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International Journal of Biochemistry & Physiology

Ferritin Heavy Chain: From Redox Cycling to Cancer Biology

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Review Article

Volume 3 Issue 2

Received Date: April 13, 2018

Published Date: April 23, 2018

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Abstract

Iron is an essential nutrient for physiological cellular functions: as cofactor for key enzymes, it is involved in DNA duplication and repair thus representing a key element for cell replication, metabolism and growth. Due to its main role in iron storage, ferritin has been largely referred as redox-related protein for many years. However, increasing evidences suggest that perturbations of intracellular steady state amount of ferritin, and particularly of its heavy subunit (FHC), are key events in the pathogenesis of cancer initiation and progression. In the past decade many studies have demonstrated that FHC participates in cancer related pathways such as growth suppressor evasion, angiogenesis, epithelial to mesenchymal transition (EMT), dysregulation of chemokine signalling and enhanced stem cell expansion. The molecular mechanisms whereby FHC exerts these activities are either iron-dependent or iron-independent. Among the latters, the ability to regulate critical oncogenes (*c-myc*, NF-kB) or tumor suppressors (*p53*) as well as to modulate oncomiRNAs expression and chemokine signalling (CXCR4) strongly suggests that FHC is a much more versatile protein than simply iron storage. The deep understanding of these novel and still not completely characterized functions, as well as the discovery of other potential properties, position ferritin as a promising target in cancer therapy.

Keywords: Ferritin; FHC; Iron; Cancer

Abbreviations: FHC: ferritin heavy chain; EMT: epithelial to mesenchymal transition; ROS: reactive oxygen species; FLC: ferritin light chain; IRE: iron responsive element; IRP: iron regulatory protein; UTR: untranslated regione; ARE: antioxidant responsive element; TNFα: tumor necrosis factor alpha; IL-1α: interleukin-1α; HIF-1α: hypoxia inducible factor 1 alpha; DAXX: death domain-associated protein; NF-kB: nuclear factor kappa-light-chain-enhancer of activated B cells; VEGF: Vascular-Endothelial Growth Factor; PI3K: phosphatidylinositol 3-kinase; SDF-1: stromal cell-derived factor 1; CXCR-4: C-X-C chemokine receptor type 4; MOR: Mu opioid receptor; JNK-1: c-Jun N-terminal kinases; ASK1: Apoptosis signal-regulating kinase 1; LIP: labile iron pool; TGF-β1: Transforming growth factor-beta1, CSC: cancer stem cells.

Ferritin: The Iron Storage Protein

The fine homeostasis of iron, the most abundant and ubiquitously distributed metal element in our body, is among the most highly regulated biochemical pathway in the cell [1]. Iron acts as co-factor enabling the function of critical enzymes, including mitochondrial enzymes involved in respiratory complexes, enzymes involved in DNA synthesis as well as detoxifying enzymes such as peroxidase and catalase. Therefore, iron is implicated in many biochemical and physioloogical activities such as oxygen and electrons transport, energy metabolism, cell cycle regulation and DNA synthesis [1,2]. However, its ability to gain and lose electrons also leads iron to catalyse the generation of reactive oxygen species (ROS) by Fenton chemistry [3]. Through this reaction, less stable ferrous ions (Fe^{2+}) are converted into the ferric form (Fe^{3+}), thus consuming hydrogen peroxide (H_2O_2) and producing hydroxyl radicals (•OH) which, in turn, cause lipid and protein peroxidation and DNA breakage [3,4].

Ferritin is the main iron storage protein that captures and "buffers" the intracellular labile iron in a non-toxic and readily available form thus playing a key role in maintaining the cellular redox homeostasis [5-7]. In mammalian cells, ferritin is localized in cytoplasm, mitochondria and nucleus [6,7]. The cytosolic form is a globular protein, constituted by twenty-four subunits of heavy- (H; FHC; FTH) and light-type (L; FTL) assembled to form a shell with a central cavity where up to 4500 atoms of iron can be sequestered [8,9]. Ferritin H and L subunits share a homology of 50-56% in aminoacid sequence but are encoded by two different genes, both belonging to complex multigene families. FHC and FTL exert different functions: FHC has a ferroxidase and antioxidant activity and is devoted to rapid iron uptake and release while FTL has no ferroxidase activity but can alter the microenvironment to facilitate long-term iron storage [10,11]. The knock-down of the H-ferritin is embrionically lethal while its conditional inactivation in mice makes the animal more sensitive to oxidative damage [12]. It has been reported that the composition of the ferritin shell is not fixed but is rather widely variable and plastic. Depending on the metabolism patterns, the ratio of H to L subunits in ferritin can vary in a tissue-specific manner, with FTL being predominant in liver and spleen while FHC predominantly in muscle, brain, and heart [6,10]. Furthermore, the H-to-L ratio is modified in response to many stimuli such as during inflammatory and infectious conditions, differentiation and developmental transitions and in response to xenobiotic stress [6,10].

