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The many faces of the octahedral ferritin protein

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Abstract Iron is an essential trace nutrient required for the active sites of many enzymes, electron transfer and oxygen transport proteins. In contrast, to its important biological roles, iron is a catalyst for reactive oxygen species (ROS). Organisms must acquire iron but must protect against oxidative damage. Biology has evolved siderophores, hormones, membrane transporters, and iron transport and storage proteins to acquire sufficient iron but maintain iron levels at safe concentrations that prevent iron from catalyzing the formation of ROS. Ferritin is an important hub for iron metabolism because it sequesters iron during times of iron excess and releases iron during iron paucity. Ferritin is expressed in response to oxidative stress and is secreted into the extracellular matrix and into the serum. The iron sequestering ability of ferritin is believed to be the source of the anti-oxidant properties of ferritin. In fact, ferritin has been used as a biomarker for disease because it is synthesized in response to oxidative damage and inflammation. The function of serum ferritin is poorly understood, however serum ferritin concentrations seem to correlate with total iron stores. Under certain conditions, ferritin is also associated with pro-oxidant activity. The source of this switch from anti-oxidant to pro-oxidant has not been established but may be associated with unregulated iron release from ferritin. Recent reports demonstrate that ferritin is involved in other aspects of biology such as cell activation, development, immunity and angiogenesis. This review examines ferritin expression and secretion in correlation with anti-oxidant activity and with respect to these new functions. In addition, conditions that lead to pro-oxidant conditions are considered.

Keywords Ferritin · Iron storage · Anti-oxidant · Pro-oxidant · Iron-regulation

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Cytosolic iron storage

Ferritin is a hollow spherical protein complex of 24 subunits that assemble into a hollow spherical structure with an external 12-nm diameter and a hollow internal 8-nm diameter cavity (Crichton and Declercq 2010). Up to 4,500 iron atoms can be mineralized inside the 2 nm thick protein shell. The protein cage prevents other biological molecules in the cytosol from reacting with the iron mineral (Arosio et al. 2009). Individual iron ions can diffuse into and out of ferritin through eight channels located at the threefold symmetry axis of ferritin (Fig. 1) (Theil et al. 2008; Watt et al. 2010).

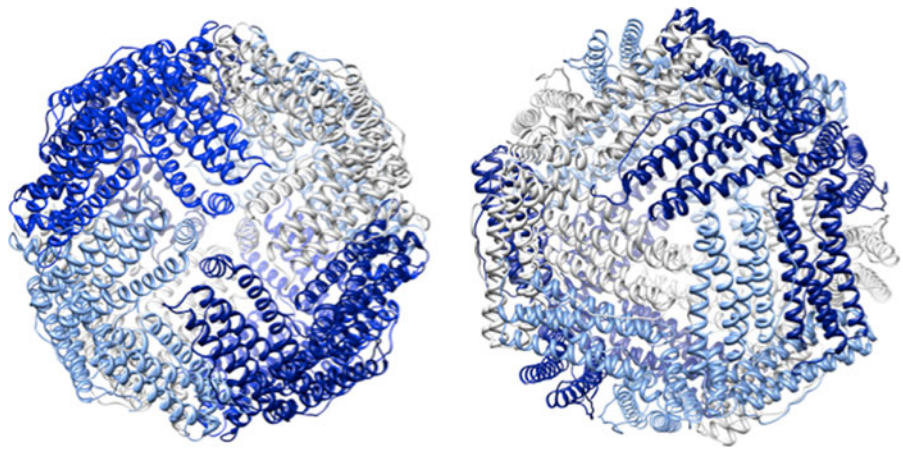

Fig. 1 Ferritin Structure. A *ribbon* diagram representing the ferritin structure. *Left image* represents the fourfold symmetry axis showing one of the hydrophobic channels. *Right image* represents the threefold axis showing one of the hydrophilic channels. Iron entry and exit is proposed to occur through the threefold channels

The 24-subunits that assemble into ferritin are composed of two types of polypeptide chains called the H and L subunits. The H ferritin subunit possesses the catalytic iron binding sites that make up the ferroxidase center (Lawson et al. 1991). The L ferritin subunits possess amino acid residues known as the nucleation sites that provide ligands for binding Fe^{3+} ions that initiate crystal growth inside ferritin (Santambrogio et al. 1996). Ferritin recognizes and binds two Fe^{2+} ions in the ferroxidase center where the Fe^{2+} ions are oxidized by di-oxygen to Fe^{3+} (Lawson et al. 1989). The oxidized Fe^{3+} ions migrate out of the ferroxidase center and into the interior of the ferritin cavity where Fe^{3+} binds to the nucleation sites for mineralization (Santambrogio et al. 1996). The process of iron loading and mineral formation inside ferritin along with the roles of the H and L subunits was recently reviewed (Bou-Abdallah 2010).

