MOLECULAR ONCOLOGY XXX (2016) 1–13

available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/molonc

Enhanced efficacy of combined HDAC and PARP targeting in glioblastoma

Rikke D. Rasmussen[a,1], Madhavsai K. Gajjar[a,1], Kamilla E. Jensen[a], Petra Hamerlik[a,b,*]

[a]Brain Tumor Biology Group, Danish Cancer Society Research Center, Strandboulevarden 49, 2100-DK, Copenhagen, Denmark

[b]Department of Radiation Biology, The Finsen Center, Copenhagen University Hospital, Blegdamsvej 9, 2100-DK, Copenhagen, Denmark

ARTICLE INFO

Article history:
Received 20 October 2015
Received in revised form
23 December 2015
Accepted 30 December 2015
Available online ■

Keywords:
Glioblastoma
Genotoxic stress
DNA repair
SAHA
Olaparib

ABSTRACT

Recent clinical trials have demonstrated that targeting chromatin remodeling factors is as a promising strategy for the treatment of glioblastoma (GBM). We and others have shown constitutive activation of DNA damage response (DDR) pathways in gliomas and suggested that targeting the DDR may improve the currently grim prognosis for patients. Based on our previous findings that inhibition of poly(ADP-ribose) polymerase (PARP) increases radiosensitivity of the notoriously radio-resistant GBM cells, we hypothesized that epigenetic down-regulation of the DDR responses and induction of oxidative stress via HDAC inhibition would contribute to more efficient targeting of this deadly disease. Our data show that SAHA, an HDAC class I + II inhibitor, in combination with olaparib (PARP inhibitor): i) enhanced inhibition of GBM cell survival, ii) induced apoptosis, and iii) impaired cell cycle progression. These results provide a pre-clinical rationale for combined administration of SAHA and olaparib, which are already individually in clinical trials.

1. Introduction

Glioblastoma (GBM) is among the deadliest of solid cancers with striking genomic instability and therapeutic resistance. Despite extensive efforts, the prognosis of patients suffering from this aggressive disease remains poor with median survival of approximately 15 months (Chen et al., 2012; Huse et al., 2011; Stupp et al., 2005; Tanaka et al., 2012). The standard of care represents maximal-safe surgical resection followed by chemo-radiation (Stupp et al., 2005). Based on successful pre-clinical models, numerous clinical trials have investigated the efficacy of novel therapies, but over the past few decades, only limited success in increasing the survival of GBM patients has been achieved.

High intra- and inter-tumoral heterogeneity, together with complex cellular plasticity and de-regulated signaling pathways, are the plausible causes of resistance to existent therapies in GBM. Several reports have shown constitutive activation of the DNA damage response (DDR) in malignant gliomas due to ongoing oxidative and replication stress

* *Corresponding author*. Brain Tumor Biology Group, Danish Cancer Society Research Center, Strandboulevarden 49, 2100-DK, Copenhagen, Denmark. Tel.: +45 35 25 74 05.
E-mail address: pkn@cancer.dk (P. Hamerlik).

[1] These authors contributed equally.

http://dx.doi.org/10.1016/j.molonc.2015.12.014

Please cite this article in press as: Rasmussen, R.D., et al., Enhanced efficacy of combined HDAC and PARP targeting in glioblastoma, Molecular Oncology (2016), http://dx.doi.org/10.1016/j.molonc.2015.12.014

(Bartkova et al., 2010; Rivera et al., 2015; Squatrito et al., 2010; Venere et al., 2014).

Proper repair of DNA lesions requires them to be accessible to DNA repair machinery. DNA accessibility can be modulated by several mechanisms including post-translational modification of histones thereby either stabilizing or destabilizing nucleosome structure. Histone deacetylation is mediated by histone deacetylases (HDACs). HDACs catalyze removal of acetylated residues from histones, leading to chromatin condensation and transcriptional repression. Chromatin condensation, moreover, impairs recruitment of DNA repair factors and results in accumulation of DNA breaks. In the past several years, HDAC inhibitors have been used as radio- and chemo-sensitizers in GBM (Lucio-Eterovic et al., 2008; Singh et al., 2015, 2011; Xu et al., 2011). They induce differentiation, growth arrest and apoptosis in numerous malignant

