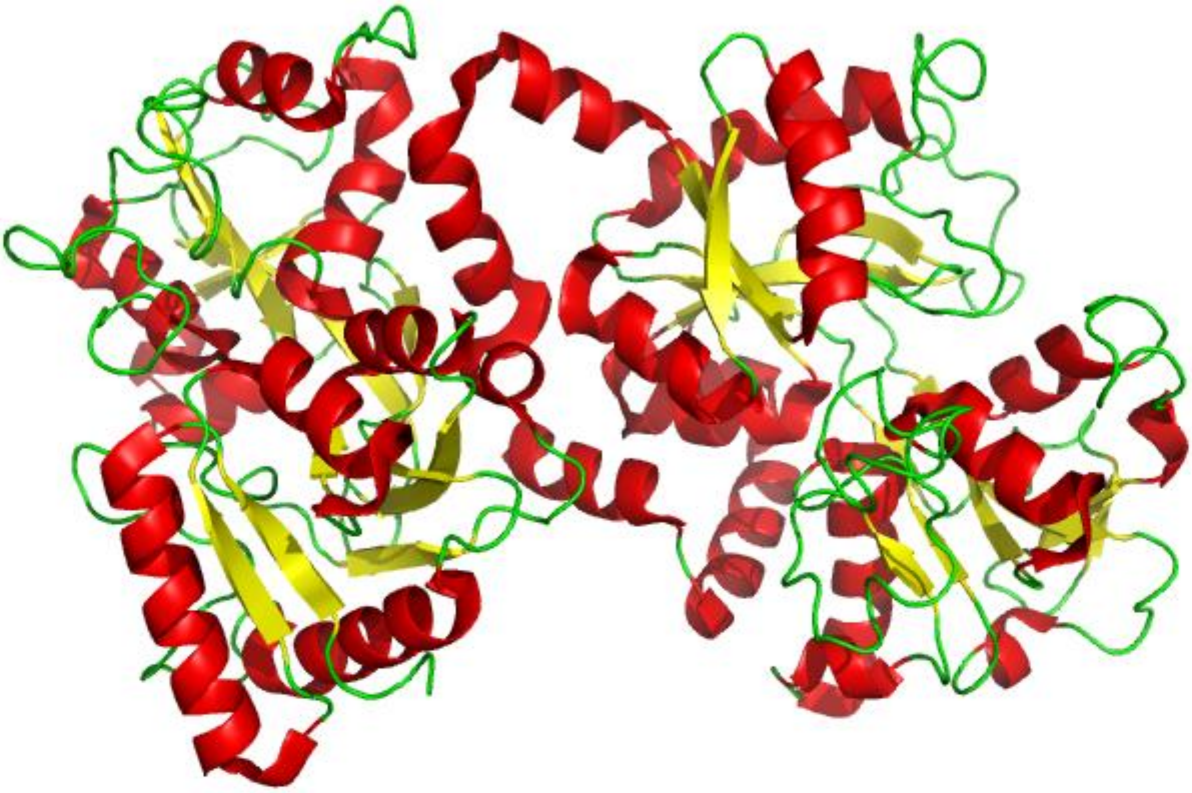

The Role of Iron Proteins in Human Biology

Mentored and Supervised by:

Chatzigeorgiou Louiza, BSc Chemistry, University of Patras

Research & Writing by CLC's students:

Athina Christoforou / Athina Drandaki /

Maida Kourounlian / Malvina-Christina Nikolaidi

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Introduction

The critical role of iron in health and disease has been recognized since antiquity, with early medical applications documented among the Egyptians, Hindus, Greeks, and Romans. In the 17th century, iron was employed in the treatment of chlorosis, a condition resulting from iron deficiency. However, its essential function was conclusively established in 1932 through compelling evidence demonstrating the necessity of inorganic iron for haemoglobin synthesis.

