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Estrogen-dependent changes in serum iron levels as a translator of the adverse effects of estrogen during infection: A conceptual framework

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ABSTRACT

Elevated levels of estrogen often associate with increased susceptibility to infection. This has been attributed to the ability of estrogen to concomitantly enhance the growth and virulence of pathogens and suppress host immunity. But the exact mechanism of how estrogen mediates such effects, especially in cases where the pathogen and/or the immune components in question do not express estrogen receptors, has yet to be elucidated. Here we propose that translating the adverse effects of estrogen during infection is dependent to a significant degree upon its ability to manipulate iron homeostasis. For elevated levels of estrogen alter the synthesis and/or activity of several factors involved in iron metabolism including hypoxia inducible factor 1α (HIF-1α) and hepcidin among others. This leads to the inhibition of hepcidin synthesis in hepatocytes and the maintenance of ferroportin (FPN) integrity on the surface of iron-releasing duodenal enterocytes, hepatocytes, and macrophages. Intact FPN permits the continuous efflux of dietary and stored iron into the circulation, which further enhances pathogen growth and virulence on the one hand and suppresses host immunity on the other. This new conceptual framework may help explain a multitude of disparate clinical and experimental observations pertinent to the relationship between estrogen and infection.

Introduction

Elevated levels of estrogen (E2 or 17β-estradiol) often associate with increased susceptibility to infection, urogenital ones in particular [1–6]. The ability of estrogen to influence infection dynamics has traditionally been attributed to its ability to enhance microbial pathogenesis and suppress host immunity. However, invoking estrogen receptor (ER) engagement as an explanation for such disparate effects of estrogen on the pathogen and the host during infection is insufficient. In that, the effects of estrogen on both pathogen and host are highly coordinated. Coordination, by default, suggests the presence of – a yet to be identified – regulatory mechanism or an intermediate molecule that engages these two variables in tandem. Furthermore, numerous pathogens and immune components lacking ERs are subject to a similar set of estrogen-mediated-effects as those expressing such receptors. Again, this suggests that, besides its ability to directly manipulate microbial pathogenesis and host immunity, estrogen may indirectly influence these variables through an intermediary molecule that is yet to be identified. In this report, we hypothesize that iron is a likely candidate to fulfill this role. This is based on the observation that elevated levels of estrogen associate with increased levels of serum iron [7] and that increased iron availability precipitates a set of effects very similar to those precipitated by estrogen itself, vis-à-vis, enhanced microbial pathogenesis [8] and suppressed immunity [9]. To arrive at this hypothesis in a logical manner however, a brief discussion of the relationship between estrogen and microbial pathogenesis, estrogen and immunity, iron and microbial pathogenesis, iron and immunity, and then estrogen and iron are in order.

Estrogen enhances microbial pathogenesis

Several lines of evidence suggest that pathogens can respond to estrogen-mediated signals. For instance, pathogens like *Saccharomyces cerevisiae* [10], *Paracoccidioides brasiliensis* [11], and *Candida albicans* [12] express ERs and/or estrogen binding proteins (EBP) capable of mediating signals that alter pathogen survival, growth, and virulence. Estrogen was shown to promote *C. albicans* germination, adhesion and hyphal growth formation [13] as well as entry, attachment, and growth of *Chlamydia trachomatis* in various mammalian culture systems [14].

Estrogen suppresses host immunity

It is traditionally thought that estrogen-immune system interactions enhance immunity. In that, females tend to mount stronger

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immune responses against infection and exhibit higher rates of autoimmunity disorders as compared with males [6,15]. Direct interactions between the immune system and estrogen which occur through ERs on/in macrophages, B cells, and $CD8^+$ T cells have been implicated in this interplay [16]. That said, numerous experimental and clinical findings suggest that estrogen can exert immunosuppressive effects on host immunity. Elevated levels of estrogen have been shown to associate with diminished production of C-reactive protein [17], antimicrobial peptides like β-defensin 2 [18] and -defensins 1–3 [19], pro-inflammatory cytokines (IL-1β, TNF-α, TGF-β, IFN-γ, IL-6, IL-23, and CCL2, TLR2, TLR6, IL-8, and TNF-α) [20–22], and suppressed polymorphonuclear [23] and mononuclear [19] cell activity during infection. The production of anti-inflammatory cytokines like IL-4, IL-5, IL-10 has been reported to upregulate during infection in hosts with elevated levels of estrogen [21,24]. Furthermore, the expression of markers associated with suppressor (CD152) [25] or regulatory T cells (Foxp3) has been reported to upregulate in response to high estrogen levels [21]. Elevated levels of estrogen were also shown to induce the differentiation of non-protective Th2-type responses [24] and the expansion of $CD4^+CD25^+$ Treg cells during infection [20,21].

