

Original Article

Oncogene advance online publication 2 October 2006; doi: 10.1038/sj.onc.1210018

Inhibition of IGF-I receptor in anchorage-independence attenuates GSK-3 β constitutive phosphorylation and compromises growth and survival of medulloblastoma cell lines

K Urbanska^{1,2}, J Trojanek¹, L Del Valle¹, M B Eldeen¹, F Hofmann³, C Garcia-Echeverria³, K Khalili¹ and K Reiss¹

¹Department of Neuroscience, Center for Neurovirology, Temple University, Philadelphia, PA, USA ²Faculty of Biotechnology, Department of Cell Biology, Jagiellonian University, Krakow, Poland ³Novartis Institutes for Biomedical Research, Novartis Pharma AG, Basel, Switzerland

Correspondence: Professor K Reiss, Department of Neuroscience, Center for Neurovirology, Temple University School of Medicine, Biology Life Sciences Bldg. Room 230, 1900 North 12th Street, Philadelphia, PA 19122, USA. E-mail: kreiss@temple.edu

Received 6 June 2006; Revised 17 August 2006; Accepted 18 August 2006; Published online 2 October 2006.

Abstract

We have previously reported that insulin-like growth factor-I (IGF-I) supports growth and survival of mouse and human medulloblastoma cell lines, and that IGF-I receptor (IGF-IR) is constitutively phosphorylated in human medulloblastoma clinical samples. Here, we demonstrate that a specific inhibitor of insulin-like growth factor-I receptor (IGF-IR), NVP-AEW541, attenuated growth and survival of mouse (BsB8) and human (D384, Daoy) medulloblastoma cell lines. Cell cycle analysis demonstrated that G1 arrest and apoptosis contributed to the action of NVP-AEW54. Interestingly, very aggressive BsB8 cells, which derive from cerebellar tumors of transgenic mice expressing viral oncoprotein (large T-antigen from human polyomavirus JC) became much more sensitive to NVP-AEW541 when exposed to anchorage-independent culture conditions. This high sensitivity to NVP-AEW54 in suspension was accompanied by the loss of GSK-3 β constitutive phosphorylation and was independent from T-antigen-mediated cellular events (Supplementary Materials). BsB8 cells were partially rescued from NVP-AEW541 by GSK3 β inhibitor, lithium chloride and were sensitized by GSK3 β activator, sodium nitroprusside (SNP). Importantly, human medulloblastoma cells, D384, which demonstrated partial resistance to NVP-AEW541 in suspension cultures, become much more sensitive following SNP-mediated GSK3 β dephosphorylation (activation). Our results indicate that hypersensitivity of medulloblastoma cells in anchorage-independence is linked to GSK-3 β activity and suggest that pharmacological intervention against IGF-IR with simultaneous activation of GSK3 β could be highly effective against medulloblastomas, which have intrinsic ability of disseminating the CNS via cerebrospinal fluid.

Keywords:

IGF-I receptor, NVP-AEW541, GSK3 β , medulloblastoma, anchorage-independence

© 2006 Nature Publishing Group