Colon Cancer Stem Cells Dictate Tumor Growth and Resist Cell Death by Production of Interleukin-4

Matilde Todaro, Mileidys Perez Alea, Anna B. Di Stefano, Patrizia Cammareri, Louis Vermeulen, Flora Iovino, Claudio Tripodo, Antonio Russo, Gaspare Gulotta, Jan Paul Medema and Giorgio Stassi

Department of Surgical and Oncological Sciences, Cellular and Molecular Pathophysiology Laboratory, University of Palermo, 90127 Palermo, Italy

Department of Surgical and Oncological Sciences, Oncological Unit, University of Palermo, 90127 Palermo, Italy

Department of GENUROT, University of Palermo, 90127 Palermo, Italy

Human Pathology Department, University of Palermo, 90127 Palermo, Italy

Laboratory for Experimental Oncology and Radiobiology, Academic Medical Center, 1105AZ, Amsterdam, the Netherlands

Received 2 February 2007; revised 8 June 2007; accepted 3 August 2007. Published: October 10, 2007. Available online 10 October 2007.

Referred to by: Chemotherapy and Cancer Stem Cells

Cell Stem Cell, Volume 1, Issue 4, 11 October 2007, Pages 353-355
Jeremy N. Rich, Shideng Bao
PDF (146 K)

Summary

A novel paradigm in tumor biology suggests that cancer growth is driven by stem-like cells within a tumor. Here, we describe the identification and
characterization of such cells from colon carcinomas using the stem cell marker CD133 that accounts around 2% of the cells in human colon cancer. The CD133+ cells grow in vitro as undifferentiated tumor spheroids, and they are both necessary and sufficient to initiate tumor growth in immunodeficient mice. Xenografts resemble the original human tumor maintaining the rare subpopulation of tumorigenic CD133+ cells. Further analysis revealed that the CD133+ cells produce and utilize IL-4 to protect themselves from apoptosis. Consistently, treatment with IL-4Rα antagonist or anti-IL-4 neutralizing antibody strongly enhances the antitumor efficacy of standard chemotherapeutic drugs through selective sensitization of CD133+ cells. Our data suggest that colon tumor growth is dictated by stem-like cells that are treatment resistant due to the autocrine production of IL-4.

Author Keywords: CELLCYCLE; STEMCELL

Article Outline

Introduction
Results
Colon Cancer Contains Stem-like Cells
CD133+ Cells Mediate Tumor Growth in Xenotransplants
Spheroid Cultures of Colon Cancer Stem-like Cells
Colon Spheres Can Generate Tumors upon Xenotransplantation
CD133+ Cells Are Resistant to Cell Death Due to IL-4 Production
IL-4 Inhibition Enhances Tumor Response to Oxaliplatin and 5-FU
Anti-IL-4 Sensitizes Cancer Stem-like Cells
Discussion
Experimental Procedures
Tissue Collection, Isolation, and Culture of Cancer Cells
Magnetic Sorting and Flow Cytometry
In Vitro Cell Death Analysis
Histochemistry, Immunohistochemistry/Fluorescence, and TUNEL Staining
Protein Isolation and Western Blotting
Real-Time PCR
Evaluation of Tumorigenicity and Toxicity
Statistical Analysis
Acknowledgements
Supplemental Data
References