Iron enhances microbial pathogenesis

Due to its significant redox potential, iron plays an important role in various metabolic processes involved in pathogen growth and virulence [26]. Depriving pathogens of iron through sequestration is therefore considered an important component of innate immunity [27]. Pathogens extract iron from heme and other molecules by expressing ferric reductase [28] and iron-chelating siderophores and hemophores [29] among other mechanisms. High pathogenicity islands present in pathogenic strains of *Yersinia* and several members of the enterobacteriaceae encode yersiniabactin-mediated iron acquisition proteins [30]. Iron storage bacterioferritins BfrA and BfrB have been reported to play a crucial role in the survival and pathogenesis of *Mycobacterium tuberculosis* [31]. Synthesis of proteins involved in iron-uptake and utilization was shown to upregulate in human blood cultures of methicillin-resistant *Staphylococcus aureus* [32].

At the clinical level, susceptibility of liver transplant patients to invasive aspergillosis, cryptococcosis, and zygomycosis positively correlates with iron overload [33]. Hence, use of iron chelators (deferasirox) in conjunction with liposomal amphotericin B significantly improves survival and reduces fungal burden in mice with invasive pulmonary aspergillosis (IPA) [8,34]. Increased serum iron in patients with hematological malignancies also associates with increased risk of IPA. Replacing the siderophoric iron chelator deferoxamine with the non-siderophoric deferasirox, which deprives pathogens of iron, was reported to better protect against mucormycosis in immunocompromised patients [34].

Iron suppresses host immunity

Although immune cells and molecules require iron for proper functioning, iron overload can associate with immunosuppression and hence increased susceptibility to infection [9,35–37]. For example, the candidacidal activity of neutrophils and macrophages and their ability to produce nitric oxide and IL-12 greatly diminishes in *C. albicans*-infected mice with iron-overload [38]. Increased iron availability in HEp-2 cells infected with *C. trachomatis* was shown to reduce indoleamine 2,3-dioxygenase (IDO; an enzyme that catalyses tryptophan metabolism) expression and reduce IFN–induced inhibition of infection [39]. Liver transplant patients with increased iron availability can be easily weaned off immunosuppressive therapy suggesting that endogenous iron in such patients exerts the immunosuppressive effect needed for graft survival [40]. Treatment of *C. albicans*-infected iron-overloaded mice with the iron chelator deferoxamine was reported to resolve the infection, restore phagocytic function and re-direct Th differentiation from a non-protective (IL-4 producer) to a protective (IFN- producer) phenotype [38].

Role of estrogen in iron homeostasis

Serum iron derives from dietary iron in duodenal enterocytes, recycled iron in reticuloendothelial macrophages, and stored iron in hepatocytes. Ferroportin (FPN) on the lateral surface of enterocytes and the plasma membrane of macrophages and hepatocytes efflux iron to plasma. Plasma iron combines with transferrin for delivery to target cells through transferrin receptor 1 (TfR1). Iron efflux through FPN is negatively regulated by the hepatocyte-derived peptide hormone hepcidin, which degrades cell surface-expressed FPN [41]. Increased demand for iron (iron deficiency, hypoxia, etc.) downregulates hepcidin synthesis while elevated levels of serum iron upregulate it. Hypoxia activates a number of proteins like the transcription factor hypoxia inducible factor 1α (HIF-1α) [42] and the growth differentiation factor 15 (GDF15) [43] to downregulate hepcidin synthesis. Cleavage of membrane hemojuvelin (HJV), a co-receptor of the bone morphogenetic protein (BMP), by the serine protease matriptase 2 (TMPRSS6) also occurs in response to increased iron demand [44]. Conversely, iron-transferrin complexes in excess displace the hepcidin-regulator HEF from TfR1 permitting it to bind to TfR2, which then initiates signals that upregulate hepcidin synthesis [41,45]. Additionally, BMP binds with its receptor or the co-receptor HJV [46] to activate "similar to mothers against decapentaplegic 4" or SMAD4 transcription factor, which directly activates the hepcidin gene promoter [47].

