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Iron Metabolism Regulation and Diseases

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Abstract

Iron is an essential trace element for human being because it functions as a crucial redox catalyst and takes part in many critical cellular processes. However, iron is redox-active and can produce harmful reactive oxygen species (ROS), inducing oxidative stress damage. Iron metabolism has been long investigated both in physiological and pathological conditions. Both iron deficiency and overload could promote the initiation and development of multiple disorders, such as infection, autoimmune diseases, and cancers.

Dysfunction of iron metabolism also exert deleterious effects on pregnancy, leading to several pregnancy complications. This review emphasizes the importance of the iron metabolism during the development of disease and the effect of iron metabolism on maternal and fetal physiology. Since the change of iron metabolism is so significant and some of the variations are irreversible, we believe that iron prophylaxis should be considered in all diseases and pregnancies.

Keywords: *Iron Metabolism; Infection; Autoimmune Diseases; Cancers; Pregnancy Complications*

Abbreviations: ROS: reactive oxygen species; DMT1: divalent metal transporter 1; TfR1: transferrin receptor 1; STEAP3: six-transmembrane epithelial antigen of the prostate 3; Lcn2: Lipocalin 2; LIP: labile iron pool; IRPs : iron-regulatory proteins; IRE: iron-responsive elements; UTRs: untranslated regions; IL-1: interleukin-1; iNOS: inducible nitric oxide synthase; NO: nitric oxide; Nramp1: natural resistance macrophage protein 1; TAMs: tumor-associated macrophages; RA: rheumatoid arthritis; MS: multiple sclerosis; MHC II: major histocompatibility complex II; MRI: magnetic resonance imaging; EAE: experimental autoimmune encephalomyelitis; ecESCs: ectopic endometrial stromal cells; n-euESCs: normal eutopic endometrial stromal cells

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Iron Metabolism and Its Regulation

Introduction of Iron Metabolism

Iron is necessary in various critical biological processes involving oxygen transportation (as heme of hemoglobin), ATP generation (as cofactors of many proteins involved in the tricarboxylic acid cycle and electron transport chain), and DNA biosynthesis (as ribonucleotide reductase cofactor) (Bogdan., *et al*. Cited Pages). Meanwhile, iron, with redox activity, can produce reactive oxygen species (ROS), inducing oxidative stress and initiating the signaling pathway of cell death (Ray, Huang and Tsuji Cited Pages). Therefore, maintaining a sufficient and appropriate amount of iron is essential to normal cell function.

In humans, approximately 1-2 mg of dietary iron is absorbed in the duodenum and proximal jejunum per day to balance the daily losses. Enterocytes can directly took in ferrous iron through the divalent metal transporter 1 (DMT1) on the apical membrane (Gunshin., *et al*. Cited Pages), while ferric iron needs to be reduced to ferrous form by ferric reductase duodenal cytochrome B (Dcytb), before it can be absorbed (McKie., *et al*. Cited Pages). Then, cytosolic iron can be pumped into the circulation through the only known iron exporter ferroportin (Fpn) on basolateral membrane of intestinal enterocytes.

Hephaestin, a multicopper oxidase, is required to oxidize ferrous iron to ferric form, before most of enterocytic iron transported in the circulation bond to transferrin. Circulating iron also exists in a non-transferrin bound form, especially when serum iron level is high and transferrin is saturated. Transferrin receptor 1 (TfR1) is widely expressed on different cells surface and is responsible for uptake of transferrin-bound iron through endocytosis. After internalized, the endocytic vesicle is acidified, releasing iron from transferrin (Qian and Tang Cited Pages). The apo-transferrin, still bound to TfR1, recycles back to the cell surface. Iron is then reduced into its soluble form by ferrireductase six-transmembrane epithelial antigen of the prostate 3 (STEAP3), and released to the cytosol via DMT1.

Besides, other iron uptake mechanisms exist in some cells. Lipocalin 2 (Lcn2)-dependent endocytosis of an iron-loaded siderophore has been proposed to regulate the survival of kidney cells (Devireddy., *et al*. Cited Pages). Resident macrophages obtain large quantities of iron via phagocytosis of senescent erythrocytes and clearance of hemoglobin and haem released in the circulation during intravascular hemolysis. Haptoglobin and haemopexin capture free hemoglobin and free haem respectively and they are internalized by macrophages through the receptor CD163 and CD91 (Kristiansen., *et al*. Cited Pages; Hvidberg., *et al*. Cited Pages).