Iron is indispensable for all living organisms due to its involvement in key biological processes, including oxygen transport, electron transfer, redox reactions, hydroxylation, and nucleotide biosynthesis, facilitated by iron-containing proteins. A comprehensive understanding of these proteins' roles within the respiratory system is of paramount importance, as their dysfunction can result in severe conditions such as anaemia, cardiovascular disease, and respiratory disorders. Furthermore, ongoing research into iron-containing proteins is pivotal for advancing therapeutic strategies and diagnostic techniques for these diseases.

1. The Role of Iron Proteins

Iron is a critical micronutrient that supports a wide range of biological functions in the human body. One of its most vital roles is in the form of iron proteins—specialized molecules that contain iron and are essential to processes such as oxygen transport, energy production, and cellular respiration. The structural and functional versatility of iron makes it suitable for integration into many protein systems, allowing the body to regulate oxygen, manage electron flow, and store iron safely. Understanding iron proteins provides insight into how our bodies harness and control this powerful yet potentially harmful element for life-sustaining functions.

1.1 What Are Iron Proteins?

Iron proteins are biological molecules that contain iron atoms as an integral part of their structure. These proteins are essential for a wide range of physiological processes, including oxygen transport, electron transfer, and iron storage. The iron atoms within these proteins can switch between oxidation states, enabling them to participate in redox reactions vital to metabolism and respiration.

Some of the most well-known iron proteins include those that bind oxygen, like hemoglobin and myoglobin, as well as those involved in cellular energy production, such as cytochromes in the mitochondria. Other iron proteins help with iron storage and transport, including ferritin and transferrin, which protect the body from the toxic effects of free iron. These proteins work together to ensure iron is available where it is needed, while keeping it safely controlled within the body.

1.2 The Role of Iron Proteins in the Body

Iron proteins serve multiple essential roles in the human body by facilitating key biochemical and physiological processes. One of their most fundamental functions is in oxygen handling. Iron proteins are central to both the transport and the cellular utilization of oxygen. The iron atom in these proteins can bind oxygen reversibly, allowing them to pick up oxygen in the lungs and release it where it is needed in tissues. This dynamic function supports both physical activity and basic cellular metabolism.

Beyond oxygen transport, iron proteins are involved in electron transfer reactions within cells. Iron can switch between Fe^{2+} and Fe^{3+} oxidation states, making it ideal for shuttling electrons in the mitochondrial electron transport chain, a process that generates the majority of the body's ATP. Iron-sulfur proteins and cytochromes are examples of iron-containing proteins that participate in this vital function.

Iron proteins are also crucial for iron storage and regulation. Ferritin stores excess iron safely within cells to prevent damage from free radicals generated by free iron. Transferrin circulates in the bloodstream, binding iron tightly and delivering it to cells through specific receptor-mediated pathways. These mechanisms maintain iron homeostasis and protect the body from both deficiency and toxicity.

Furthermore, iron proteins contribute to immune defense and DNA synthesis. They are involved in the production of reactive oxygen species used by immune cells to attack pathogens, and iron-dependent enzymes help in the synthesis of nucleotides. In short, iron proteins are essential to oxygen management, energy production, metabolism, immune function, and the regulation of iron itself, underscoring their critical role in human health.

1.3 Structure of Iron Proteins

Iron proteins are complex molecules built from both a protein component and one or more iron-containing groups. The structure of these proteins allows them to carry out a wide range of biological functions, primarily through their ability to interact with oxygen, electrons, and other small molecules. The iron atom itself is typically found in two oxidation states—ferrous (Fe^{2+}) and ferric (Fe^{3+})—which allows it to participate in redox reactions essential for life.

Many iron proteins contain a prosthetic group known as a heme, which is an iron atom held at the center of a porphyrin ring. The porphyrin structure is made up of four pyrrole subunits arranged in a ring, with nitrogen atoms pointing inward to coordinate with the iron. This stable arrangement allows iron to bind and release small molecules like oxygen, carbon monoxide, and nitric oxide. Other iron proteins, especially those involved in electron transport, may contain iron-sulfur clusters rather than heme. These clusters are composed of iron atoms bonded to inorganic sulfur atoms and stabilized by cysteine residues from the protein. The iron-sulfur clusters can also shift between oxidation states, making them crucial in transferring electrons during metabolic processes.