Clinical and experimental evidence suggest that, like hypoxia, elevated levels of estrogen manipulate iron homeostasis. For instance, ovariectomy results in decreased serum iron, iron binding capacity, and iron response protein-1 binding activity [48]. In contrast, use of oral contraceptives in humans [49] and estrogen treatment in ovariectomized mice [7,48] both associate with increased levels of serum iron and total iron-binding capacity. Furthermore, the activity of enzymes (superoxide dismutase, glutathione peroxidase, and catalase) [7] and the expression of genes (lactotransferrin, ceruloplasmin ferroxidase, lipocalin 2, and FPN) [50] involved in iron metabolism were shown to upregulate in the presence of elevated levels of estrogen. Genistein, which exhibits estrogen-like activities, has also been shown to significantly increase iron export through the ERβ-dependent p38 MAPK-C/EBP pathway in astrocytes [48].

Estrogen could influence iron homeostasis by acting on various molecules that regulate iron release (Fig. 1). Elevated levels of estrogen were reported to reduce the transcription of hepcidin [7,51]; an effect that can be reversed by the addition of estrogen antagonists (ICI 182780). Binding of estrogen to estrogen response elements (EREs) in the murine hepcidin gene was reported to downregulate hepcidin transcription and increase iron release [51,52]. Furthermore, *in vitro* studies have shown that estrogen can upregulate the expression of HIF-1α in ovarian cancer cell lines (ES-2 and SKOV3) through the activation of the serine/threonine kinase signaling pathway [53]. Conversely, inflammatory cytokines (IL-1, IL-6, IL-22, TGF-β1, and TLR5) were shown to associate with increased hepcidin synthesis [54,55] in a JAK-STAT3-dependent manner [56]. It is worth remembering that elevated levels of estrogen associate with suppressed production of IL-6 and other inflammatory cytokines [21,22]. Collectively, estrogen has the potential to directly reduce hepcidin synthesis and hence increase serum iron levels.

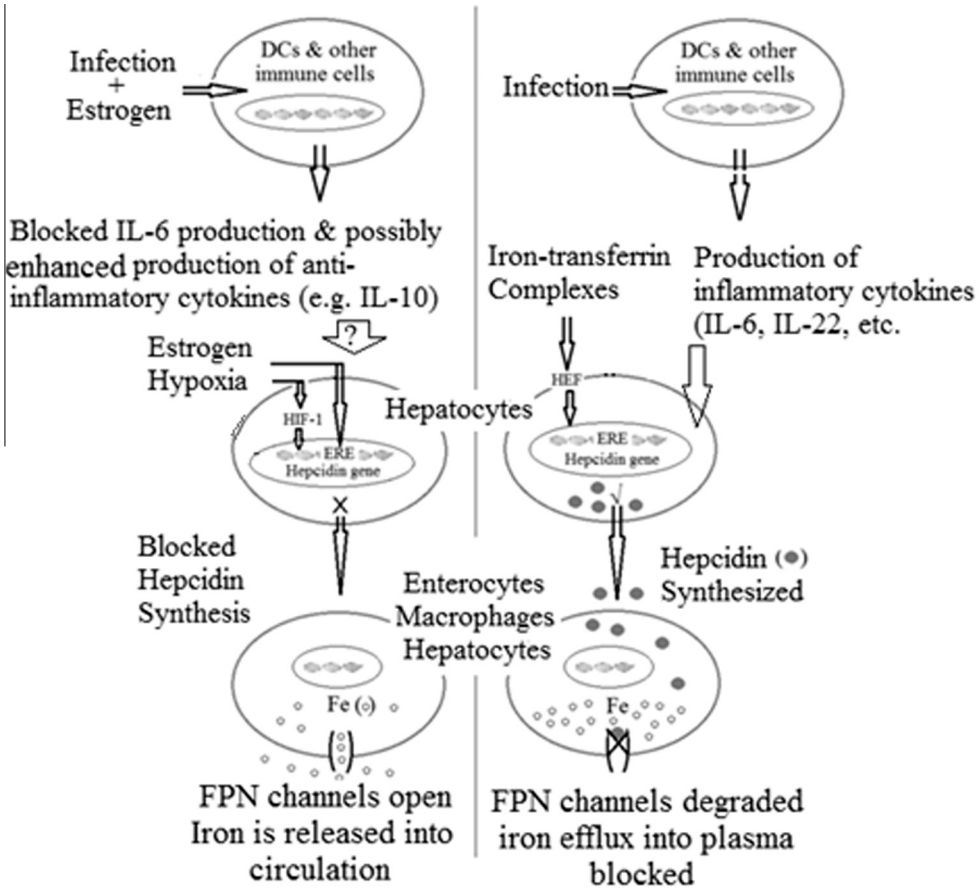

Fig. 1. A tentative model showing how estrogen manipulates iron homeostasis. IL-6 and increased availability of iron-transferrin complexes enhance hepcidin synthesis therefore degrading FPN and blocking further release of dietary and stored iron. Estrogen, on the other hand, blocks IL-6 production (while possibly enhancing the production of anti-inflammatory cytokines) and interacts with the hepcidin gene via EREs. Consequently, hepcidin synthesis is blocked, integrity of FPN channels is maintained and iron release into circulation continues.

