Human Stem Cell Toxicology: Chapter 9

Metakaryotic cancer stem cells are constitutively resistant to x-rays and chemotherapeutic agents but sensitive to many common drugs.

Elena V. Gostjeva¹, Vera V. Koledova¹, Liyuan Bai¹, Kailin C. Duan¹, Meghan Nelson², Parul Agnihotri³, Deborah Moshinsky⁴, Li Ping Wu⁴, Lawrence Zukerberg⁵, Daniel C. Chung⁶, Susan Tsai⁷, Douglas Evans⁸, Aoy Tomita-Mitchell⁹, Michael Mitchell¹⁰, and William G. Thilly*¹

Abstract

After radio- and chemo-therapy human tumors display many dead eukaryotic cells with pyknotic nuclei. But amitotic metakaryotic cells with hollow, bell shaped nuclei appear unaffected as expected of treatment-resistant cancer stem cells. These same phenomena may be observed in vitro using any of many tumor- or metastasis-derived cell lines the immortality of which is conferred by the presence of amitotic, metakaryotic cancer stem cells. About 5% of human colonic adenocarcinoma-derived HT-29 cells in exponential growth are immortal metakaryotic stem cells that increase by symmetric amitoses and continuously create mortal mitotic eukaryotic cells by asymmetric amitoses. Two assays for agents/conditions cytocidal to metakaryotic stem cells have been devised: (a.) microscopic recognition of necrotic metakaryotic nuclei and (b.) survival of cells forming large immortal colonies visibly containing metakaryotic stem cells in vitro. X-rays and chemotherapeutic agents (alkylating agents, antimetabolites and mitocides) kill eukaryotic cells but not metakaryotic cells at doses commonly used in cancer therapy. In contradistinction, multiple classes of common drugs are preferentially cytocidal to metakaryotic stem cells including NSAIDS, bacteriocides and drugs used to treat diabetes or hypertension. Given lesion penetrance and treatments of sufficient duration, regimens using multiple metakaryocidal drugs offer means to treat and prevent cancers.