Iron entering the cytoplasm either forms labile iron pool (LIP), or combines to ferritin for storage. Free iron catalyzes generation of toxic ROS via Fenton/Haber–Weiss reaction, which is known to induce oxidation of proteins, lipids, nucleic acids, carbohydrates and other cellular components, resulting in cell death, tissue damage, cell mutation and even tumorigenesis (Terman and Kurz Cited Pages). Ferritin, with ferroxidase property, consumes the same reagents of Fenton reaction, hence ferritin not only controls the intracellular ferrous iron availability but also exerted antioxidant functions (Arosio, Elia and Poli Cited Pages).

Regulation of Iron Homeostasis

Two regulatory systems balance human iron metabolism. One has systemic impacts, depending on hepcidin and the iron exporter ferroportin, while the other mainly functions cellular iron metabolism via iron-regulatory proteins (IRPs) -iron-responsive elements (IRE) axis at post-transcriptional scale.

Regulation of Systemic Iron Homeostasis

Hepcidin, a hormone mainly secreted by hepatocytes, seems to be the key regulatory molecule in systemic iron homeostasis maintenance (Peslova., *et al*. Cited Pages; Jordan., *et al*. Cited Pages). Multiple stimuluses' have regulatory function on the synthesis of hepcidin at the transcriptional scale. Both intracellular and extracellular iron concentrations increase hepcidin transcription, so does inflammation (Bartnikas, Andrews and Fleming Cited Pages; Wrighting and Andrews Cited Pages). Whereas, enhanced erythropoiesis decreases hepcidin generation (Tanno and Bhanu., *et al*. Cited Pages; Tanno and Miller Cited Pages; Tanno and Rabel., *et al*. Cited Pages).

In turn, hepcidin regulates recycling iron level by controlling ferroportin expression on iron-efflux cells involving recycling macrophages in spleen and liver (which contain large quantities of iron from red blood cells), duodenal enterocytes (which take charge of dietary iron absorption), and hepatocytes (which act as an iron depot). Hepcidin's direct combination to ferroportin is speculated to cause a conformational change, inducing the endocytosis of both molecules and degradation of lysosomal ensuing (Nemeth., *et al*. Cited Pages). Multistory suppression of iron efflux gives rise to an overall reduction in plasma iron concentration.

Regulation of Cellular Iron Homeostasis

Cellular iron homeostasis is regulated by iron regulatory proteins – iron response element regulatory system post-transcriptionally. IRP1 and IRP2, two orthologous RNA-binding proteins, interact with conserved cis-regulatory stem-loop structures named IREs, located in the 5' or 3' untranslated regions (UTRs) of target mRNAs, altering mRNAs stability or translation. In high iron conditions, IRP1 containing a Fe/S center acts as cytosolic aconitase unsuitable for IRE binding. IRP2, without aconitase activity or Fe/S center, is degraded by an iron-sensing ubiquitin ligase F-box/LRR-repeat protein 5 (FBXL5) instead (Thompson., *et al*. Cited Pages).

According to the location of IRE on 5'-UTR or 3'-UTR, the IRPs–IRE regulatory axis affects target gene expression in opposite ways. 5'-UTR IREs exist in genes which encode proteins decreasing cellular labile iron amount like ferritin and ferroportin, while 3' -UTR IREs are usually found in genes of proteins facilitating iron uptake involving TfR1 and DMT1 (Puig, Askeland and Thiele Cited Pages). In iron-deficiency cells, IRP1/2 response is activated, binds to 3'-UTR and stabilizes TfR1 mRNA, enhancing cellular iron uptake.

On the contrary, IRPs' combination to the 5'-UTR suppresses ferroportin and ferritin translation, thus inhibiting iron export from the cell and promoting release of stored iron into cytoplasm respectively (Sanchez., *et al*. Cited Pages). While in the circumstance of adequate iron storage, IRP1/2 activity is suppressed.

Disorder of Iron Metabolism and Related Diseases

Abnormal Iron Metabolism in Infection

As the fact that iron is essential for multiple biological processes of both prokaryotic and eukaryotic cells and that iron exerts significant influences on microbial proliferation and pathogenicity as well as immune cell characteristics and host immune responses, iron metabolism regulation is crucial in host–pathogen interaction (Nairz and Schroll., *et al.* Cited Pages). Most pathogenic bacteria, many viruses, involving HCV and HIV, fungi and parasites have a necessary demand of iron. Host's iron overload situation makes it more available for invading pathogens to obtain iron, which increases host's susceptibility to infection.