The labile iron pool (LIP) in the cytosol is an essential pool of free iron for activating other iron-containing proteins (Kruszewski 2003). Several mechanisms allow iron to be released from ferritin as the LIP is depleted (Romeo et al. 2001; De Domenico et al. 2009; Kidane et al. 2006). Recent studies have examined how this reaction might occur in vivo (De Domenico et al. 2009) and in vitro (Theil et al. 2008; Johnson et al. 2011; Watt et al. 2010).

In addition to iron storage and iron release roles, ferritin can act as both an anti-oxidant and as a pro-oxidant and also functions in roles that do not follow the classical function of ferritin as an iron storage protein (Arosio et al. 2009). Ferritin is involved in inflammation, cellular development, neurological development and angiogenesis (Wang et al. 2010; Shi et al. 2008; Alkhateeb and Connor 2010; Coffman et al. 2008; Parthasarathy et al. 2002). In addition, ferritin is used as a biomarker for diseases (Beard et al. 2006). This review examines these new roles for ferritin and attempts to explain how an iron storage protein can be so versatile in biological systems.

Ferritin gene regulation

The ferritin genes that express H and L ferritin have been extensively studied and many aspects of ferritin mRNA transcription have been characterized (Torti and Torti 2002). In addition, protein expression is also controlled post-transcriptionally by iron response proteins that bind to ferritin mRNA for H and L ferritin and prevent the mRNA from interacting with the ribosome for protein translation (Outten and Theil 2009; Theil 2007). Both of these regulatory mechanisms control the amount of ferritin that is expressed in the cell or secreted from the cell. Our goal in discussing regulation is not to review the mechanistic details of ferritin regulation (for reviews see (Torti and Torti 2002)) but to identify conditions that stimulate ferritin mRNA transcription or stimulate ferritin protein synthesis. With this information we will attempt to correlate ferritin mRNA synthesis and protein expression with functions for ferritin that are not directly related to iron storage.

Although there is an increase of ferritin mRNA transcription in response to iron citrate, it is much less than expected for a protein whose purpose is to store

iron (Dickey et al. 1987; Theil 2007). The lack of transcriptional control by iron is based primarily on the fact that a steady pool of ferritin mRNA exists in the cell and is regulated by the iron response proteins (Section "Post-transcriptional regulation"). Heme is a stronger inducer of ferritin than iron citrate because it acts both as a transcriptional inducer using Bach 1 and at a translational level using IRP-2 (see below) (Hintze et al. 2007; Hintze and Theil 2006).

In contrast to the weak response of ferritin mRNA transcription induced by incubation with iron, oxidative stress causes 80-fold greater expression of ferritin mRNA than iron (Hintze and Theil 2005). Genes that respond to oxidative stress are up-regulated by the antioxidant response element (ARE) and in addition to inducing ferritin mRNA transcription, the ARE up-regulates enzymes such as thioredoxin reductase 1, and quinone reductase (Torti and Torti 2002). The fact that ferritin is expressed in response to oxidant stress may indicate an important role for ferritin in decreasing the labile iron pool to minimize the potential for reactive oxygen species (ROS) formation (Picard et al. 1998). When sufficient reducing power is present the LIP may be less dangerous to the cell because of mechanisms to remove ROS. When oxidative stress increases, the reducing power to eliminate ROS is not available. Consistent with this observation is the fact that phorone, a molecule that limits radical defense mechanisms by reducing glutathione concentrations causes the transcriptional induction of both H and L ferritin genes (Cairo et al. 1995).

The induction of ferritin by inflammatory cytokines has been reviewed (Torti and Torti 2002). Tumor necrosis factor alpha (TNFα) and interleukins (particularly IL-1 and IL-6) appear to be the best triggers that initiate the synthesis of ferritin in relation to the inflammatory response. These cytokines preferentially induce H chain ferritin (Torti et al. 1988; Wei et al. 1990). The subunit content of ferritin formed under inflammatory conditions produced ferritin with a higher H subunit content (Torti et al. 1988). TNF-alpha treatment resulted in a greater proportion of iron incorporated into ferritin, consistent with the observation that the cell sequesters the LIP in response to cellular stresses (Fahmy and Young 1993). In contrast, cells treated with iron induce the synthesis of L ferritin (Smirnov et al. 1999).

