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Review

Targeting iron metabolism in cancer therapy

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Abstract

Iron is a critical component of many cellular functions including DNA replication and repair, and it is essential for cell vitality. As an essential element, iron is critical for maintaining human health. However, excess iron can be highly toxic, resulting in oxidative DNA damage. Many studies have observed significant associations between iron and cancer, and the association appears to be more than just coincidental. The chief characteristic of cancers, hyper-proliferation, makes them even more dependent on iron than normal cells. Cancer therapeutics are becoming as diverse as the disease itself. Targeting iron metabolism in cancer cells is an emerging, formidable field of therapeutics. It is a strategy that is highly diverse with regard to specific targets and the various ways to reach them. This review will discuss the importance of iron metabolism in cancer and highlight the ways in which it is being explored as the medicine of tomorrow.

Key words: Iron metabolism, Cancer, Therapy, Chelation, Ferroptosis

Introduction

Iron is essential for cell vitality. It is found in proteins that perform a variety of functions including biomolecule synthesis, oxygen transport and homeostasis, and respiration [1]. Iron is a critical component of many proteins involved in nucleic acid metabolism and repair, as well as cell cycle progression [2]. Because iron is an integral component of anatomy and physiology and its bioavailability is scarce, iron stores are tightly regulated within the body in order to ensure conservation and mitigate toxicity [3].

The oxidation-reduction (redox) ability of iron is at the heart of its importance as a handler of oxygen and electrons, but it is in this same role that it harbors its dangers [4]. Iron is able to easily interconvert between the ferrous state (Iron [II]) and ferric state (Iron [III]) and may exist in a wider range of oxidation states [4]. In cellular metabolism, iron largely draws its negative effects from the reduction of oxygen. Due to oxygen's atomic nature, its reduction must proceed in a stepwise fashion of individual electron additions and reactive intermediates [5]. During this process, the Fenton reaction can occur between ferrous iron and hydrogen peroxide to generate the highly reactive hydroxyl radical [5]. Oxygen reduction intermediates are known as reactive oxygen species (ROS) and have been linked to lipid, protein, nucleic acid, and various signaling pathway damage [6]. As such, iron has become a key target of interest in the progression and treatment of diseases including cancer. This review will discuss aspects of the therapeutic potential of iron metabolism for cancer. First, we will present a brief overview of the role of iron in the body and discuss aspects of the therapeutic potential of iron for the treatment of cancer.

Cellular Metabolism of Iron

Iron Absorption and Recycling:

In a standard diet, inorganic iron (Fe^{3+}) from plant origin accounts for 80–90%, whereas the remaining 10% is heme iron (Fe^{2+}) associated with meat intake [7]. Ingested inorganic iron must first be reduced to its ferrous form for solubility and absorption by enterocytes. Reduction of iron is achieved through ferrireductases, specifically duodenal cytochrome B (DcytB), and potentially in