Many microbes highly surviving on the sufficient iron supply have developed diverse pathways steeling iron from host's storage. Gram-positive pathogens like B. anthracis acquire iron mainly through heme/hemoprotein receptors on cell surface or through the secretion of hemophores (Cassat and Skaar Cited Pages). Gram-negative pathogens obtain host's iron by siderophores and heme/hemoprotein receptors, as well as by transferrin or lactoferrin binding proteins (TBPs/LBPs) (Anzaldi and Skaar Cited Pages; Reniere., *et al.* Cited Pages). Intracellular pathogens also utilize siderophores and some even make direct use of free cytosolic iron and ferritin bound iron (Olakanmi., *et al*. Cited Pages).

However, the host immune system also established defense mechanism hindering the availability of iron for microbes by various cytokines, proteins and hormones to limit pathogen growth and to strengthen specific immune effector pathways, a strategy termed as "nutritional immunity" (Barber and Elde Cited Pages). According to the primary location of pathogens, iron homeostasis is regulated in different ways. Under the circumstance of extracellular infection, hepatocyte-derived hepcidin acts on ferroportin, resulting in ferroportin degradation and decreased iron efflux of macrophage.

This effect is further enhanced by hepcidin generated by macrophages respond to the simulation of interleukin-1 (IL-1) and IL-6, as well as by suppressive effect of IFN-γ on the transcription of ferroportin. Consequently, systemic hypoferremia incurs and iron available for extracellular pathogens is reduced. At the same time, intracellular iron increases with the rise of ferritin expression induced by iron

and cytokines like TNF-α, IL-1β, and IL-6 (Armitage., *et al*. Cited Pages; Vecchi., *et al*. Cited Pages). In contrast, in the case of intracellular infection, although hepcidin plays a suppressive role on ferroportin expression at the post-translational level, this effect appears to be surpassed by largely increased ferroportin transcription induced by activated inducible nitric oxide synthase (iNOS).

INOS promotes generation of nitric oxide (NO) and activation of transcription factor Nrf2, which directly facilitates ferroportin transcription, eventually giving rise to enhancement of iron efflux and decline of intracellular iron level (Nairz and Schleicher., *et al*. Cited Pages). Besides, natural resistance macrophage protein 1 (Nramp1), pumping iron into cytoplasm and facilitating iron discharge, further deprives microbes dwelling in the phagosome from iron supply (*Diaz-Ochoa*., *et al*. Cited Pages). Iron also interact with host's anti-microbial responses. On the one hand, iron makes synergistic effects towards anti-microbial radical formation like reactive oxygen species, and reactive nitrogen species, both of which injure microbes and ambient tissues (Koskenkorva-Frank., *et al*. Cited Pages).

On the other hand, iron levels influence the host immune state. It is indicated that macrophage polarization is related with iron metabolic level. M1-macrophages (express high levels of CD80, CD86, TNF-α, IL-12/23) usually express higher ferritin and hepcidin level and lower ferroportin level, contributing to iron sequestration. While, M2-macrophages (express high levels of CD163, CD209, CD206, IL-10 and IDO) demonstrate an iron release phenotype, with low level of ferritin and hepcidin but high level of ferroportin and Lcn2 (Recalcati., *et al*. Cited Pages). M1-macrophages are associated with inflammation with higher antigen presenting capacities and elevated generation of TNF-α, IL-12, IL-23, and reactive oxygen species. While M2-macrophages possess immunosuppressive properties with the increased production of IL-10 and TGF-β and participate apoptotic cells clearance and tissue remodeling with ample expression of mannose and scavenger receptors (Mantovani., *et al*. Cited Pages). Whereas, whether iron metabolism regulates the immune cells function and the detailed mechanism need to be further revealed.

Disturbed Iron Metabolism in Cancer

Iron has long been related with tumorigenesis and cell proliferation for its contribution to free radical generation and providing nutrients for cancer cells, and cancer cells are proposed to mound intracellular iron through dysregulation of iron metabolism. Intercellular iron uptake in multiple cancers are increased. TfR1 is highly expressed in several cancers, including breast cancer, leucocythemia, lymphoma, lung cancer, bladder cancer and glioma (Daniels., *et al*. Cited Pages).