Some iron proteins like ferritin do not use a ring structure to protect the iron. Instead, ferritin stores iron in a mineral-like core inside a spherical protein shell. This protects cells from the toxic effects of free iron while allowing for the controlled release of iron when needed. Transferrin, another iron-binding protein, circulates in the blood and binds iron tightly for safe transport, using specific protein structures to coordinate iron with oxygen and nitrogen atoms from amino acid side chains.

Overall, the structural complexity of iron proteins makes them highly adaptable for various functions, especially in processes requiring electron transfer, oxygen binding, or iron storage. Their three-dimensional structures have evolved to optimize iron's chemical properties and prevent damage from free iron, which can generate harmful reactive oxygen species.(1–3)

2. Structure and Function of Heme

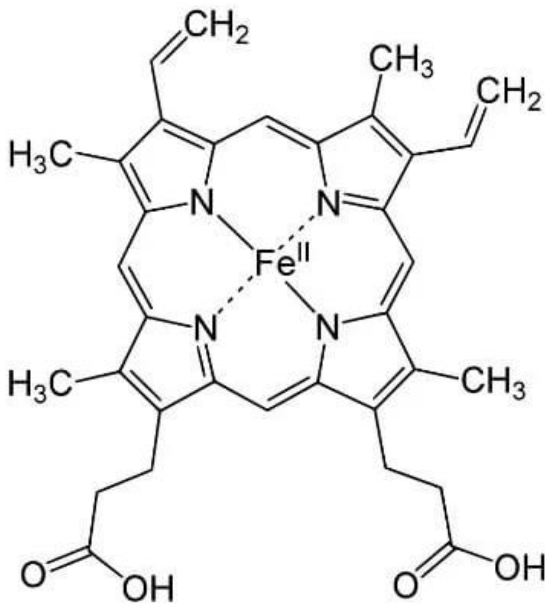
Heme is a vital organic molecule that plays a central role in many biological processes, particularly those involving oxygen transport and redox reactions. It functions as a prosthetic group, meaning it is a non-protein component that is tightly bound to certain proteins to enable their activity. Heme is especially important in proteins such as hemoglobin, myoglobin, cytochromes, and various enzymes. These proteins are collectively known as hemoproteins. What makes heme functionally powerful is its structure, which allows it to interact with oxygen and other small molecules.

At the core of the heme molecule lies a porphyrin ring, a large, planar, and heterocyclic structure composed of four connected pyrrole subunits. Each pyrrole is a five-membered ring containing four carbon atoms and one nitrogen atom. The four nitrogen atoms from the pyrrole rings are arranged in such a way that they all point inward, coordinating a single iron ion (Fe^{2+}) at the center of the ring. This iron ion is the active site of the heme molecule. It is capable of forming six coordination bonds: four with the nitrogen atoms of the porphyrin ring, one with a nearby amino acid residue from the protein (often a histidine), and one that is available for binding to molecules such as oxygen, carbon monoxide, or nitric oxide.

The iron ion in heme can switch between two oxidation states, ferrous (Fe^{2+}) and ferric (Fe^{3+}). In the Fe^{2+} state, the heme can reversibly bind oxygen, which is essential for the functioning of oxygen-transport proteins like hemoglobin and oxygen-storage proteins like myoglobin. When oxygen binds to the Fe^{2+} ion, it forms a coordination bond in which the oxygen molecule donates a pair of electrons. This interaction can slightly shift the oxidation state of iron and cause conformational changes in the protein that affect its activity and interactions.

Heme is not only limited to oxygen binding. In cytochromes, another family of heme-containing proteins, the primary function of the heme is to facilitate electron transfer. In this context, the iron atom cycles between Fe^{2+} and Fe^{3+} as it accepts and donates electrons during redox reactions. This is crucial in cellular respiration and energy production, particularly within the electron transport chain in mitochondria. Some cytochromes also participate in detoxification, such as the cytochrome P450 enzymes, which metabolize drugs and harmful chemicals in the liver.

