0031-3998/07/6203-0239
PEDIATRIC RESEARCH
Vol. 62, No. 3, 2007
Printed in U.S.A.

SCIENCE – IN THE NEWS

Cancer Stem Cells: The Root of the Problem

Emerging evidence suggests that many, if not all, cancers are characterized by two distinct populations: differentiated cells, forming the tumor bulk, and rare cancer stem cells (CSC), responsible for initiation and maintenance of disease. CSC have been described in cancers of the brain, breast, pancreas, prostate and colon, as well as leukemia and myeloma. These rare CSC are phenotypically distinct from the prevalent differentiated tumor cells, and they generate tumors with populations of both stem cells and differentiated cells comprising the tumor bulk. Despite dramatic responses to initial chemotherapy, many cancers return. This clinical observation suggests cells capable of regenerating the tumor persist within this presumed minimal residual disease – the CSC. This is the so-called "dandelion phenomenon" of recurrent malignancy following a complete response to chemotherapy. A dandelion cut off at ground level appears to be gone; however, the roots remain, and the dandelion regrows. Unless the roots are targeted, the dandelion or cancer will return, regardless of aggressive measures to eradicate the visible disease or their apparent success (1).

Clinically translating evidence of CSC presents several challenges. CSC have been identified because they are more similar to normal stem cells than to differentiated tumor cells. Eradicating CSC may be more difficult because agents that preferentially target CSC may also affect normal stem cells. Additionally, CSC are predicted to resemble normal stem cells, dividing less frequently than differentiated tumor cells. This may pose difficulties in evaluating new therapies because agents targeting CSC may take longer to work than conventional chemotherapy. When designing clinical trials, investigators may reconsider traditional endpoints (*e.g.*, response rate, progression-free survival) as CSC-targeted therapy may affect the root of the cancer while the visible tumor appears unaffected. Overall survival (OS) remains the ideal indicator of cancer control, but novel markers of response are clearly needed as trials with OS as an endpoint require more time and patients to complete (2). Currently, clinical trials are underway using a dual approach with novel CSC-targeted therapy and traditional chemotherapy against differentiated tumor cells.

Although many CSC have been identified in adult cancers, pediatric cancers provide the opportunity to isolate and describe CSC from many diseases that can be cured. That is, presumed CSC from many pediatric cancers *are* susceptible to conventional therapy. For example, it is likely that the CSC of acute lymphocytic leukemia (ALL) are different in the curable pediatric disease than in the highly resistant Ph+ positive ALL of adults. What features distinguish the CSC of curable pediatric cancers from those of resistant adult tumors? Additionally, how are these CSC similar to or distinct from normal stem cells? As the cancer stem cell story continues to unfold, curable pediatric tumors represent a model to uncover successful CSC-targeted therapies and, ultimately, develop novel CSC-targeted therapies, particularly in diseases where current therapies fall short.–*Tara L. Lin, Cecilia Fu, and Kathleen M. Sakamoto*

REFERENCES

1. Jones RJ, Matsui WH, Smith BD 2004 Cancer stem cells: are we missing the target? J Natl Cancer Inst 96:583–585
2. Huff CA, Matsui W, Smith BD, Jones RJ 2006 The paradox of response and survival in cancer therapeutics. Blood 107:431–434