The expression of STEAP2 and STEAP3, which reduce ferric iron to ferrous form and facilitate iron uptake, also increase in cancers (Grunewald., *et al*. Cited Pages). Lcn2, taking up iron in an alternative pathway by a complex with siderophore bound iron, overexpresses in some cancers as well, including breast, pancreatic and liver cancer (Leng, Wu and Arlinghaus Cited Pages; Zhang, Fan and Mei Cited Pages). Contrarily, iron storage and efflux both decrease via the degradation of ferritin and ferroportin, which evidenced by genetics and cohort studies (Pinnix., *et al*. Cited Pages; Radulescu., *et al*. Cited Pages; Kakhlon, Gruenbaum and Cabantchik Cited Pages), giving rise to the higher level of labile iron pool. It is demonstrated that patients with lower iron import and/or higher iron export, which means lower intracellular labile iron, have significantly more pleasant prognosis (Miller., *et al*. Cited Pages).

Besides, immune cells surrounded tumors, especially macrophages, seem to possess the phenotype prone to iron efflux, which facilitates tumor growth by providing iron for tumor cells (Recalcati., *et al*. Cited Pages) tumor-associated macrophages (TAMs) surrounded tumor, which is similar to M2-polarized macrophages, exhibit a gene expression profile prone to iron release with increased ferroportin and decreased ferritin (Cairo., *et al*. Cited Pages). Thus, more iron is available for tumor cells. Recently, increased expression of Lcn2 has been found in TAMs, which suggests that Lcn2 and siderophores as alternative iron trafficking molecules also participate in the tumor microenvironment formation and tumor progression (Jung and Weigert., *et al*. Cited Pages).

Since the fact that tumor cells are able to induce macrophages towards TAM-like macrophage phenotype (Ma., *et al*. Cited Pages; Raggi., *et al*. Cited Pages) and that the expression of genes involved in iron metabolism differ in macrophage polarization (Corna., *et al*. Cited Pages), it has been hypothesized that tumor cells may educate surrounding immune cells like macrophages to donating iron for their growth(Jung and Mertens., *et al*. Cited Pages).

Disordered Iron Metabolism in Autoimmune Diseases

Disorders of iron metabolism are also associated with a variety of autoimmune diseases. Moreover, many genes involved in iron regulation have been identified as susceptibility genes to autoimmune diseases (Davidson and Diamond Cited Pages). Studies have demonstrated that the gene polymorphisms of NRAMP1, which transfers iron into cytoplasm and helps iron efflux, is closely related to autoimmune diseases involving rheumatoid arthritis (RA), multiple sclerosis (MS), and diabetes mellitus type 1.

NRAMP1 abnormality affects the expression of IL-1, TNF and major histocompatibility complex II (MHC II). It also plays an important role in macrophage activation and differentiation. There are four alleles of SLC11A1 (which encoding NRAMP1) in human genome. The activation of promoter of allele 3 is in close connection with autoimmune diseases for its effective stimulation of NRAMP1 expression (Ates., *et al*. Cited Pages; Stober., *et al*. Cited Pages; Searle and Blackwell Cited Pages).

Iron deposition is found in situ tissues in various autoimmune diseases, as seen in central nervous system of MS patients, and synovial fluid of RA patients. By histochemical technique and nuclear magnetic resonance imaging (MRI), abnormal deposition of iron has been found in ectocinerea and alba of MS patients, even since the early stage (Bagnato., *et al*. Cited Pages) and the extent of iron accumulation tightly corresponds the progress of the disease.

Moreover, in experimental autoimmune encephalomyelitis (EAE), the ideal model of MS, iron chelators like desferrioxamine and dexrazoxane, have been proved to attenuate the disease (Pedchenko and LeVine Cited Pages). Large amounts of free iron, lactoferrin and other iron binding proteins are also found in synovial fluid of patients with RA (Ahmadzadeh, Shingu and Nobunaga Cited Pages) and desferrioxamine is suggested to be beneficial to patients with RA and consequent anemia (Fudman, Till and Fox Cited Pages; Polson., *et al*. Cited Pages).

However, the mechanism underlying how iron deposition or excess functions on autoimmunity is still unclear. In patients with MS, iron ions were found to be concentrated mainly in macrophages and astrocytes, promoting the expression of proinflammatory cytokines TNFα, IL-1β and metalloproteinase-9 (MMP-9) and enhancing inflammatory response (Mehta., *et al*. Cited Pages). Oxidative stress caused by excessive iron also induces tissue damage.