Studies have shown that oxidized lipoproteins dramatically stimulate L ferritin synthesis in THP-1 macrophage cells (Ramm et al. 1994). The response appears to be peroxisome proliferated and may involve PPAR gamma (Storey et al. 2009; Wang et al. 2010). Adipokines are known to induce inflammation and can stimulate ferritin expression (Aso et al. 2010).

Ferritin mRNA transcription is stimulated slightly by iron, significantly by oxidative damage and inflammation. H ferritin is increased in response to oxidative damage and inflammation whereas L ferritin is increased in response to iron. Since H ferritin possesses the ferroxidase center for rapid oxidation of Fe(II), it appears that in response to oxidative stress or inflammation, ferritin acts to sequester the LIP in the cytosol to prevent the formation of ROS. Since L ferritin possesses the nucleation sites and sequesters iron better than H ferritin, and L ferritin mRNA is increased in response to iron, L ferritin acts for long-term storage of iron. Thus, H ferritin appears to regulate free cytosolic iron in a protective role and L ferritin functions as an iron storage subunit.

Post-transcriptional regulation

The post-transcriptional regulation of ferritin allows for rapid production of ferritin in response to iron or oxidative stress and inhibits ferritin synthesis in the absence of these signals (Theil 2007). In contrast, transferrin receptor-1 (TfR-1) mRNA has stable expression of transferrin receptor in the absence of iron but the mRNA is degraded in the presence of iron. This allows the cell to rapidly store or import iron depending on cellular iron levels. The iron response proteins (IRP-1 and IRP-2) are essential for controlling response to iron levels.

The regulation of ferritin synthesis (Fig. 2) is controlled by IRP-1 or IRP-2 binding to a hairpin structure in the 5′ mRNA of the ferritin transcript known as the iron response element (IRE) (Zahringer et al. 1976; Shull and Theil 1982; Theil 2007). When bound, the IRP proteins block binding of the mRNA to the ribosome and prevent the synthesis of ferritin. In the case of transferrin receptor-1 (TfR-1), IRPs bind to hairpin loops in the 3′ mRNA, preventing nuclease degradation of the mRNA and allowing

