

## Iron-Containing Heme Homeostasis: Critically Impacts on Pulmonary Physiological and Pathological Processes and Balance between Health and Disease

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Proteins, the building blocks of life are the major source of nutrients. Digested proteins release amino acids to the body for cellular energy generation. In addition to amino acids, proteins also provide metal, particularly iron that is most abundant in the human body. One adult human body requires approximately 3 - 4 grams of iron. Heme and non-heme iron are two forms found in dietary iron. Heme iron is mainly found in meat (hemoglobin and myoglobin), poultry and fish, is well absorbed whereas plants account for the majority of non-heme iron with less well absorption. Functional iron in the form of heme in human body contains more than 95%. Several previous studies demonstrated that heme is efficiently absorbed by the enterocytes in the duodenum of the small intestine. Heme directly affects several human physiological and pathological processes.

Transportation of efficient oxygen red blood cells (RBCs) depends on the hemoglobin presentation. Hemoglobin contains four heme groups that have capability of oxygen binding via their central iron atom. Around 20 - 25 mg of iron are daily required to maintain adequate erythropoiesis. Deoxyribonucleic acid synthesis and repair, transcription, and energy production in the mitochondria are other fundamental metabolic processes (provided mainly by reticuloendothelial macrophages that recycle iron from senescent RBCs) that require iron in addition to hemoglobin synthesis. Potential of iron mainly fluctuates between divalent ferrous (Fe<sup>2+</sup>) and trivalent ferric (Fe<sup>3+</sup>) iron. This transition metal makes free iron very reactive and much toxic. Exposure to these reactive oxygen species (ROS) can damage nucleic acids, proteins, and lipids contributing to cell and tissue damage. In response to both ex-

posures to circulating iron and inhaled iron-containing particles, the respiratory tract, including lung cells can secrete antioxidant molecules, such as ascorbic acid (vitamin C), mucin, and reduced glutathione. Additionally, human airway can secrete lactoferrin and transferrin, and glycoproteins that have capability of binding iron and maintaining a chemically inert form. Iron bound to lactoferrin and transferrin can be taken up by epithelial cells via lactoferrin receptor (LfR) and transferrin receptor 1, respectively. Excessive pulmonary iron can override these pulmonary protective mechanisms contributing to pulmonary oxidative stress that is indicated by increasing nitrotyrosine levels protein carbonyl modifications.

In conclusion, several acute and chronic pulmonary diseases are related to disrupted pulmonary iron homeostasis. When considering human nutrition and health, heme should be a significant factor. Pulmonary adaptation is needed in the environmental and behavioral stress conditions, such as high-altitude exposure, exercise, etc.

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