Hypothesis

We hypothesize that infection in hosts with elevated levels of estrogen initiates a complex interplay between the estrogen, iron, pathogen, and immunity. The outcome of this interplay heavily bears on whether the infection takes hold or resolves (Fig. 2). In that, high levels of estrogen block hepcidin synthesis both directly by acting on the hepcidin gene and indirectly by suppressing the synthesis of inflammatory cytokines (IL-1, IL-6, etc.) capable of inducing hepcidin synthesis. Increased serum iron enhances microbial pathogenesis and further suppresses the immune response enabling the infection to take hold. In contrast, low levels of estrogen and/or strong proinflammatory (IL-1, IL-6, IL-22, etc.) responses induce hepcidin synthesis, which reduces iron availability and therefore hinder infection progression.

Implications

Focusing on iron as a translator of the biological effects of estrogen should help in furthering our understanding of the relationship between estrogen and infection; this is especially true as it relates to women. At the basic biology level, this hypothesis provides a means to better interpret numerous clinical and experiment findings regarding the role of estrogen in infection. In that, the literature is replete with examples where elevated levels of estrogen may predispose to [1–6] or protect against [57] various forms of infection. By considering the status of iron therefore, many of these conflicting findings could be sorted out or at least reconsidered. Additionally, increased levels of estrogen often associate with

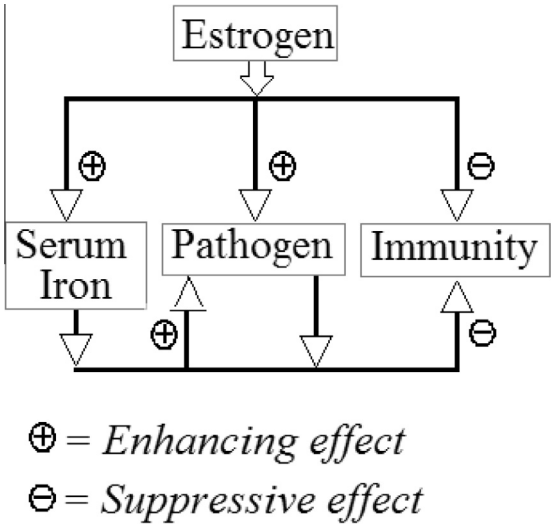

Fig. 2. A tentative model showing the overall role of estrogen in infection. Estrogen directly enhances pathogen growth and virulence and exerts direct suppressive effects on the immune response. Virulent pathogens and increased serum iron further suppress immunity resulting therefore in increased host susceptibility to infection.

increased host resistance to viral infections [58–60]. According to our hypothesis (Fig. 2), it is logical to predict that as viruses can hardly benefit from increased iron availability under the influence of estrogen and as the immunosuppressive effects exerted by microbial pathogens are lacking in this case, the ability of the host to resist infection is enhanced. At the clinical level, evaluating the status of both estrogen and iron in patients at high risk of opportunistic (microbial and fungal) infections like organ transplant patients, diabetics, and cancer patients undergoing chemotherapy or radiotherapy could provide invaluable insights into how such patients could better be managed. Appreciating the role of the estrogen-iron axis during infection may open the door for significant improvements in conventional antimicrobial therapy [17]. Furthermore, taking the relationship between estrogen and iron into account may be of help in better understanding and countering some of the side effects that associate with steroid-based therapeutic modalities such as hormonal replacement therapy, anti-inflammatory corticosteroids, and contraceptive pills. Besides infection, the interplay between estrogen and iron could further complicate various disease states including cancer [61], hemochromatosis [62], thalassemia [63], and sickle cell disease [36]. However, the bearing of such interplay on the progression and/or complication of these and many other disease states has yet to be addressed. In conclusion, understanding the role of estrogen in disease could better be served by thinking about iron.

Conflict of interest

The authors declare that neither one of them has any conflict of interest regarding any material described in this manuscript.

Authors' contributions

M. Hamad was responsible for the conception of the idea, literature review, hypothesis formulation and preparation of the manuscript. S. Awadallah heavily participated in discussing and advancing the main idea of the paper, review of the literature, and manuscript preparation. Both authors have read the manuscript and approve of its submission, in its current form, to Medical Hypotheses.

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