

## Preface: Iron and Cancer

Iron is an essential trace nutrient for nearly all living organisms. The element readily donates or accepts electrons and is the key working component of many enzymes involved in oxidation and re-reduction reactions and of proteins that transport or store oxygen. Rapidly proliferating cancer cells require increased biosynthetic activity and therefore are highly dependent on their iron supply. In turn, the presence of cancer cells in the body elicits inflammatory responses which affect iron homeostasis, partly through the induction of the iron-regulatory hepatic hormone hepcidin. Increased hepcidin concentrations cause the endocytosis of the cellular iron exporter ferroportin, leading to iron sequestration in macrophages, decreased iron absorption in the proximal duodenum, and the development of a characteristic anemia of cancer caused in part by restriction of the iron availability to developing erythrocytes in the marrow. The two-way interaction between cancers and systemic iron homeostasis is the subject of this volume, which was inspired by recent advances in this area.

Iron can be carcinogenic: in excessive amounts, iron is toxic to cells, probably by catalyzing the production of reactive oxygen species. Iron-induced tissue injury in the liver can initiate carcinogenesis, and hepatocarcinoma is a common complication of cirrhosis in the setting of iron overload disorders, especially hereditary hemochromatosis (Article 1).

Cancer cells evolve clonally, favoring molecular adaptations that help make sufficient iron available for their rapid proliferation. In turn, iron-related molecular adaptations impact cancer prognosis and are potential targets for therapy. In some cases, the heightened dependence of cancer cells on iron can

be therapeutically targeted through iron chelators (Article 2). In breast cancer, the suppression of the cellular iron exporter ferroportin (Article 3) is a strong adverse prognostic marker and another potential therapeutic target. In myeloma, the over-expression on cancer cells of the transferrin receptor (TfR1) through which tumors take up transferrin-bound iron allows therapeutic targeting by antibodies (Article 4).

Although human tumors evolve from their host's cells, they often display neoantigens or secrete factors that elicit an inflammatory response, contributing to the clinically important anemias associated with cancer (Articles 4–6). The pathogenesis of these anemias is mediated by inflammatory cytokines, in part through a direct suppressive effect on erythropoiesis and in part through the stimulation of the iron hormone hepcidin and the restriction of iron supply to erythropoiesis. The cytokine-mediated mechanisms of anemia of cancer are particularly prominent and best understood in myeloma (Article 4) and Hodgkin lymphoma (Article 5). Anemia can be a major cause of cancer-associated morbidity and an appropriate target for palliative therapy, but concerns about the side effects of the available treatments have led to reconsideration of the indications and relative roles of erythropoiesis-stimulating agents, iron, and transfusions in cancer therapy (Article 6).

Guest Editor:

Tomas Ganz, PhD

Departments of Medicine and Pathology  
David Geffen School of Medicine, UCLA,  
Los Angeles, CA