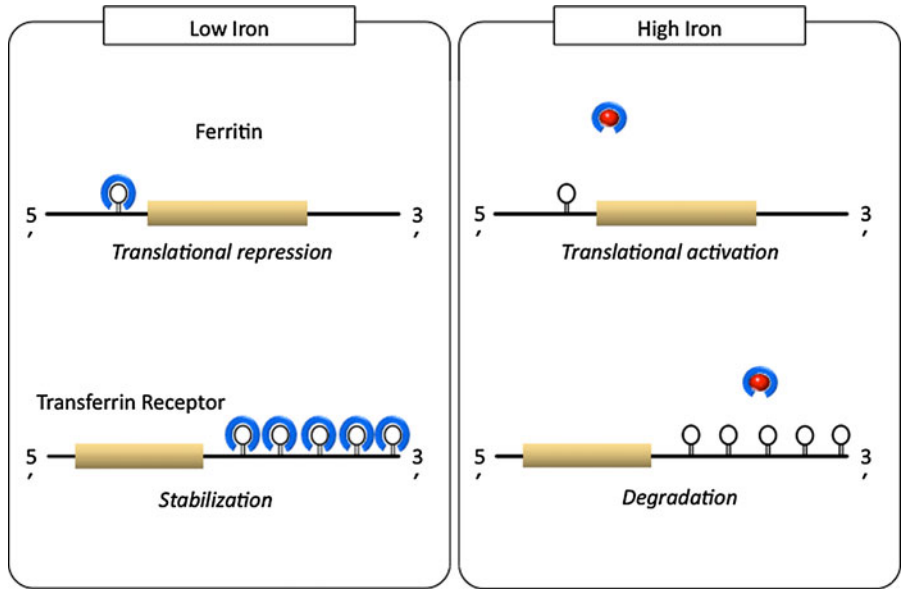

Fig. 2 Model representing how the iron response proteins control protein expression by interacting with iron response elements found in mRNA. The *left panel* represents low iron conditions. The protein expression of ferritin and other proteins (see text) is controlled by the binding of an iron response protein (IRP) to the iron response element (IRE) in the 5′ region of the mRNA. The IRE/IRP interaction prevents the mRNA from binding to a ribosome and prevents protein expression. In contrast, transferrin receptor possesses IREs in the 3' region of the mRNA. This stabilizes the mRNA against degradation and allows prolonged translation of the mRNA. The *right panel* represents high iron conditions. When cellular iron concentrations are elevated, the IRP proteins detect the iron and are released from the IREs. This allows translation of the mRNA for ferritin and increases the rate of TfR-1 degradation

prolonged synthesis of TfR-1 to increase the iron content of cells.

IRP-1 is a bi-functional protein (Rouault and Tong 2005). In the absence of iron, it functions as the IRP-1 protein and binds the IRE of the H and L ferritin mRNA and other mRNAs with IRE for other iron proteins such as TfR-1, mitochondrial aconitase, ferroportin and aminolevulinate synthase, preventing translation of these proteins (Theil 2007). When iron is present, a 4Fe–4S cluster assembles in IRP-1 converting it into a cytosolic aconitase enzyme (Rouault and Tong 2005). The structural change between IRP-1 and cytosolic aconitase is considerable and changes the conformation so the enzyme can only function as an aconitase or IRP-1. The iron sulfur cluster of IRP-1 is sensitive to hydrogen peroxide and is dismantled converting the aconitase to the IRP-1 protein under oxidative conditions (Pantopoulos et al. 1997; Regan et al. 2008).

In contrast to IRP-1, IRP-2 does not possess an iron sulfur cluster (Wallander et al. 2006). IRP-2 is regulated by oxidative conditions in the cell and is active when Cys residues are reduced but upon oxidation and disulfide bond formation, IRP-2 is degraded (Zumbrennen et al. 2009). This suggests that when the cell has a reducing environment it is able to bring iron into the cytosol because it can appropriately respond to the potential generation of radicals. When oxidative stress is present, ferritin is synthesized to store free iron and TfR-1 is degraded to prevent more iron from coming into the cell. IRP-2 and IRP-1 appear to complement each other at high oxygen tension but IRP-2 is the only functional repressor at low oxygen tension (Hanson et al. 2003). L ferritin appears to be more regulated by IRP-2 than by IRP-1 (Hintze and Theil 2005). Both IRP-1 and IRP-2 were shown to bind heme and this accelerated the degradation of both proteins (Goessling et al. 1994; Goessling et al. 1998).

Serum ferritin

Inflammation stimulates the synthesis and secretion of ferritin into the serum (Fahmy and Young 1993; Koorts and Viljoen 2007; Torti and Torti 1994).

Cytokine induction experiments indicate that the H-chain ferritin is preferentially expressed during inflammation (Torti and Torti 2002). Several studies have shown that ferritin can be secreted from hepatoma cells or macrophages when exposed to inflammatory cytokines or iron, respectively (Tran et al. 1997; Yuan et al. 2004). Ferritin mRNA found on polysomes in the endoplasmic reticulum (ER) and chemicals that inhibit secretion of proteins from the ER and Golgi apparatus suggest that ferritin is secreted by the ER, Golgi apparatus mechanism (Madani and Linder 1992).

Evaluation of total body iron stores is important in determining the iron status of an individual. Serum ferritin concentrations were shown to be a good marker for total body stores for healthy individuals (Krause and Stolc 1979; Cook et al. 1974; Ponka et al. 1998). This test is accurate for healthy individuals but great deviations occur in other diseases, particularly inflammatory diseases where serum ferritin is markedly elevated due to inflammation and oxidative damage (Lee and Jacobs 2004). Therefore the usefulness of serum ferritin as a marker for iron stores in disease states is much less useful in determining whole organism iron status in disease states. However, the fact that serum ferritin levels increase in response to inflammation and oxidative damage (Section "Ferritin gene regulation") has provided a diagnostic biomarker for these conditions.

