Intracellular Reduction/Activation of a Disulfide Switch in Thiosemicarbazone Iron Chelators

Invention

Novel molecular design extends the reach of iron chelators to applications in cancer chemotherapy. This invention not only recognizes the higher demand of iron that characterizes cancer cells, but also takes into account other physiological differences between malignant cells and the surrounding tissue. Specifically, taking advantage of the reducing environment found in the cytoplasm of cancer cells in order to apply redox-directed chelators.

Background

Basic and clinical research has improved significantly the prognosis and number of treatment options for cancer patients in the past decades. Broad-spectrum cytotoxins and their unwanted side effects, however, continue to be part of cancer chemotherapy in the clinical practice. Current research efforts are responding to the pressing need for more targeted, less toxic treatment options. Such approaches are necessarily based on new or previously overlooked information on the genetic and/or metabolic makeup of cancer cells, particularly on peculiarities that differentiate them from normal cells within the same tissue. We pursue the molecular design of strategies to study and exploit an aspect of cancer metabolism that is not targeted by current clinical chemotherapy, namely the altered iron metabolism of malignant cells.

In order to sustain their rapid proliferation rates, cancer cells require higher iron content when compared to normal cells. As such, the use of small-molecule scavengers (chelators) of iron ions could deprive cancer cells of this essential supply, thereby slowing or halting cancer growth. Indeed, chelation therapy has been employed clinically for decades in cases of iron overload conditions associated with genetic disorders, such as thalassemia and hemochromatosis. The key to the success of chelation therapy in cancer treatment, however, is the ability to target iron ions in malignant cells without affecting iron levels in the bloodstream and in normal tissue. Lacking such selectivity, currently available chelators were found to elicit adverse side effects when employed in the context of cancer research.
Applications

• Cancer chemotherapy

Advantages

• Recognizing the increased iron metabolism that characterizes cancer cells,
• Our research program launches a new study of molecular tools to manipulate intracellular iron levels with chelation strategies specifically designed around the physiological characteristics that distinguish malignant cells from the surrounding tissue.

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