Dysfunctional Iron Metabolism in Pregnancy Complications

During pregnancy, the mother has to enhance her iron stores in order to provide the baby with adequate amounts. International clinical guides recommend that iron supplement should begin from 4 or 5 months of pregnancy, 0.3g ferrous sulfate per day, until the full-term pregnancy. Sufficient but moderate iron supplement during pregnancy is vital for the maintenance of pregnancy and the growth of offspring. Prenatal iron deficiency is associated with numbers of persistent short-term and long-term developmental deficits of multiple organs, even after enough iron supplement.

Recent animal studies have demonstrated that abnormal gene expression and epigenetic changes are related with prenatal iron deficiency in some brain diseases (Georgieff Cited Pages). Other disorders, including high blood pressure, altered nephron morphology, lipid metabolism changes and obesity (McArdle, Gambling and Kennedy Cited Pages), are also found linked with iron deficiency during pregnancy, especially during the first trimester (de Rooij., *et al*. Cited Pages).

However, iron overload may also have adverse effects. It has been illustrated that high level of serum iron causes an increased risk of hypertensive disorders during pregnancy. The serum iron level of preeclampsia women is higher than that of healthy pregnant women, and it increases with the exacerbation of the disease (Song, Luo and Zhang Cited Pages). For pregnant women at high risk, blind and inappropriate iron supplementation may accelerate the progression of preeclampsia.

Excessive iron load produces toxic free radicals with strong reducing activity, increases oxidative stress responses, promotes vascular epithelial cells and endothelial cells damage, and finally leads to the occurrence of preeclampsia (Song, Luo and Zhang Cited Pages).

Besides, higher amounts of catalytic Fe (II) are also found in ectopic endometrial stromal cells (ecESCs) of endometriosis, which is one of the leading reasons for infertility, than in normal eutopic endometrial stromal cells (n-euESCs).

EcESCs express higher level of TfR1 both in vivo and in vitro as well as lower level of ferroportin in vivo than n-euESCs do, which is similar to the change of iron metabolism happened in cancers (Mori., *et al*. Cited Pages). A cohort study also indicated that the mRNA level of SLC40A1 (which coding ferroportin) in granulosa cells from infertile women decreased while serum level of hepcidin increased (Moreno-Navarrete., *et al.* Cited Pages).

Previous studies suggested the association of premature birth and low birth weight with iron deficiency(Allen Cited Pages), but recently it is pointed out that preterm birth, as an oxidative stress related disease, may also be induced by iron overload(Sakata., *et al.* Cited Pages). Although the function of iron metabolism during pregnancy is still unclarified, it seems that iron metabolism does play a potential role in the maintenance of normal pregnancy and abnormal iron metabolism may contribute to the pathogenesis of pregnancy complications.

As maternal iron deficiency anemia and iron overload both lead to adverse pregnancy outcomes, more researches are needed to definite the appropriate amounts of iron supplementation during pregnancy, and to design effective interventions maintaining proper level of iron metabolism both systemically and locally.

Summary and Perspectives

Iron is one of the necessary trace element of human body, and it is proved that dysfunctional iron metabolism plays an essential role in the pathogenesis of multiple diseases. Both iron deficiency and overload are blame for the initiation and development of diseases like infection, autoimmune diseases, and cancers. But the detailed mechanisms are still unrevealed and some evidences seem contradictory. Moreover, whether iron metabolism takes part in immune regulation in diseases and what the mechanism is, need to be closely followed. Further researches in these areas will give us more avenues for understanding and preventing from diseases.

A very important point, despite the abundant iron transported from mother to fetus is critical to successful pregnancy, locally excessive iron does harm. The role of iron metabolism in maternal-fetal microenvironment formation and in related pregnancy complications pathogenesis remain poorly characterized. Blind and inappropriate iron supplementation during pregnancy is no doubt harmful to the maintenance of pregnancy or the growth of offspring. As the significant role of iron metabolism in relevant diseases is increasingly evidenced, more attentions should be focused on the definition of appropriately systematical and local iron levels and the controlling avenues, which may provide possible new ways guiding the clinical iron supplement and the diseases treatment during pregnancy.

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Conflict of interest

The authors have no financial conflicts of interest.

References

1. Ahmadzadeh N., *et al*. "Iron-Binding Proteins and Free Iron in Synovial Fluids of Rheumatoid Arthritis Patients". *Clinical Rheumatology* 8.3 (1989): 345-51.
2. Allen LH. "Anemia and Iron Deficiency: Effects on Pregnancy Outcome". *The American Journal of Clinical Nutrition* 71.5 (2000): 1280S-1284S.
3. Anzaldi L L and E P Skaar. "Overcoming the Heme Paradox: Heme Toxicity and Tolerance in Bacterial Pathogens". *Infection and Immunity* 78.12 (2010): 4977-89.