While heme is essential to life, it must be tightly regulated. Free heme, outside of proteins, can be highly reactive and potentially toxic, as it can promote the formation of reactive oxygen species (ROS) that damage cells. For this reason, the body has evolved careful mechanisms to synthesize, transport, utilize, and degrade heme safely. Heme synthesis is a multistep process that occurs partly in the mitochondria and partly in the cytoplasm of cells, especially in the liver and bone marrow. When heme is broken down, it produces biliverdin, bilirubin, and free iron, which are processed and excreted or recycled.(4,5)



heme *b*

3. The importance of Oxygen in the Body

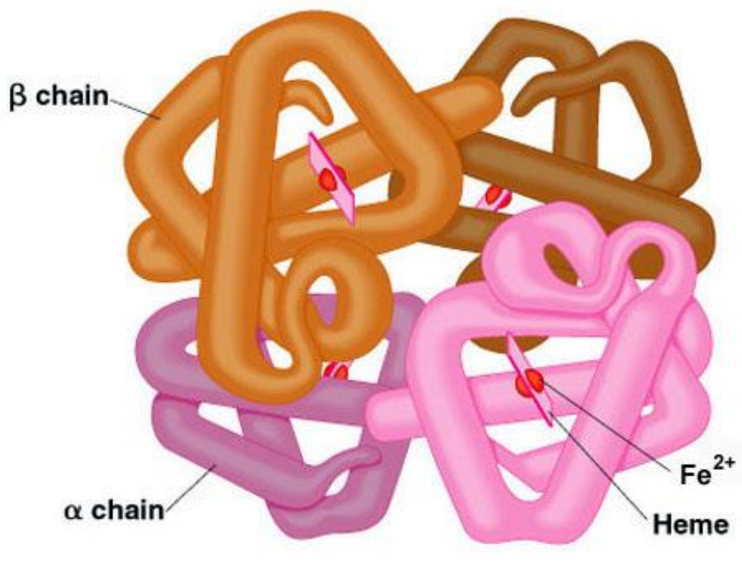
Oxygen is essential for life because it plays a critical role in the production of energy in cells. Every cell in the human body needs a continuous supply of oxygen to survive and function properly. The primary way the body uses oxygen is through a process called aerobic respiration, which occurs in the mitochondria. In this process, oxygen helps break down glucose and other nutrients to produce ATP, the main energy currency of the cell. Without oxygen, cells would have to rely on anaerobic respiration, which produces far less energy and leads to the buildup of lactic acid, causing fatigue and muscle pain.

In addition to energy production, oxygen is also crucial for maintaining healthy tissues. It supports the immune system by enabling white blood cells to kill bacteria more effectively. It helps with tissue repair, wound healing, and brain function. The brain is especially sensitive to changes in oxygen levels. Even a short period of oxygen deprivation can cause dizziness, confusion, unconsciousness, and eventually permanent brain damage if not corrected. Oxygen is also vital for maintaining proper circulation. It causes blood vessels to dilate, improving blood flow and delivering more nutrients to organs.

Furthermore, oxygen supports the function of key enzymes involved in metabolism and detoxification. It helps the liver process toxins and convert them into forms that can be excreted. The body also uses oxygen to form signalling molecules like nitric oxide, which regulates blood pressure and immune responses. Oxygen is not just needed for energy; it is a building block of many chemical reactions that keep the body alive and balanced. Without enough oxygen, all systems of the body begin to fail, and prolonged oxygen deprivation leads to organ failure and death. This is why the transport, delivery, and utilization of oxygen are so tightly regulated by iron proteins and why maintaining healthy oxygen levels is so important for life.(6–8)