Patients with iron overload conditions, such as hemochromatosis and β-thalassemia, have high serum ferritin concentrations. As indicated above, this response might be due to iron levels, or the oxidative damage associated with free iron. Non-transferrin bound iron (NTBI) is common in these patients because the iron binding proteins are saturated. The result is oxidative stress caused by ROS formation from free iron. Hemochromatosis patients have predominantly L serum ferritin that contains very little iron. One would expect that serum ferritin secreted in response to elevated iron levels would result in iron-loaded ferritin. However, if the response is associated with oxidative damage, serum ferritin might perform another role that has not yet been identified. Examination of the H and L ferritin expression profiles (Sections "Ferritin gene regulation", "Post-transcriptional regulation") shows that H ferritin responds to oxidative damage and L ferritin responds to iron (Torti and Torti 2002). Kurz showed that cells could absorb ferritin in response to high cytosolic iron levels, decrease the LIP and improve its oxidative stress status by sequestering the iron in the newly incorporated ferritin (Kurz 2008; Kurz et al. 2007). Therefore, the secretion of apo L ferritin into the serum may be an attempt to provide additional ferritin to iron-overloaded cells.

Inflammation is common in kidney disease and diabetes patients and the serum ferritin levels in these patients are known to be significantly elevated (Steven Fishbane 2004). Conditions such as chronic kidney disease are carefully monitored and studied for the relationship between iron, serum ferritin and anemia. Inflammation leads to the production of hepcidin, the iron hormone that regulates iron release from iron-rich cells (Ganz and Nemeth 2009). During inflammation, hepcidin causes the endocytosis of ferroportin, the iron export protein, decreasing the iron levels in serum. Such conditions lead to low transferrin saturation levels and ultimately to anemia.

Several recent studies measured the iron content of serum ferritin in healthy individuals ($\sim$1,100–1,200 Fe/ferritin) and patients with inflammation ($\sim$800 Fe/ferritin) (ten Kate et al. 1997; Herbert et al. 1997). The iron content of serum ferritin from both the healthy population and those suffering from inflammation was significantly higher than from patients with hemochromatosis or thalassemia (100–200 Fe/ferritin) (Yamanishi et al. 2002; Worwood et al. 1976; Nielsen et al. 2000; Arosio et al. 1977). Although the iron/ferritin concentration is slightly lower in patients with inflammation than for healthy individuals, the total iron in serum ferritin is approximately fourfold higher due to the significant increase in total serum ferritin present in the bloodstream (normal individuals 110–140 ng ferritin/ml ferritin vs. inflammation patients 450–500 ng ferritin/ml) (ten Kate et al. 1997; Herbert et al. 1997). This may suggest that serum ferritin plays a role in iron redistribution during inflammation, especially with the recent characterization of ferritin receptors (Section "Ferritin receptors") that recognize and internalize serum ferritin by endocytosis.

Ferritin receptors

Treatment of cells with ferritin showed saturable binding on the cell surface, suggesting the presence

of ferritin receptors. In fact, two classes of ferritin-binding receptors were identified. One receptor recognized both H and L ferritin where the second only recognized H ferritin (Moss et al. 1992).

Several ferritin receptors have been characterized. Tim-2 is a mouse ferritin receptor expressed in liver, kidney, T cells, B cells and oligodendrocytes (Chen et al. 2005; Chakravarti et al. 2005; Todorich et al. 2008). The Tim-2 receptor is specific for H ferritin. Tim-2 is present in mice but no human analog has been found. Tim-2 expression is increased with inflammation, which correlates with H ferritin expression (Chakravarti et al. 2005; Chen et al. 2005). A human ferritin receptor has been identified and was shown to be transferrin receptor-1 (TfR-1) (Li et al. 2010). TfR-1 is specific for H ferritin as no L ferritin binding was observed. Transferrin only partially inhibited H ferritin binding to TfR-1 indicating the ferritin and transferrin-binding sites do not overlap. Ferritin enters the endosome or lysosome by endocytosis. Recent work by Li et al. described the Scara5 receptor that is used to deliver iron to kidney cells during embryonic development (Li et al. 2009). The authors build a case that at different stages of development and in different cells an alternate iron delivery system independent of transferrin or transferrin receptor is functioning. Scara5 is shown to be a novel ferritin receptor and delivers iron to the cell by receptor-mediated endocytosis. In contrast to Tim-2 and TfR-1, Scara 5 binds L ferritin. Iron delivery by serum ferritin to other cell types has also been documented. Macrophages have been shown to secrete iron in the form of ferritin (Sibille et al. 1988) and hepatocytes and erythroid precursor cells (Leimberg et al. 2008) are able to use iron from the secreted ferritin.

