



Endotoxin testing in about 15 minutes

HOME HELP FEEDBACK SUBSCRIPTIONS ARCHIVE SEARCH SEARCH RESULT

QUICK SEARCH: [advanced]	
Author:	Keyword(s):
Go	
Year:	Vol: Page:

First published online July 12, 2007

Stem Cells Vol. 25 No. 10 October 2007, pp. 2524 -2533

doi:10.1634/stemcells.2007-0166; www.StemCells.com

© 2007 AlphaMed Press

CANCER STEM CELLS

Cyclopamine-Mediated Hedgehog Pathway Inhibition Depletes Stem-Like Cancer Cells in Glioblastoma

Eli E. Bar^a, Aneeka Chaudhry^a, Alex Lin^a, Xing Fan^a, Karisa Schreck^b, William Matsui^c, Sara Piccirillo^d, Angelo L. Vescovi^d, Francesco DiMeco^c, Alessandro Olivi^{b,c}, Charles G. Eberhart^{a,c}

Departments of ^aPathology,

^bNeurosurgery, and

^cOncology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA;

^dDepartment of Biotechnology and Biosciences, University of Milan Bicocca, Milan, Italy;

^eIstituto Nazionale Neurologico "Carlo Besta," Milan, Italy

Key Words. Hedgehog • Glioma • Stem cell

Correspondence: Charles G. Eberhart, M.D., Ph.D., Johns Hopkins University School of Medicine, Department of Pathology, 720 Rutland Avenue, Ross Building 558, Baltimore, Maryland 21205, USA. Telephone: 410-502-5185; Fax: 410-955-9777; e-mail: ceberha@jhmi.edu

Received March 7, 2007; accepted for publication June 29, 2007.

First published online in STEM CELLS EXPRESS July 12, 2007.

Brain tumors can arise following deregulation of signaling pathways normally activated during brain development and may derive from neural stem cells. Given the requirement for Hedgehog in non-neoplastic stem cells, we investigated whether Hedgehog blockade could target the stem-like population in glioblastoma multiforme (GBM). We found that Gli1, a key Hedgehog pathway target, was highly expressed in 5 of 19 primary GBM and in 4 of 7 GBM cell lines. Shh ligand was expressed in some primary tumors, and in GBM-derived neurospheres, suggesting a potential mechanism for pathway activation. Hedgehog pathway blockade by cyclopamine caused a 40%–60% reduction in growth of adherent glioma lines highly expressing Gli1 but not in those lacking evidence of pathway activity. When GBM-derived neurospheres were treated with cyclopamine and then dissociated and seeded in media lacking the inhibitor, no new neurospheres formed, suggesting that the clonogenic cancer stem cells had been depleted. Consistent with this hypothesis, the stem-like fraction in gliomas marked by both aldehyde dehydrogenase activity and Hoechst dye excretion (side population) was significantly reduced or eliminated by cyclopamine. In contrast, we found that radiation treatment of our GBM neurospheres increased the percentage of these stem-like cells, suggesting that this standard therapy preferentially targets better-differentiated neoplastic cells. Most importantly, viable GBM cells injected intracranially following Hedgehog blockade were no longer able to form tumors in athymic mice, indicating that a cancer stem cell population critical for ongoing growth had been removed.

Disclosure of potential conflicts of interest is found at the end of this article.

This Article
▶ Full Text
▶ Full Text (PDF)
▶ All Versions of this Article: 2007-0166v1 2007-0166v2 25/10/2524 <i>most recent</i>
▶ Alert me when this article is cited
▶ Alert me if a correction is posted
▶ Citation Map
Services
▶ Similar articles in this journal
▶ Similar articles in PubMed
▶ Alert me to new issues of the journal
▶ Download to citation manager
▶ Reprints/Permissions
Google Scholar
▶ Articles by Bar, E. E.
▶ Articles by Eberhart, C. G.
PubMed
▶ PubMed Citation
▶ Articles by Bar, E. E.
▶ Articles by Eberhart, C. G.

HOME HELP FEEDBACK SUBSCRIPTIONS ARCHIVE SEARCH SEARCH RESULT

STEM CELLS THE ONCOLOGIST CME ALPHAMED PRESS JOURNALS

Endotoxin testing in about 15 minutes

Copyright © 2007 by AlphaMed Press.