4. Hemoglobin: Structure and Function

Hemoglobin is a protein found in red blood cells whose primary function is to transport oxygen from the lungs to the tissues. It also helps in transporting carbon dioxide, a byproduct of metabolism, back to the lungs for exhalation. Structurally, hemoglobin is composed of four polypeptide chains: two alpha and two beta chains. Each chain is folded into a globular structure with multiple alpha-helices and contains a heme group. Therefore, one hemoglobin molecule has four heme groups and can bind up to four oxygen molecules. When oxygen binds to one heme group, hemoglobin undergoes a conformational change that increases its affinity for oxygen at the remaining sites, a phenomenon known as cooperative binding. Likewise, the release of oxygen also involves structural changes. Dysfunction in hemoglobin or a deficiency in iron can lead to anemia, fatigue, pregnancy complications, and cardiovascular issues. Hemoglobin is a conjugated protein because it includes both protein (globin) and non-protein (heme) components.(9)



5. Myoglobin: Structure and Function

Like Hemoglobin, Myoglobin is a globular protein that contains a heme group. It is mainly found in myocyte cells of the heart and skeletal muscle. Furthermore, some studies have shown it is also found in tumors possibly aiding oxygenation and neutralization of free radicals. Myoglobin consists of 154 amino acids folded into 8 α helices, a heme prosthetic containing a $Fe2+$, a proximal histidine bonded to the fifth coordination site, and a distal histidine which allows for hydrogen bonding to regulate the affinity of ligands for Myoglobin.

Upon the initial discovery of Myoglobin in 1921, investigative work showed that oxygen could reversibly bind to the 6th coordination site of myoglobin, creating an oxygen dissociation curve much steeper than hemoglobin. This meant that Myoglobin has a higher affinity for oxygen and can bind to oxygen more readily at a lower partial pressure. (Partial pressure is a measure of the concentration of a particular gas. The main role of myoglobin, which was first identified, is oxygen storage. Studies on skeletal muscle showed that myoglobin releases oxygen upon contraction of the muscle, thus maintaining high oxygen levels for aerobic respiration. This mechanism prevents anaerobic respiration from occurring, which causes a buildup of lactic acid. Lactic acid can cause muscle cell damage if it is not removed readily. Myoglobin also plays a crucial role in marine mammals, as it releases oxygen during deep dives where there is no ventilation occurring.

In 1959, Wittenberg, having found new evidence, suggested that Myoglobin increased the diffusion of oxygen into cells. His study showed that cells containing myoglobin had higher rates diffusion of oxygen into mitochondria. Subsequent studies showed that the high affinity of myoglobin for Oxygen was able to compete with the ability of oxygen to dissolve in solution. Myoglobin binds to $O2$ in the cell membrane, helping maintain a steep concentration gradient. It then offloads oxygen near the mitochondria, where the oxygen levels are significantly lower. The role of myoglobin is quite controversial because some studies showed

that even though Myoglobin increased oxygen supply to mitochondria, it didn't increase the rate of aerobic respiration/ ATP production. Overall, it is agreed that this role of myoglobin plays a more crucial role in mitochondrial function under hypoxic conditions (eg, during exercise) than it does under normal conditions.

Furthermore, Myoglobin regulates nitric oxide concentrations by acting both as a scavenger and a producer depending on the oxygen concentration. Under high oxygen concentration, Myoglobin rapidly binds to NO, as high concentrations can cause permanent mitochondrial damage. Under low oxygen concentrations, Myoglobin reduces nitrites into nitric oxide. The NO produced can regulate various cellular processes, like mitochondrial respiration. Furthermore, NO is a vasodilator that relaxes smooth muscle in the artery wall, leading to greater blood flow and increased oxygen delivery to tissues.