4. Armitage A E., *et al*. "Hepcidin Regulation by Innate Immune and Infectious Stimuli". *Blood* 118.15 (2011): 4129-4139.
5. Arosio P., *et al*. "Ferritin, Cellular Iron Storage and Regulation". *IUBMB Life* 69.6 (2017): 414-22.
6. Ates O., *et al*. "NRAMP1 (SLC11A1) Variants: Genetic Susceptibility to Multiple Sclerosis". *Journal of Clinical Immunology* 30.4 (2010): 583-586.
7. Bagnato F., *et al*. "Tracking Iron in Multiple Sclerosis: A Combined Imaging and Histopathological Study at 7 Tesla". *Brain* 134.Pt 12 (2011): 3602-3615.
8. Barber MF and NC Elde. "Nutritional Immunity. Escape From Bacterial Iron Piracy through Rapid Evolution of Transferrin". *Science* 346.6215 (2014): 1362-1366.
9. Bartnikas TB., *et al*. "Transferrin is a Major Determinant of Hepcidin Expression in Hypotransferrinemic Mice". *Blood* 117.2 (2011): 630-637.
10. Bogdan AR., *et al*. "Regulators of Iron Homeostasis: New Players in Metabolism, Cell Death, and Disease". *Trends in Biochemical Sciences* 41.3 (2016): 274-286.
11. Cairo G., *et al*. "Iron Trafficking and Metabolism in Macrophages: Contribution to the Polarized Phenotype". *Trends in Immunology* 32.6 (2011): 241-247.
12. Cassat JE and EP Skaar. "Metal Ion Acquisition in Staphylococcus Aureus: Overcoming Nutritional Immunity". *Seminars in Immunopathology* 34.2 (2012): 215-235.
13. Corna G., *et al*. "Polarization Dictates Iron Handling by Inflammatory and Alternatively Activated Macrophages". *Haematologica* 95.11 (2010): 1814-1822.
14. Daniels, T. R., *et al*. "The Transferrin Receptor and the Targeted Delivery of Therapeutic Agents Against Cancer". *Biochimica et Biophysica Acta* 1820.3 (2012): 291-317.
15. Davidson A and B Diamond. "Autoimmune Diseases". *The New England Journal of Medicine* 345.5 (2001): 340-350.
16. de Rooij SR., *et al*. "Prenatal Undernutrition and Cognitive Function in Late Adulthood". *Proceedings of the National Academy of Sciences of the United States* 107.39 (2010): 16881-16886.
17. Devireddy LR., *et al*. "A Cell-Surface Receptor for Lipocalin 24P3 Selectively Mediates Apoptosis and Iron Uptake". *Cell* 123.7 (2005): 1293-1305.
18. Diaz-Ochoa VE., *et al*. "Transition Metal Ions at the Crossroads of Mucosal Immunity and Microbial Pathogenesis". *Frontiers in Cellular and Infection Microbiology* 4 (2014): 2.
19. Fudman E J., *et al*. "Deferoxamine Induced Decreases of Lipid Peroxides in Rheumatoid Arthritis". *The Journal of Rheumatology* 14.4 (1987): 686-691.
20. Georgieff MK. "Long-Term Brain and Behavioral Consequences of Early Iron Deficiency". *Nutrition Reviews* 69 Supple 1 (2011): S43-48.
21. Grunewald TG., *et al*. "The STEAP Protein Family: Versatile Oxidoreductases and Targets for Cancer Immunotherapy with Overlapping and Distinct Cellular Functions". *Biology of the Cell* 104.11 (2012): 641-657.
22. Gunshin H., *et al*. "Cloning and Characterization of a Mammalian Proton-Coupled Metal-Ion Transporter". *Nature* 388.6641 (1997): 482-488.
23. Hvidberg V., *et al*. "Identification of the Receptor Scavenging Hemopexin-Heme Complexes". *Blood* 106.7 (2005): 2572-2579.
24. Jordan JB., *et al*. "Hepcidin Revisited, Disulfide Connectivity, Dynamics, and Structure". The Journal of Biological Chemistry 284.36 (2009): 24155-24167.
25. Jung M., *et al*. "Interleukin-10-Induced Neutrophil Gelatinase-Associated Lipocalin Production in Macrophages with Consequences for Tumor Growth". *Molecular and Cellular Biology* 32.19 (2012): 3938-3948.
26. Jung M., *et al*. "Lipocalin-2 and Iron Trafficking in the Tumor Microenvironment". *Pharmacological Research* 120 (2017): 146-156.
27. Kakhlon O., *et al*. "Ferritin Expression Modulates Cell Cycle Dynamics and Cell Responsiveness to H-ras-induced Growth Via Expansion of the Labile Iron Pool". *Biochemical Journal* 363.Pt 3 (2002): 431-436.