Generally, intracellular ferritins amount is regulated by iron and oxidative stress suggesting that their major function is the parsimonious regulation of iron and ROS metabolism. The iron dependent regulation mainly occurs at post-tanscriptional level by the IRE/IRP machinery: in the presence of low iron, the iron regulatory proteins 1 and 2 (IRP1 and IRP2) bind to the iron reponsive element (IRE) in the 5'UTR of the ferritin mRNA thus inhibiting its translation; in high iron condition IRPs lose their affinity thus allowing the activity of the translation machinery [13-17]. However, an increasing number of reports show that the fine tuning of intracellular ferritin amounts is also operated by other factors such as during oxidative stress, inflammation and hypoxia [6,18]. In response to intracellular oxidative stress, ferritin and other antioxidant proteins are regulated at the transcriptional level by a *cis* regulatory element named Antioxidant Responsive Element (ARE) [19]. In particular the transcription of FHC gene is activated by H_2O_2 in a JunD-dependent manner, thus protecting against the essential oxidative insult [20].

Iron and its homeostasis are intimately linked to the inflammatory response. Iinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-1α (IL-1α), transcriptionally induce the H subunit of ferritin, thus inducing an accumulation of H-rich acidic isoferritins and substantially altering the shell subunits composition [21,22]. The regulatory elements responding to cytokines have been mapped in a *cis*-acting element (FER2) located 4.8 kb upstream of the FHC transcriptional start site. During inflammation, two of the multiple NF-kB subunits, p50 and p65, also bind to this regulatory region causing H-ferritin up-regulation and thus suppressing the generation of ROS [23].

Several reports highlight that hypoxia is intimately tied to the local iron status mainly acting on translational efficiency of ferritin subunits. Both short-term and long-term hypoxia conditions affect, though in different ways, IRP binding activity thus modulating ferritin expression [24,25]. By using different cancer *in vitro* models, it has been demonstrated that while a short-term hypoxia treatment is able to induce ferritin synthesis by decreasing IRP1 binding activity, long-term hypoxia conditions increase IRP2 expression and function thus leading to a decrease in ferritin synthesis along with an increase in iron uptake [24,25].

Ferritin and Cancer Biology

Numerous studies demonstrate with certainty that pathways of iron acquisition, efflux, storage and regulation are all perturbed in cancer, suggesting that the control of iron metabolism is a central aspect of carcinogenesis and cancer progression [26,27]. Consistent with this scenario, accumulating evidence indicate that ferritin, and above FHC, may be a relevant factor in most of cancer hallmarks such as enhanced cell growth and proliferation, angiogenesis, epithelial to

mesenchymal transition (EMT), dysregulation of chemokine signalling and more recently enhanced stem cell expansion [28,18]. Early informations about the relationship between ferritin and cancer stem from the observation that an increase in total ferritin as well as a shift toward acidic (H-rich) ferritins occurs in the serum of patients with various malignancies [29]. The specific mechanisms through which ferritin severely impact on these intricate processes is far from being totally defined; however, it appears that the involvement of ferritin in cancer biology is related both to its role of iron scavenger and to iron-independent activities such as oncogenes and/or tumor suppressors dysregulation and perturbation of oncomiRNAs networks [28,18]. Furthermore, we and others have demonstrated that ferritin can affect tumor cells either as oncogene or tumor suppressor in a context- or disease- specific manner thus making this picture even more complex.

Ferritin and Cancer Cell Growth

One of the main abnormalities resulting in the development of cancer is the rapid and uncontrolled cell growth that is driven either by the hyperactivation of pro-survival signalling pathways, such as those of AKT, ERK and PI3K, or by the failure of pro-apoptotic signals [30,31]. A deep survey of the literature highlights that the link between ferritin and cancer cell growth is very complex and often conflicting since it is exerted in a cell-specific manner and through different mechanisms. In human metastatic melanoma MM07 cells and in erytholeukemia K562 cells, FHC-silencing is accompanied by decreased growth activity through the substantial modification of a repertoire of transcripts, miRNAs and proteins expression [32,33]. In particular, in K562 cells, the FHC-dependent modulation of miR-125b affects RAF1/pERK1/2 expression leading to a reduced proliferation rate in the FHC-silenced cells [33]. On the contrary, in SKOV-3 ovarian cancer cells, the FHC knock-down lead to a significant increase of cell proliferation rate along with an enhanced glucose consumption and an accelerated metabolism [34]. In MCF-7 epithelial breast cancer cell lines, the analysis of the relationship between ferritin and cancer cell growth return conflicting results. In 2013, Alkhateeb, et al. demonstrated that both apo- and holo-ferritin increased MCF-7 cell proliferation thus suggesting an iron-independent function [35]. Subsequently, in 2017, results from our laboratory showed that the knock-down of the sole H subunit of ferritin increased MCF-7 cell proliferation rate and that this was significantly affected by the FHC silencing-induced ROS production [36].

