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BRAT1 depletion impairs DNA damage repair in glioblastoma cell lines

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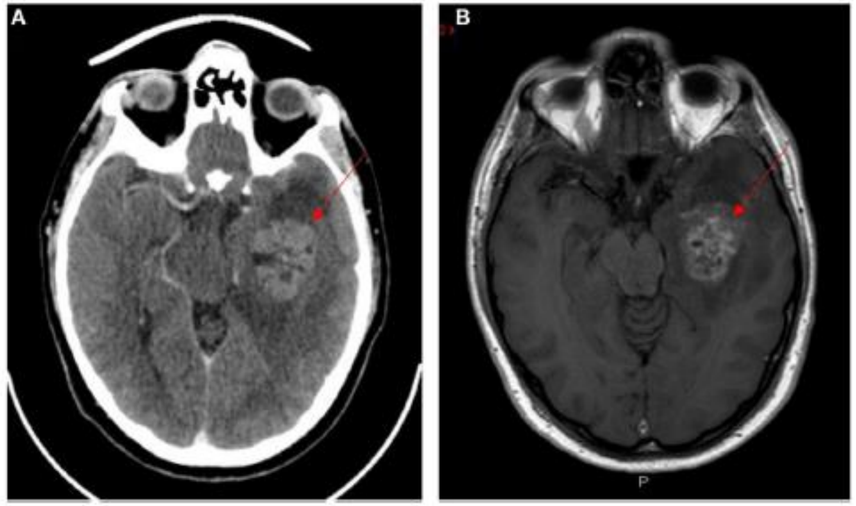
