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Cancer Stem Cells

Implications for Development of More Effective Therapies

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SUMMARY

Despite advances in the development of cytotoxic chemotherapies, the fact remains that for most common malignancies, metastatic disease remains incurable. Recent work has suggested that most, if not all, malignancies are driven by a small subpopulation of cells that have stem cell characteristics. These “tumor stem cells” are thought to arise either from normal tissue stem cells or from early progenitor cells through dysregulation of self-renewal pathways. The partial differentiation of cancer stem cells may result in tumor heterogeneity. One of the characteristics of this heterogeneity may be reflected in the resistance of cancer stem cells to cytotoxic chemotherapy. Evidence is presented that current chemotherapeutic regimens selectively target more differentiated cells in tumors, while sparing the tumor stem cell component. This may account for relapse following tumor regression. The mechanisms contributing to the resistance of tumor stem cells to cytotoxic agents may involve increased efficiency of DNA replication and repair mechanisms in stem cells, changes in cell cycle parameters, and the overexpression of antiapoptotic and transporter proteins in these cell populations.

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The tumor stem cell model of carcinogenesis has fundamental implications for the development of new cancer therapeutic agents, as well as for the design of clinical trials utilizing these agents. Strategies aimed at the targeting of cancer stem cell populations may lead to more effective therapies for the treatment of advanced malignancies.

**Key Words:** Cytotoxic chemotherapy; dysregulation; tumor heterogeneity; tumor stem cells; tumor stem cell model.

1. **INTRODUCTION**

Despite numerous advances in the development of antineoplastic agents, the fact remains that for most common malignancies, advanced disease remains incurable. Cytotoxic chemotherapies are often able to induce regression of cancer in patients, relieving symptoms, and improving quality of life. However, for most common malignancies, the tumors ultimately recur and become resistant to these agents. Recent work has suggested that most, if not all, malignancies, may contain a small subpopulation of cells that have stem cell characteristics. These “tumor stem cells” may drive tumorigenesis, and may display resistance to agents in our current pharmacologic armamentarium. In this chapter, we review recent evidence suggesting that cancers may arise from normal stem cells or their immediate progenitors, producing tumor heterogeneity and are driven by a “cancer stem cell” population. We explore potential molecular mechanisms accounting for resistance of these cancer stem cells to cytotoxic chemotherapy. Finally, based on an understanding of the biology of basic stem cell processes, we propose new strategies for therapeutic development that specifically target the cancer stem cell population. Targeting of this critical cell population may result in more effective treatments for advanced cancers.

2. **TISSUE-SPECIFIC STEM CELLS AND THE ORIGIN OF CANCER**

All tissues in the body are derived from the differentiation of organ-specific stem cells. These stem cells are defined by their capacity to undergo self-renewal, as well as to differentiate into the cell types that compose each organ. These tissue-specific stem cells are distinguished from embryonic stem cells in that their differentiation is largely restricted to cell types within a particular organ. Stem cells, by their long-lived nature, are subject to the accumulation of multiple mutations required for carcinogenesis. Over 40 yr ago, it was postulated that these tissue-specific stem cells may be the cell of origin of cancer (1). Normal stem cells and their transformed counterparts share many characteristics, including the capacity for self-renewal, differentiation (although this is dysregulated in tumors), immortality as evidenced by telomerase expression, resistance to apoptosis, and ability to migrate and home to distant organ sites. Several recent reviews have explored the concept of the stem cell origin of tumors (2–6). Recent studies of chronic myelogenous leukemia suggest that progenitor cells may also acquire mutations that allow them to self-renew (6–8). A separate but related issue concerns the generation of tumor heterogeneity and the presence within tumors of tumor stem cells. If tumors arise through the transformation of stem or early progenitor cells and display various levels of differentiation, then tumor heterogeneity may be created, at least in part, by the aberrant differentiation of tumor stem cells and progenitor cells. Indeed, strong evidence has accumulated over the past decade that there exists within most, if not all tumors, a “stem cell population” that drives tumorigenesis. This was first demonstrated in human leukemia by John Dick’s group (9). They demonstrated that only a rare population of cells