Another mechanism through which ferritin could affect tumor growth is mediated by the modulation of either pro- or anti- apoptotic signals [28,18]. The tumor suppressor p53 is affected by alterations of the intracellular iron and redox state [37,38]. Furthermore, several reports suggest the existence of a complex link between p53 and ferritin often characterized by a regulatory feedback loop exerted in a context-specific manner. Zhang, et al. show that iron depletion and increased ROS production post-transcriptionally enhanced p53 that, in turn, increases FHC expression in order to prevent the propagation of the cell damage [39]. Conversely, results from our laboratory indicate that p53 inhibits H ferritin gene expression thus suppressing its ROS-scavenging activity and enhancing the pro-apoptotic effects of p53 [40]. Moreover, it has been also demonstrated that FHC physically binds p53 and stabilizes the protein level under oxidative stress conditions [41].

Several other studies suggest that ferritin act also a central hub in different anti-apoptotic pathways presumably by its anti-oxidant properties. In 1999, Xu, et al. demonstrated that the over expression of Bcl-xL, that protect astrocytes from glucose deprivation, is accompanied by the up-regulation of both L- and H-ferritins [42]. In line with these data, Yang, et al. showed that down-regulation of ferritin in MCF-7 cells results in increased apoptosis through the suppression of Bcl-2 mRNA [43]. Subsequently, in 2003, Cozzi, et al. found that H-ferritin exerts a negative regulation on TNF-induced apoptosis of HeLa cells in an iron-independent manner [44]. Additionally, it has been demonstrated that ferritin is also part of the anti-apoptotic activity of NF-kB. During inflammation, NF-kB antagonizes TNF-induced apoptosis by suppressing the accumulation of ROS. To this, NF-kB induces FHC, as antioxidant protein, which in turn promotes iron sequestration, inhibits ROS accumulation and prevents sustained JNK cascade activation [23]. Finally, a recent paper by Liu, et al. highlights, for the first time, that FHC is also able to suppress apoptotic signals by phisically interacting with the death domain-associated protein (Daxx), a highly conserved nuclear protein with pro-apoptotic functions through the Fas-Daxx-ASK1-JNK1 signaling pathway [45]. Overall, all these data indicate that ferritin play a dual role in the control of apoptosis that deserve further investigations in order to use this protein as powerful tool for differentially killing cancer cells.

Ferritin and Angiogenesis

Angiogenesis, the complex process whereby new blood and lymphatic vessels form to supply nutrients and oxygen, is required for invasive tumor growth and metastasis and constitutes an important point in the control of cancer progression. It is finely modulated in response to a variety of chemical signals and factors among which vascular endothelial growth factor (VEGF) is one of the most important and a major target for cancer therapy [30,31]. Interestingly, numerous studies suggest the existence of a potential but still

uncompletely defined relationship between iron, ferritin and angiogenesis [46]. It has been demonstrated that iron deficiency promotes both expression and secretion of VEGF: in 1996, Beerepoot, et al. demonstrated for the first time that iron depletion, induced by treatment with iron chelator deferoxamine, promotes both expression and secretion of VEGF in several human, murine and rat cancer cells [47]. Accordingly, two more recent studies in breast cancer also showed that low iron levels lead to decreased ferritin expression and ehanced VEGF expression, through the increase of HIF-1α levels. These results were also confirmed *in vivo* and proposed as molecular basis of the high recurrence of breast cancer in young patients [48,49]. Conversely, a study by Harned, et al. highlights that the H-ferritin silencing and the consequent alteration in ferritin H:L ratio causes decreased nuclear translocation of HIF1-alpha and VEGF secretion [50].

Ferritin and Chemokine Signalling

Chemokines, chemotactic cytokines normally involved in the control of immune cell homing and migration, play a key role in the regulation of tumor growth by directly affecting tumor cells or indirectly affecting tumor microenvironment [30,31]. The chemokine CXCL12, also called stromal cell-derived factor-1 (SDF-1), binds the G-protein-coupled receptor CXCR4, which, through multiple divergent pathways, modulates chemotaxis, cell adhesion, survival and proliferation [51,52]. Several studies have demonstrated that CXCR4 is over expressed in human cancers where it exerts an oncogenic effect by contributing to tumor growth, EMT, metastasis and therapeutic resi stance [53,54]. Indeed, Roccaro, et al. demonstrated that CXCR4 over epression promotes the acquisition of an EMT-like phenotype in multiple myeloma (MM) cells leading to higher bone metastasis and extramedullary disease dissemination *in vivo* [55]. Accordingly, Grundker, et al. showed that CXCL12 induces the over expression of EMT genes in MCF-7 and T-47-D breast cancer cells [56].

