INDUCTION OF DIFFERENTIAL STRESS RESISTANCE AND USES THEREOF

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application Ser. No. 60/908,636, filed Mar. 28, 2007, and U.S. Provisional Application Ser. No. 60/942,561, filed Jun. 7, 2007, the contents of which are incorporated herein by reference in their entirety.

FUNDING

The present invention was made, at least in part, with the financial support of NIH/NIA grants AG20642 and AG025135. The government has certain rights in the invention.

FIELD OF THE INVENTION

The present invention, in general, relates to methods for treating cancer. In particular, the present invention provides methods for enhancing the effectiveness of chemotherapy by inducing differential stress resistance in normal cells and cancer cells via short-term starvation, cell growth inhibitors, or reduced caloric or glucose intake.

BACKGROUND OF THE INVENTION

Until recently, the treatment of cancer has been largely focused on the development of therapeutic agents or techniques that kill cancer cells. For example, most chemotherapeutic drugs work by impairing mitosis (cell division), effectively targeting fast-dividing cells. As these drugs cause damage to cells they are termed cytotoxic. Some drugs work by causing cells to undergo apoptosis (so-called "cell suicide"). Unfortunately, scientists have yet to be able to locate specific features of malignant and immune cells that would make them uniquely targetable (barring some recent examples, such as the Philadelphia chromosome as targeted by imatinib). This means that other fast dividing cells such as those responsible for hair growth and for replacement of the intestinal epithelium (lining) are also affected.

Because chemotherapy affects cell division, both normal and cancerous cells are susceptible to the cytotoxic effects of chemotherapeutic agents. Success of conventional chemotherapeutic regiment is based on the principle that tumors with high growth fractions (such as acute myelogenous leukemia and the lymphomas, including Hodgkin's disease) are more sensitive to chemotherapy because a larger proportion of the targeted cells are undergoing cell division at any given time. This strategy often results in undesirable side-effects such as hair loss and normal tissue/organ damage. It also has severe limitations on the dosage of chemotherapeutic agents that can be administered to a patient, thus, limiting the effective range of chemotherapy.

SUMMARY OF THE INVENTION

The present invention provides a novel approach to cancer therapy by providing a method to differentially enhance the resistance of normal cells to chemotherapeutic agents, thereby, improving the effectiveness of chemotherapeutic agents in killing cancerous cells. By making normal cells more resistant to chemotherapeutic agents, a patient's tolerance for cytotoxicity is improved, which, in turn, also improves the effectiveness of chemotherapy.

More specifically, in one aspect, the invention features methods of inducing differential stress resistance in a subject with cancer. One method comprises starving the subject for 24-60 (e.g., 48) hours and administering to the subject a chemotherapy agent. The method may further comprise administering to the subject a cell growth inhibitor.

Another method of the invention comprises administering a cell growth inhibitor to the subject and administering to the subject a chemotherapy agent. For example, by using a cell growth inhibitor, the serum concentration of IGF-I in the subject may be reduced by 75-90%.

Another method of the invention comprises reducing the caloric intake or the glucose intake by the subject and administering to the subject a chemotherapy agent. For example, the caloric intake may be reduced by 10-100%, and the blood glucose concentration in the subject may be reduced by 20-50%.

In another aspect, the invention features methods of contacting a cancer cell with a chemotherapy agent and methods of increasing resistance of a non-cancer cell to a chemotherapy agent. One method comprises starving the cell for 24-60 (e.g., 48) hours and contacting the cell with a chemotherapy agent. The method may further comprise contacting the cell with a cell growth inhibitor.

Another method of the invention comprises contacting the cell with a cell growth inhibitor and contacting the cell with a chemotherapy agent.

Another method of the invention comprises cultivating the cell in a medium with reduced serum, IGF-I, or glucose concentration and contacting the cancer cell with a chemotherapy agent. For example, the serum concentration in the medium may be reduced by 10-90%, the IGF-I concentration in the medium may be reduced by 10-100%, and the glucose concentration in the medium may be reduced by 20-50%.

A chemotherapy agent may be a DNA alkylating agent, oxidant, or topoisomerase inhibitor. Examples of chemotherapy agents include, but are not limited to, methyl methanesulfonate, cyclophosphamide, etoposide, doxorubicin, and menadione. Examples of cancer include, but are not limited to, glioma, neuroblastoma, pheochromocytoma, and prostate cancer.

A cell growth inhibitor inhibits, e.g., IGF-I, IGF-IR, GH, Akt, Ras, Tor, or Erk. Examples of cell growth inhibitors include, but are not limited to, IGFBPs, IGF-R blocking antibodies, and small molecule inhibitors such as octreotide.

The above-mentioned and other features of this invention and the manner of obtaining and using them will become more apparent, and will be best understood, by reference to the following description, taken in conjunction with the accompanying drawings. These drawings depict only typical embodiments of the invention and do not therefore limit its scope.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1**. A) DSR of short-term starvation (STS) against acute H_2O_2 or menadione treatments. Survival of wild type (DBY746), sch9/aktΔ, RAS2^{val19}, sch9/aktΔras2Δ and sch9/aktΔRAS^{val19} after a 48-hour starvation and exposure to H_2O_2 (400 mM, 60 min) and to menadione (1 mM, 30 min). The cultures were diluted in K-phosphate buffer to an initial OD_{600} 1 for both treatments. Serial dilutions were spotted onto YPD plates and incubated at 30° C. for 2-3 days. This experiment was repeated at least 3 times with similar results. A representative experiment is shown. B, C) DSR against chronic CP and MMS treatments in mixed cultures. sch9/aktΔ and sch9/aktΔRAS2^{val19} were mixed and incubated for 2