28. Koskenkorva-Frank TS., *et al*. "The Complex Interplay of Iron Metabolism, Reactive Oxygen Species, and Reactive Nitrogen Species: Insights Into the Potential of Various Iron Therapies to Induce Oxidative and Nitrosative Stress". *Free Radical Biology & Medicine* 65 (2013): 1174-1194.
29. Kristiansen M., *et al*. "Identification of the Haemoglobin Scavenger Receptor". *Nature* 409.6817 (2001): 198-201.
30. Leng X., *et al*. "Relationships of Lipocalin 2 with Breast Tumorigenesis and Metastasis". *Journal of Cellular Physiology* 226.2 (2011): 309-314.
31. Ma R., *et al*. "Tumor Cell-Derived Microparticles Polarize M2 Tumor-Associated Macrophages for Tumor Progression". *Oncoimmunology* 5.4 (2016): e1118599.
32. Mantovani A., *et al*. "The Chemokine System in Diverse Forms of Macrophage Activation and Polarization". *Trends in Immunology* 25.12 (2004): 677-686.
33. McArdle HJ., *et al*. "Iron Deficiency during Pregnancy: The Consequences for Placental Function and Fetal Outcome". *Proceedings of the Nutrition Society* 73.1 (2014): 9-15.
34. McKie AT., *et al*. "An Iron-Regulated Ferric Reductase Associated with the Absorption of Dietary Iron". *Science* 291.5509 (2001): 1755-1759.
35. Mehta V., *et al*. "Iron is a Sensitive Biomarker for Inflammation in Multiple Sclerosis Lesions". *PLoS One* 8.3 (2013): e57573.
36. Miller LD., *et al*. "An Iron Regulatory Gene Signature Predicts Outcome in Breast Cancer". *Cancer Research* 71.21 (2011): 6728-6737.
37. Moreno-Navarrete JM., *et al*. "Ferroportin mRNA is Down-Regulated in Granulosa and Cervical Cells from Infertile Women". *Fertility and Sterility* 107.1 (2017): 236-242.
38. Mori M., *et al*. "Ovarian Endometriosis-Associated Stromal Cells Reveal Persistently High Affinity for Iron". *Redox Biology* 6 (2015): 578-586.
39. Nairz M., *et al*. "Nitric Oxide-Mediated Regulation of Ferroportin-1 Controls Macrophage Iron Homeostasis and Immune Function in Salmonella Infection". *The Journal of Experimental Medicine* 210.5 (2013): 855-873.
40. Nairz M., *et al*. "The Struggle for Iron - a Metal at the Host-Pathogen Interface". *Cellular Microbiology* 12.12 (2010): 1691-1702.
41. Nemeth E., *et al*. "Hepcidin Regulates Cellular Iron Efflux by Binding to Ferroportin and Inducing its Internalization". *Science* 306.5704 (2004): 2090-2093.
42. Olakanmi O., *et al*. "Intraphagosomal Mycobacterium Tuberculosis Acquires Iron from Both Extracellular Transferrin and Intracellular Iron Pools. Impact of Interferon-Gamma and Hemochromatosis". *The Journal of Biological Chemistry* 277.51 (2002): 49727-49734.
43. Pedchenko TV and SM LeVine. "Desferrioxamine Suppresses Experimental Allergic Encephalomyelitis Induced by MBP in SJL Mice". *Journal of Neuroimmunology* 84.2 (1998): 188-197.
44. Peslova G., *et al*. "Hepcidin, the Hormone of Iron Metabolism, is Bound Specifically to Alpha-2-Macroglobulin in Blood". *Blood* 113.24 (2009): 6225-6236.
45. Pinnix ZK., *et al*. "Ferroportin and Iron Regulation in Breast Cancer Progression and Prognosis". *Science Translational Medicine* 2.43 (2010): 43r-56r.
46. Polson RJ., *et al*. "Treatment of Rheumatoid Arthritis with Desferrioxamine". *QJM: An International Journal of Medicine* 61.236 (1986): 1153-1158.
47. Puig S., *et al*. "Coordinated Remodeling of Cellular Metabolism During Iron Deficiency through Targeted mRNA Degradation". *Cell* 120.1 (2005): 99-110.
48. Qian Z M and PL Tang. "Mechanisms of Iron Uptake by Mammalian Cells". *Biochimica et Biophysica Acta* 1269.3 (1995): 205-214.
49. Radulescu S., *et al*. "Luminal Iron Levels Govern Intestinal Tumorigenesis after Apc Loss *in Vivo*". *Cell Reports* 2.2 (2012): 270-282.
50. Raggi F., *et al*. "Regulation of Human Macrophage M1-M2 Polarization Balance by Hypoxia and the Triggering Receptor Expressed on Myeloid Cells-1". *Frontiers in Immunology* 8 (2017): 1097.
51. Ray PD., *et al*. "Reactive Oxygen Species (ROS) Homeostasis and Redox Regulation in Cellular Signaling". *Cell Signal* 24.5 (2012): 981-990.