In 2006, Li, et al. showed that CXCL12 promotes binding of FHC to CXCR4 in human embryonic kidney (HEK293) and HeLa cells. As a consequence, FHC is phosphorylated at serine 178 and translocated into the nucleus while CXCR4-mediated ERK1/2 activation and chemotaxis are strongly inhibited [57]. Later, the relationship between FHC and CXCR4 has been also investigated in neurons. In 2009, Sengupta, et al. found that, both in vitro (i.e. neuronal cultures) and in vivo (i.e. rat brain), the long-term treatment with Mu opioid receptor (MOR) agonists, such as morphine, inhibits CXCL12-induced activation of CXCR4 through the up-regulation of FHC. Hence, CXCR4 activity and the downstream ERK and AKT signalling pathways are repressed [58]. Accordingly, results from our laboratory indicate that FHC knock-down is accompanied, along with increased ROS production, by a significant increase in CXCR4 surface expression and signalling in MCF-7 breast cancer cells and in H460 non-small cell lung cancer cells [36]. In line with Sengupta, et al, we found that, among the downstream targets of CXCR4, FHC insists particularly on the ERK and PI3K-pAKT signalling pathways [36,58].

Ferritin and EMT

Epithelial to mesenchymal transition (EMT) is a rapid and often reversible phenomenon by which epithelial cells acquire mesenchymal, fibroblast-like properties. Particularly, through cytoskeleton re-organization, loss of cell-cell adhesion molecules, modification of cellular polarization, de novo expression of mesenchymal proteins and acquisition of stemness properties, cells undergoing EMT gain increased cell motility, invasive properties and resistance to anoikis. Hence, EMT is largely considered as a marker of metastasis and gain of invasiveness [30,31]. The analysis of the available data about H-ferritin and EMT suggests a cell type- and disease- dependent effect for FHC on EMT. In 2009, Zhang, et al, showed that cellular iron homeostasis regulated by FHC plays a critical role in TGF-β1–induced EMT of AML-12 murine cells hepatocytes and A549 non-small cell lung cancer cells. In detail, the H-ferritin decrease leads to an increase in the labile iron pool (LIP) and ROS generation, thus promoting EMT and enhancing cell proliferation and migration [59]. Accordingly with Zhang, et al., results from our laboratory highlight that in SKOV3 epithelial ovarian cancer, MCF-7 breast cancer cells and H460 non-small cell lung cancer cells the FHC knock-down lead to the acquisition of a strong EMT phenotype along with increased cell migration ability [34,36]. However, while in AML-12 cells EMT is promoted exclusively by TGF-mediated ROS increase [59], in SKOV-3 cells the EMT and the more aggressive phenotype of FHC-silenced cells was due mainly to the altered expression of miR-125b [34]. In MCF-7 and H460 cells the FHC-mediated regulation of EMT phenotype is partially due to ROS increase along with CXCR4 axis dysregulation [36].

Ferritin and Cancer Stem Cells

In the past 3 years, few research studies have supported a possible role of iron metabolism and ferritin in the expansion of cancer stem cells (CSCs) subpopulation. CSCs exhibit self-renewal capacity and are associated with cancer metastasis, tumor relapse and chemotherapeutic failure [30,31]. In human H460 and H292 NSCLC cells, the subchronic exposure to iron-induced oxidative stress leads to a remarkable increase in CSC spheroids in parallel with an increase in ABCG2 CSC marker [60]. Accordingly, Hamai, et al. demonstrate

that iron-depletion, followed by an overproduction of ROS, promotes cancer stem cell death [61]. In SKOV3 epithelial ovarian cancer cells, low FHC levels promote cancer stem cell spheroids accumulation along with the increase in stemness markers expression most likely through an iron-independent mechanism involving the regulation of miR-150 and miR-146a [34]. However, the available data are still limited and the molecular mechanism underlying ferritin action on CSCs propagation it's all to be investigated.

Conclusions

Since its key function in so many fundamental biochemical and physiological pathways, iron is considered a target of great interest in cancer research. In the past decade, ferritin and in particular the H-rich isoferritins play significant roles in many of the cancer hallmarks. Some of the FHC activities in tumor progression are directly related to the canonical iron management while others are iron-independent. The discovery of these new functions, mostly mediated by the regulation of gene, microRNA and protein expression, expands the global understanding of FHC as a more versatile protein with a strong potential as target in cancer therapy.

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