The Ferrobiology of Neoplasia

(Part II)

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Introduction

This second group of papers on the ferrobiology of neo-plastic cells begins with a wide-ranging review of the biologic significance of iron by Dr. Sussman. At various points in his paper he discusses the means of iron transport and uptake, the multiple roles of iron in the maintenance of normal cell metabolism, the role of iron as a factor in oncogenesis via free radical production, the critical importance of exogenously acquired iron to the continued proliferation of neoplastic cells, the reduction of iron demand resulting from the induction of differentiation in neoplastic cells, and the fact that elevated serum ferritin levels can serve as a marker for some tumors. The discussion of ferritin by Dr. Sussman creates a bridge to the next paper by Drs. Bomford and Munro. Starting with the well established idea that free iron is toxic and that increased ferritin synthesis is the appropriate response to excess free iron, Drs. Bomford and Munro proceed to review fascinating recent advances in our understanding of the molecular control of transcription and translation of the ferritin and transferrin receptor genes. In discussing these advances, Drs. Bomford and Munro remind us that while the heavy and light chains of ferritin may be similarly affected at the translational level by altered intracellular iron levels, their transcriptional control is quite distinct. They also remind us that tissues may vary considerably in their relative proportions of heavy and light chains and that the functional implications of this variation are not yet clear. It seems very likely that if we are to understand the ways in which neoplastic cells store and utilize iron, and if we wish to disturb those processes for therapeutic purposes, then we must achieve a better understanding of the biological roles of the ferritins. Dr. Seligman and colleagues discuss three points of immediate relevance to the general theme of iron deprivation therapy of cancer. The first is that some tumors, like hepatocytes and certain other normal cells, produce and secrete transferrin; this presumably allows the tumors to scavenge whatever free iron is available and then take it up via the transferrin receptor. This may create a state of partial competitive resistance to treatment with reagents like gallium-transferrin. The second point, and one that was also raised by Dr. Moroz in the first part of this symposium and Dr. Sussman in this part, is that some normal and neoplastic cells exhibit a capacity for transferrin-independent iron acquisition. This could mean a significant degree of resistance to the effects of anti-transferrin receptor antibodies (ATRA's). A third important point is that novel reagent combinations involving iron deprivation can and should be evaluated. In particular, Seligman et al. present (and refer to) preliminary data indicating that a combination of alpha interferon plus deferoxamine and transferrin-gallium plus deferoxamine are of interest for future investigations.

The last paper in this group, by Kemp et al, focuses on the development of knowledge concerning the effects of anti-transferrin receptor antibodies on the growth of neoplastic cells in

vitro and in vivo. A cardinal point developing in this area is that monoclonal IgG anti-transferrin receptor antibodies, which were initially ignored as potential therapeutic reagents, are now beginning to look very promising. These antibodies appear to be good at depriving tumor cells of iron when they are employed in combination with either an iron chelator such as deferoxamine or in combination with another IgG anti-transferrin receptor antibody. While there are several questions remaining about how ATRAs can best be employed as anti-tumor reagents, the prospects are encouraging and future work will no doubt lead to improved approaches. Overall, it would seem that the continued study of the ferrobiolgy of neoplastic cells holds great promise.

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