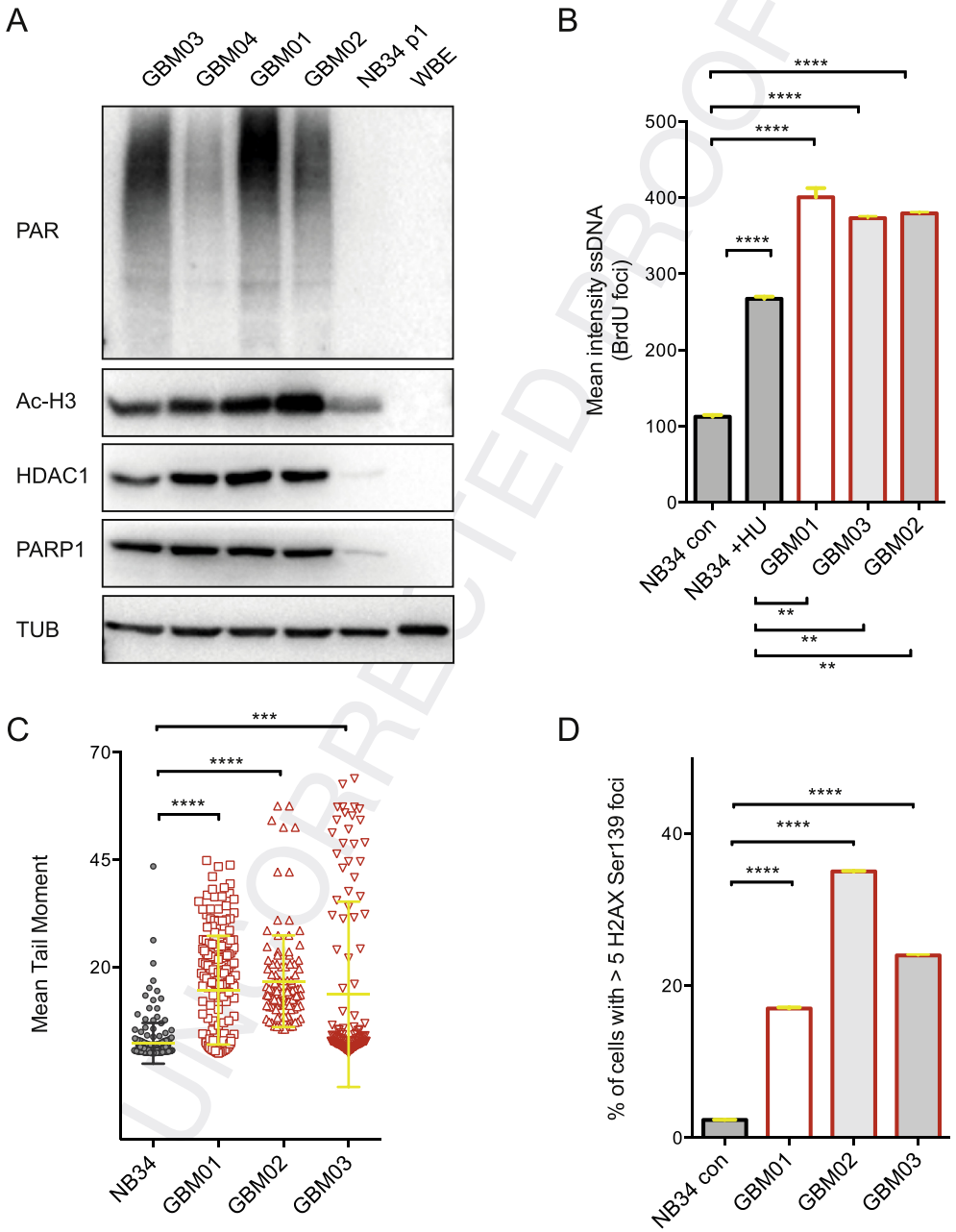

Figure 1 – Increased expression of HDAC1 and PARP1 in GBM cells correlates with higher level of SSBs and DSBs. (A) Immunoblot analysis showing increased expression of HDAC1, PARP1, acetylated H3 levels and the degree of PARYlation in 4 selected GBM xenografts (GBM01-04) in comparison to non-neoplastic brain control cells NB34 and whole brain extract (WBE). (B) The incorporation of BrdU under non-denaturation conditions was measured to evaluated the level of ssDNA in GBM01-03 and NB34 non-treated or treated with 2 mM HU for 2 hrs. (C) Mean Tail Moment was measured to compare the amount of DSBs in GBM01-03 and NB34 cells. (D) % of cells with >5H2AX Ser139 foci per cell – a marker of DSB was quantified and compared between GBM01-03 and NB34 cells. Data are shown as mean ± SD. ***p < 0.001; ****p < 0.0001.

Please cite this article in press as: Rasmussen, R.D., et al., Enhanced efficacy of combined HDAC and PARP targeting in glioblastoma, Molecular Oncology (2016), http://dx.doi.org/10.1016/j.molonc.2015.12.014