Although the transferrin receptor system using di-ferric transferrin is the predominant pathway for iron delivery, it appears that serum ferritin may play a role as a serum iron delivery molecule under certain condition. In addition, the delivery of one ferritin with 200–1,000 Fe/ferritin is much more efficient than transferrin with only 2 Fe/transferrin.

Ferritin binding proteins

Ferritin involvement in reactions not directly related to iron storage has been studied for many years and requires interactions with other proteins and cell surface receptors. On an organismal level ferritin acts in the cytosol, nucleus, mitochondria and in a secretory manner and plays many roles (Arosio et al. 2009; Recalcati et al. 2008). For example, ferritin acts as a signaling molecule to suppress the immune response in macrophages, lymphocytes and myeloid precursor cells (Recalcati et al. 2008). This occurs when H ferritin binds to TIM-2 receptors. Ferritin binding to other proteins has been demonstrated and interaction with binding partners may be important in other signaling processes.

The discovery of several ferritin binding proteins (FBPs) occurred during studies trying to quantitate ferritin concentrations in serum by immunoblot analysis. However, the ferritin epitopes were blocked by FBPs present in serum. Such studies have identified fibrinogen (Orino et al. 1993), feline ferritin binding protein (Sakamoto et al. 2009), α-casein (Sugawara et al. 2009) and α-2-macroblobulin (Santambrogio and Massover 1989) and auto-antibodies as serum ferritin binding proteins (Sakamoto et al. 2009).

In some cases these proteins have been proposed to function in clearing serum ferritin from the bloodstream. Other roles are not understood but may include using the FBP as an alternate target for surface binding proteins for targeting ferritin into cells. Another potential role of FBPs is to localize ferritin in an area where low iron concentrations is required. For example, one role of ferritin in milk may be to keep the free iron concentrations low to prevent bacterial growth. It is possible that α-casein closes the gated pores of ferritin or enhances the iron binding affinity of ferritin for iron (Theil et al. 2008).

In bacteria, several ferredoxin-like proteins have been identified in DNA regions close to ferritin (Andrews et al. 1989; Wang et al. 2007). These ferredoxin proteins have been purified and characterized as electron transfer protein containing 2Fe-2S clusters (Garg et al. 1996; Quail et al. 1996; Wang et al. 2007). The fact that ferredoxins bind to ferritin suggests they may have a role in redox chemistry associated with iron loading or iron release. In fact, the ferredoxin from *P. aeruginosa* was shown to make the heme "conductive" and allows electrons to pass through the ferritin protein shell as part of the iron release from ferritin (Weeratunga et al. 2009). FBPs may play an important role in mediating iron release or enhance the affinity of ferritin for iron binding.

Chaperone-like proteins may regulate the control of iron levels between the cytosol and the iron stored in ferritin. Shi et al. reported a cytosolic iron chaperone protein (PCBP1) that increased iron loading into ferritin in vivo (Shi et al. 2008). PCBP1 was shown to associate with ferritin by co-immuno precipitation of PCBP1 and ferritin. PCBP1 binds 3 Fe/protein and delivers iron to ferritin both in vivo and in vitro. Such a protein may play an essential role in controlling free iron levels in cells.

A similar mechanism can be implied from the gated-pore model of iron release proposed by Theil et al (2008). Amino acids that control the threefold channels of ferritin can be opened and closed by small molecules and proteins (Liu et al. 2003; 2007; Takagi et al. 1998). The opening and closing of the gated pores significantly altered the rate of iron release from ferritin. Therefore, FBPs may be proteins that open or close the channels of ferritin and regulate the concentration of free iron in the LIP.

Ferritin and high molecular weight kininogen (HK) interact and play an important role in angiogenesis. HK is a protein involved in the coagulation cascade. HK is cleaved by a serum protease kallikrein and produces two fragments that are involved in angiogenesis. Ferritin binding to HK is inhibitory to the kallikrein cleavage of HK and slows the rate of this cleavage. The products of HK cleavage are Bradykinin (BK), a pro-angiogenic peptide that induces NO release and vasodilation and two-chain kininogen (HKa) that has anti-angiogenic properties (Sharma 2005).

Ferritin binding to HK (Kd = 140 nm) also decreases the cleavage of HK by two other proteases that are active during inflammation, neutrophil elastase and mast cell tryptase (80–81). In addition ferritin binds to the cleavage product HKa with greater affinity than it binds HK ($\sim$14 nm). When bound to HKa, ferritin inhibits the anti-angiogenic activity of HKa. The inhibition of HKa by ferritin allows BK to act as a pro-angiogenic factor to increase blood vessel growth.

