Yes and PI3K Bind CD95

to Signal Invasion of Glioblastoma

Susanne Kleber,1,10 Ignacio Sancho-Martinez,1,10 Benedict Wiestler,1,10 Alexandra Beisel,1 Christian Gieffers,6

Oliver Hill,6 Meinolf Thiemann,6 Wolf Mueller,5 Jaromir Sykora,8 Andreas Kuhn,1 Nina Schreglmann,1

Elisabeth Letellier,1 Cecilia Zuliani,1 Stefan Klussmann,1 Marcin Teodorczyk,1 Hermann-Josef Gro¨ ne,2

Tom M. Ganten,8 Holger Su¨ ltmann,3 Jochen Tu¨ ttenberg,9 Andreas von Deimling,5 Anne Regnier-Vigouroux,4

Christel Herold-Mende,7 and Ana Martin-Villalba1,\*

1Molecular Neurobiology Group

2Division of Cellular and Molecular Pathology

3Division of Molecular Genome Analysis

4INSERM U701

5KKE Neuropathology

German Cancer Research Center (DKFZ), INF 581, 69120 Heidelberg, Germany

6Apogenix GmbH, Heidelberg, 69120 Heidelberg, Germany

7Department of Neurosurgery

8Department of Internal Medicine

University of Heidelberg, INF 400, 69120 Heidelberg, Germany

9Department of Neurosurgery, University of Mannheim, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany

10These authors contributed equally to this work.

\*Correspondence: a.martin-villalba@dkfz.de

DOI 10.1016/j.ccr.2008.02.003

SUMMARY

Invasion of surrounding brain tissue by isolated tumor cells represents one of the main obstacles to a curative therapy of glioblastoma multiforme. Here we unravel a mechanismregulating glioma infiltration. Tumor interaction with the surrounding brain tissue induces CD95 Ligand expression. Binding of CD95 Ligand to CD95 on glioblastoma cells recruits the Src family member Yes and the p85 subunit of phosphatidylinositol 3-kinase to CD95, which signal invasion via the glycogen synthase kinase 3-b pathway and subsequent expression of matrix metalloproteinases. In a murine syngeneic model of intracranial GBM, neutralization of CD95 activity dramatically reduced the number of invading cells. Our results uncover CD95 as an activator of PI3K and, most importantly, as a crucial trigger of basal invasion of glioblastoma in vivo.