In conclusion myoglobin has various roles most important being oxygen storage, facilitated diffusion and regulation of nitric oxide levels in cells. Through these roles Myoglobin supports various cellular functions, especially mitochondrial respiration.(10–12)

6. Other Iron Proteins

6.1 Ferritin

Ferritin is the main iron storage protein in both prokaryotic and eukaryotic cells. It is primarily found in the liver, spleen, and bone marrow. Ferritin stores iron in a soluble, non-toxic form and releases it when needed. Structurally, ferritin is composed of 24 protein subunits that form a spherical nanocage capable of holding up to 4500 iron atoms. If iron is removed, it is called apoferritin. Ferritin is mostly cytosolic, but small amounts circulate in the serum where it functions as an iron carrier. Serum ferritin levels are used clinically to assess total body iron stores and diagnose iron-deficiency anemia. Ferritin is vital for ensuring that iron is readily available for oxygen transport and cellular respiration while preventing iron toxicity.(13,14)

6.2 Transferrin

Transferrin is a glycoprotein produced in the liver that serves as the primary iron transporter in the bloodstream. It binds Fe^{3+} ions released by intestinal cells through ferroportin. This process is aided by ferroxidases such as hephaestin. Transferrin delivers iron to erythroblasts in the bone marrow and other cells through receptor-mediated endocytosis. Cells express transferrin receptors that bind iron-loaded transferrin. Once inside the cell, iron is released for hemoglobin synthesis, respiration, and metabolic functions. Transferrin levels are used to evaluate iron status. High transferrin levels indicate iron deficiency, while low levels may suggest chronic inflammation, liver disease, or iron overload. Transferrin plays an essential role in maintaining iron homeostasis, oxygen transport, DNA synthesis, and energy metabolism.(15)

6.3 Cytochromes

Cytochromes are iron-containing proteins that play a crucial role in cellular respiration. Located in the mitochondrial membrane, they serve as electron carriers in the electron transport chain. Each cytochrome contains a heme group, where the iron ion undergoes reversible oxidation and reduction. This redox ability enables efficient electron transfer. Cytochrome c is one of the most well-known members of this group and helps reduce oxygen to water at the end of the electron transport chain. This electron flow enables the pumping of protons across the mitochondrial membrane, creating a proton gradient that drives ATP synthesis. Cytochromes are also involved in detoxification, particularly through cytochrome P450 enzymes found in the liver, which metabolize toxic substances. Additionally, cytochrome c plays a role in apoptosis, or programmed cell death. When released into the cytoplasm, it activates apoptotic pathways that help eliminate damaged cells. These functions make cytochromes vital for energy production, metabolic detoxification, and cellular regulation.(16,17)

7. Conclusion

Iron proteins are truly fundamental to life, serving as the backbone for a myriad of essential biological functions within the human body. Their remarkable ability to bind, transport, and release iron and oxygen with extraordinary precision is central to sustaining life's most critical processes. From oxygen delivery by hemoglobin in our blood to oxygen storage by myoglobin in muscle tissues, these proteins ensure that cells receive the vital elements needed for survival and optimal function. Additionally, iron proteins such as ferritin and transferrin play crucial roles in regulating iron storage and transport, preventing both deficiency and toxicity, thereby maintaining iron homeostasis.

Moreover, iron-containing cytochromes are indispensable for cellular respiration and energy production, facilitating electron transport chains that power the generation of ATP, the energy currency of the cell. The multifaceted roles of iron proteins extend to protecting cells from oxidative stress, supporting immune responses, and regulating metabolic pathways. The structural complexity and functional versatility of these proteins reflect a finely tuned biological system that balances the delicate chemistry of iron with the physiological demands of the body.

Through in-depth study and analysis of iron proteins, we gain profound insights into how the body breathes, moves, and defends itself at the molecular level. Understanding these molecules not only deepens our appreciation of biological elegance but also advances medical science by improving our ability to diagnose, treat, and prevent diseases linked to iron metabolism, such as anemia, hemochromatosis, and neurodegenerative disorders.

This project has underscored how even a small, seemingly simple atom like iron, when intricately controlled by sophisticated protein machinery, can sustain the most vital and complex processes of life. As scientific research continues to unravel the mysteries of iron proteins, we move closer to unlocking new therapeutic avenues and enhancing human health on a molecular scale. The study of iron proteins thus remains a cornerstone in both biology and medicine, highlighting the extraordinary interplay between chemistry and life.

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