Another FBP is α-2-macroglobulin (Santambrogio and Massover 1989). The α-2-macroglobulin protein is an acute-phase responding serum carrier protein that transports other proteins and stabilizes them in the serum to prolong their lifetime (Petersen 1993). Conversely, α-2-macroglobulin also assists in the clearance of proteins from serum by binding to a low-density lipoprotein receptor-related protein receptor for endocytosis. In addition, α-2-macroglobulin is a protease inhibitor that possesses a protein domain called the "bait region" that binds to the active sites of almost any protease and inactivates the protease enzyme activity. α-2-macroglobulin binds and carries a variety of proteins including ferritin and the iron hormone hepcidin (Peslova et al. 2009). The exact role of α-2-macroglobulin binding ferritin has yet to be established but the links between ferritin, hepcidin and inflammation provide interesting connections that need to be further evaluated.

Fibrinogen is a serum protein involved in the blood-clotting pathway that acts as an FBP (Orino et al. 1993). The protease thrombin cuts fibrinogen to fibrin, which is then cross-linked by Factor XIII to form clots (Stassen et al. 2004). It is interesting that ferritin binds to the substrate fibrinogen and to α-2-macroglobulin, a protease inhibitor of thrombin (Santambrogio and Massover 1989). Thrombin, the protease that activates fibrinogen to the active form for clotting is inhibited by iron ions but can be activated by chelation of the iron ions (Azizova et al. 2009a, b). In fact, all serine proteases are inactivated by free iron (Rosenmund et al. 1984).

Blood clots are degraded by the protease plasmin, which is activated from a precursor called plasminogen (Sainz et al. 2007). The protease kallikrein is responsible for activation of plasmin by cleaving plasminogen (Sainz et al. 2007). As stated above, kallikrein is inhibited by α-2-macroglobulin (Colman 1994). Therefore, ferritin binds to the substrate of clot formation, fibrinogen and to α-2-macroglobulin, the inhibitor of proteases that cause the formation and break down of clots. Oxidation of fibrinogen causes dysregulation of coagulation (Azizova et al. 2009a). In addition, oxidized fibrinogen stimulates aggregation of platelets and activates leukocytes triggering an inflammatory response (Shcheglovitova et al. 2006). These observations link iron-catalyzed oxidation to inflammation and atherosclerosis (Sagastagoitia et al. 2007). A likely role for ferritin binding to these proteins involved in clotting is to sequester iron to prevent iron catalyzed oxidative damage that inhibits these processes (Syrovatka et al. 2009). Figure 3 shows all of these reactions, where ferritin binds and shows sites where ferritin may be important for sequestering iron to allow activity of the enzymes.