52. Recalcati S., *et al*. "Iron Levels in Polarized Macrophages: Regulation of Immunity and Autoimmunity". *Autoimmunity Reviews* 11.12 (2012): 883-889.
53. Reniere ML., *et al*. "The IsdG-family of Haem Oxygenases Degrades Haem to a Novel Chromophore". *Molecular Microbiology* 75.6 (2010): 1529-1538.
54. Sakata M., *et al*. "Iron-Dependent Oxidative Stress as a Pathogenesis for Preterm Birth". *Obstetrical & Gynecological Survey* 63.10 (2008): 651-660.
55. Sanchez M., *et al*. "Iron Regulatory Protein-1 and -2: Transcriptome-Wide Definition of Binding mRNAs and Shaping of the Cellular Proteome by Iron Regulatory Proteins". *Blood* 118.22 (2011): e168-179.
56. Searle S and JM Blackwell. "Evidence for a Functional Repeat Polymorphism in the Promoter of the Human NRAMP1 Gene that Correlates with Autoimmune Versus Infectious Disease Susceptibility". *Journal of Medical Genetics* 36.4 (1999): 295-299.
57. Stober CB., *et al*. "Slc11a1, Formerly Nramp1, is Expressed in Dendritic Cells and Influences Major Histocompatibility Complex Class II Expression and Antigen-Presenting Cell Function". *Infection and Immunity* 75.10 (2007): 5059-5067.
58. Tanno T., *et al*. "Expression of Growth Differentiation Factor 15 is Not Elevated in Individuals with Iron Deficiency Secondary to Volunteer Blood Donation". *Transfusion* 50.7 (2010): 1532-1535.
59. Tanno T., *et al*. "High Levels of GDF15 in Thalassemia Suppress Expression of the Iron Regulatory Protein Hepcidin". *Nature Medicine* 13.9 (2007): 1096-1101.
60. Tanno T and JL Miller. "[GDF15 Expression and Iron Overload in Ineffective Erythropoiesis]". *Rinsho Ketsueki* 52.6 (2011): 387-398.
61. Terman A and T Kurz. "Lysosomal Iron, Iron Chelation, and Cell Death". *Antioxidants & Redox Signaling* 18.8 (2013): 888-898.
62. Thompson JW., *et al*. "Structural and Molecular Characterization of Iron-Sensing Hemerythrin-Like Domain within F-box and Leucine-Rich Repeat Protein 5 (FBXL5)". *The Journal of Biological Chemistry* 287.10 (2012): 7357-7365.
63. Torti SV and FM Torti. "Iron and Cancer: More Ore to be mined". *Nature Reviews Cancer* 13.5 (2013): 342-355.
64. Vecchi C., *et al*. "ER Stress Controls Iron Metabolism through Induction of Hepcidin". *Science* 325.5942 (2009): 877-880.
65. Wrighting DM and NC Andrews. "Interleukin-6 Induces Hepcidin Expression through STAT3". *Blood* 108.9 (2006): 3204-3209.
66. Zhang Y., *et al*. "NGAL and NGALR Overexpression in Human Hepatocellular Carcinoma toward a Molecular Prognostic Classification". *Cancer Epidemiology* 36.5 (2012): 294-299.