroxidase activity [17]. Furthermore, introduction of several glutamic acid residues necessary for the ferroxidase center into L-ferritin was sufficient to increase its iron incorporation capacity to similar levels as H-ferritin [18].

L-ferritin lacks enzymatic activity and thus does not contribute to iron oxidization and uptake. However, it has a higher number of carboxy groups lining the ferritin cavity which serve as iron nucleation sites [16,19]. In vitro experiments with recombinant L-ferritin homopolymers showed that it is capable of mineralizing iron faster than H-ferritin homopolymers [19]. Moreover, the L-ferritin monomer contains a salt bridge within its helical fold which confers greater stability on the ferritin complex in acidic and reducing conditions [20].

2. Serum ferritin

In addition to its intracellular form, ferritin is also an abundant protein in circulation. This form of ferritin, termed serum ferritin, was first detected in 1948 in animals experiencing hepatic cirrhosis or shock [21]. This original observation was later confirmed in humans with various forms of liver disease [22]. Serum ferritin showed similar immunologic reactivity, molecular size and isoelectrical focusing characteristics as that of ferritin extracted from the liver or spleen [23–26]. Furthermore, serum ferritin was surprisingly iron poor with approximately 4–20% of the iron content of liver or spleen ferritin [23,24]. This relatively low iron content persisted even in patients with iron overload [23].

Serum ferritin is a reliable indicator of the body's iron stores [27–29]. Its levels are significantly lower in individuals suffering from iron-deficiency anemia or undergoing phlebotomy [27,28]. In contrast, serum ferritin levels are higher in patients with iron-overload disease and hemochromatosis [27,30]. Generally, women tend to have lower levels of serum ferritin than men [27,28,31], possibly due to loss of hemoglobin during menstruation. Serum ferritin values in healthy individuals show some variability [31]. Serum ferritin correlated positively with age, body mass index, iron supplement, and heme-iron intakes, but was inversely correlated with physical activity and aspirin use in postmenopausal women [32]. Another study examining serum ferritin in men demonstrated that serum ferritin is positively correlated with body mass index, but not with the use of dietary iron supplement [33].

Serum ferritin is elevated during chronic and acute inflammation [34–36]. Its rise correlates with the rise in other acute phase proteins such as C-reactive protein (CRP) and α_1-acid glycoprotein (AGP) [36,37]. Consistently, chronic use of aspirin lowers serum ferritin and other parameters of inflammation in patients with various inflammatory diseases [38].

The source of serum ferritin is still unclear. Several lines of evidence have demonstrated that hepatocytes, macrophages and microglia are capable of ferritin secretion in vitro [39–42]. This secretion was reflective of their intracellular iron levels and was responsive to iron loading and chelation [39,41,42]. Although the secreted ferritin in those experiments contained both the H and L subunits, their ratios varied greatly between animal strains and cell types [39–41].

Although different cells are capable of ferritin release in vitro, serum ferritin seems to be primarily derived from macrophages in vivo [43,44]. The macrophage-specific ablation of the iron response protein 2 (IRP2) – a negative regulator of ferritin expression – increased serum ferritin levels, whereas hepatocyte or intestinal epithelial-specific ablation did not affect serum ferritin levels in mice [44]. Moreover, the size and immunological reactivity of serum ferritin in mice were similar to the ferritin found in organs with major macrophage populations such as the bone marrow and spleen [43] and serum ferritin levels fell by 75% after splenectomy suggesting the macrophages from the spleen were the source of ferritin in serum [43]. Recently, a study utilizing a mouse model with macrophage-specific deletion in the iron exporter ferroportin showed a robust increase in serum ferritin levels as well as increased iron accumulation in spleen and liver macrophages [45]. This study also suggests that macrophages contribute significantly to serum ferritin. Overall, although multiple cells are capable of ferritin secretion in response to various stimuli, there is increasing evidence that, macrophages may represent a primary systemic source for serum ferritin.

The existing literature on ferritin's secretory pathway is conflicted, as evidence exists to suggest both classical and non-classical pathways. For example, a truncated and unglycosylated ferritin similar to ferritin found within lysosomes was detected in mouse serum and splenic macrophages suggesting macrophage-specific release of lysosomal ferritin [43]. In other studies, the secretion of ferritin by hepatocytes and macrophages was inhibited by brefildin A (BFA) which is a potent blocker of protein transport from the endoplasmic reticulum (ER) to the Golgi apparatus [39,40]. This study also demonstrated that the entry of the ferritin monomers into the ER system occurs under the relative absence of free cytosolic iron and that iron can induce ferritin cellular retention [39].

3. Ferritin in cancer

3.1. Ferritin expression and localization in tumor tissue

Ferritin is differentially over-expressed in tissues from multiple malignancies, including: hepatocellular carcinoma [46,47], Hodgkin's lymphoma [48], breast cancer [49–53], and pancreatic cancer [50]. Structural, immunological, and isoelectric analyses demonstrated that tumor ferritins differ in their subunit composition and are most likely composed of different ratios of the L and H subunits [54].

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