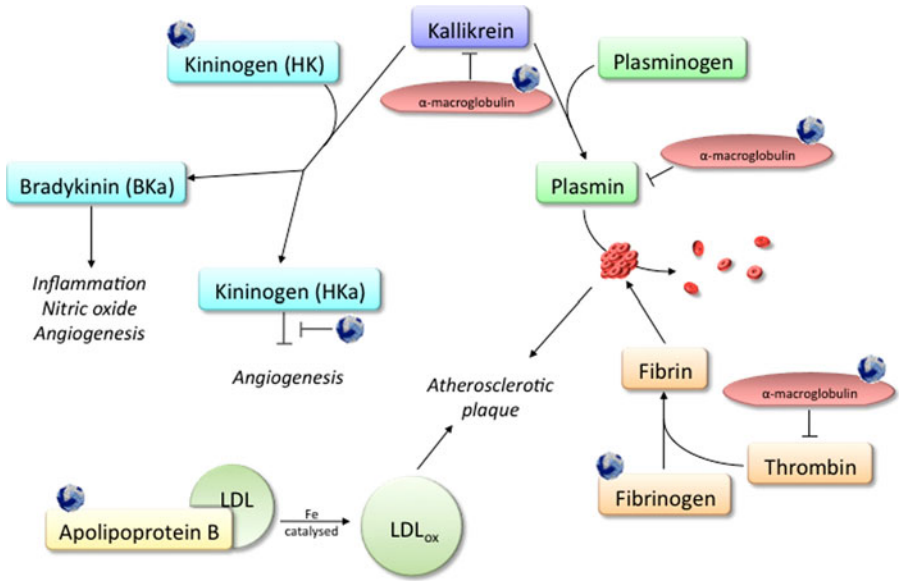

Fig. 3 Interactions of ferritin with members of the hemostatic system. Ferritin binds to many proteins and enzymes involved in angiogenesis, clotting and in the formation of atherosclerotic plaques. Many of the enzymes, serine proteases, are inhibited by free iron (NTBI). Ferritin may be recruited by these proteins to create a local microenvironment low in iron to prevent inhibition of these proteases. Pro-oxidant activity of ferritin may occur when ferritin interacts with molecules that can open the gated pores of ferritin to release iron

Ferritin is also bound in serum by apo lipoprotein B, a component of serum low-density lipoproteins (LDL) (Seki et al. 2008). Both apo lipoprotein B and ferritin bind hemin and their interactions appear to be mediated by hemin. Atherosclerotic lesions are known to contain ferritin and ferritin expression is elevated under conditions leading to atherosclerosis (Olson et al. 2010; Depalma et al. 2010). In addition, iron is a potent catalyst for oxidizing lipids found in LDL that leads to plaque formation (Gomez et al. 2010; Qayyum and Schulman 2005). Inflammation, lipid oxidation and thrombosis also lead to plaque formation (Sagastagoitia et al. 2007). Thus all of the FBPs discussed in this section appear to be related in the process of atherosclerosis.

Ferritin was also shown to be involved in activation of lipocytes indicating that ferritin and/or iron may play an important role in lipid trafficking (Ramm et al. 1994). Adiponectin, a hormone released from adipocytes is involved in regulating metabolic processes such as glucose regulation and fatty acid catabolism. It suppresses type 2 diabetes, obesity and atherosclerosis. Adiponectin was shown to up-regulate H ferritin in skeletal muscle cells (Ikegami et al. 2009). Recently low serum concentrations of high molecular weight adiponectin were correlated to high serum ferritin levels and insulin resistance in Type 2 diabetes patients (Aso et al. 2010).

The presence of ferritin binding to so many players in the angiogenesis, thrombosis and atherosclerosis pathways suggest an important role for ferritin in these processes. The observation that NTBI is a potent inhibitor of serine proteases may indicate that ferritin is present to sequester iron and prevent this inhibition (Rosenmund et al. 1984). This role might be very similar that played by the mini-ferritins or DPS proteins in bacteria (Chiancone and Ceci 2010). These mini ferritins bind to DNA in a protective role to bind and sequester any free iron to prevent DNA damage and cleavage. We propose that ferritin plays a similar role in angiogenesis, thrombosis and atherosclerosis. By binding to critical proteins in order to sequester iron and prevent inhibition and damage (Fig. 3).

If this is the case, one might question why ferritin and iron are present as pro-oxidants when these processes fail and are associated with disease states? Our hypothesis is that "trigger molecules" associated with the disease states can: (1) mobilize the sequestered iron by reduction; (2) chelate the iron; or (3) open the gated pores of ferritin to cause iron release. Based on this idea, the role of ferritin under normal conditions is to act as an anti-oxidant by sequestering iron in the microenvironment of the FBPs. However, in the presence of a "triggering molecule" or possibly a protein that can liberate the iron or open the ferritin gated pores, an initiation reaction occurs that liberates iron and starts a cascade that leads to oxidative reactions associated with diseases. Figure 3 summarizes the role of ferritin in protecting serum reactions

and simultaneously shows important points where trigger molecules might cause pro-oxidant reactions.

Summary

This review has summarized information relating to what appears to be non-iron storage roles of ferritin. In fact, we propose that FBPs recruit ferritin to locations that require very low iron microenvironments. In this process ferritin sequesters iron to protect molecules or reactions that are susceptible to iron damage. The pro-oxidant relationship of ferritin with oxidative damage diseases may occur when "trigger molecules" are present that release iron from ferritin by reduction or chelation or by opening the gated pores of ferritin.

Many conditions exist that relate iron and ferritin to the progression of diseases or neurological damage (for reviews see (Quintana and Gutiérrez 2010; Alkhateeb and Connor 2010; Arosio and Levi 2010). It is possible that mechanisms similar to those described here are also occurring in these disease states or are associated with the described damage. Using this new hypothesis may provide a way to correlate ferritin, iron and "trigger molecules" with the associated damage.

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