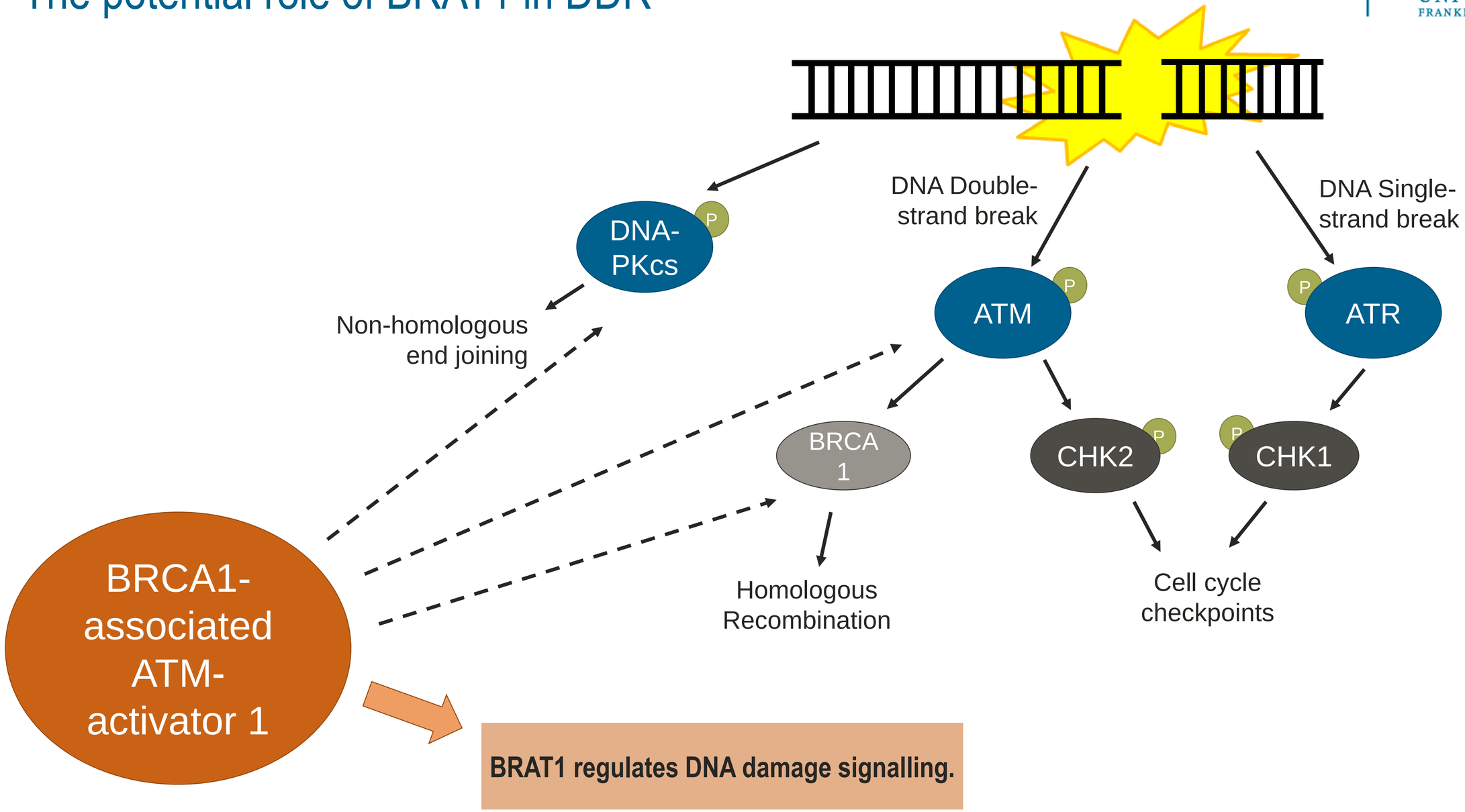
- Glioblastoma multiforme (GBM)
  - WHO grade IV astrocytoma
  - Most common brain tumor in adults
  - Diffuse and infiltrative growth



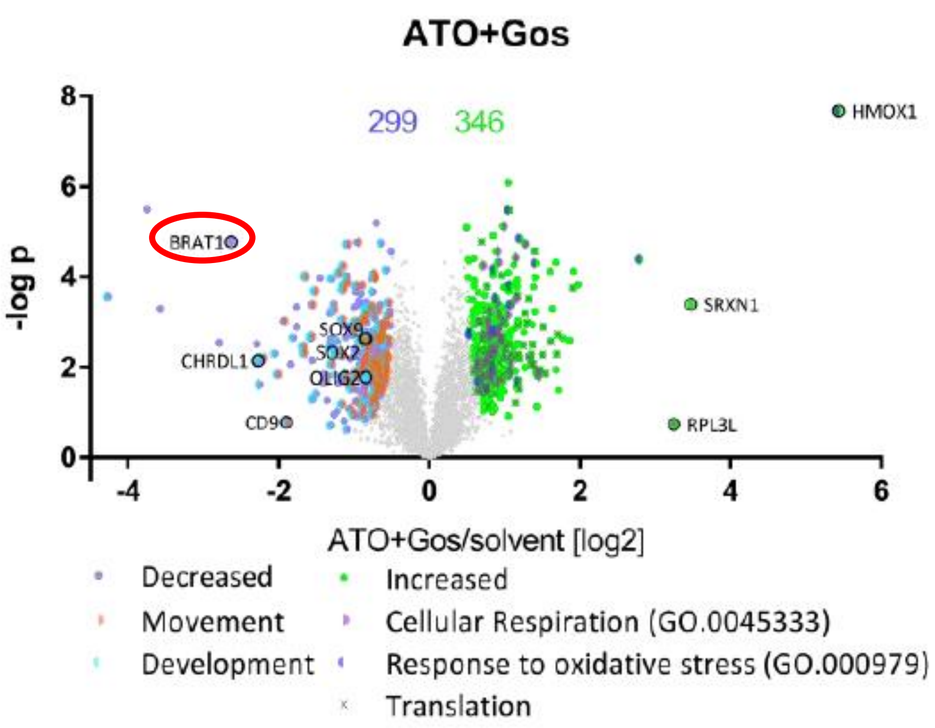
Bradshaw et al. (2016)

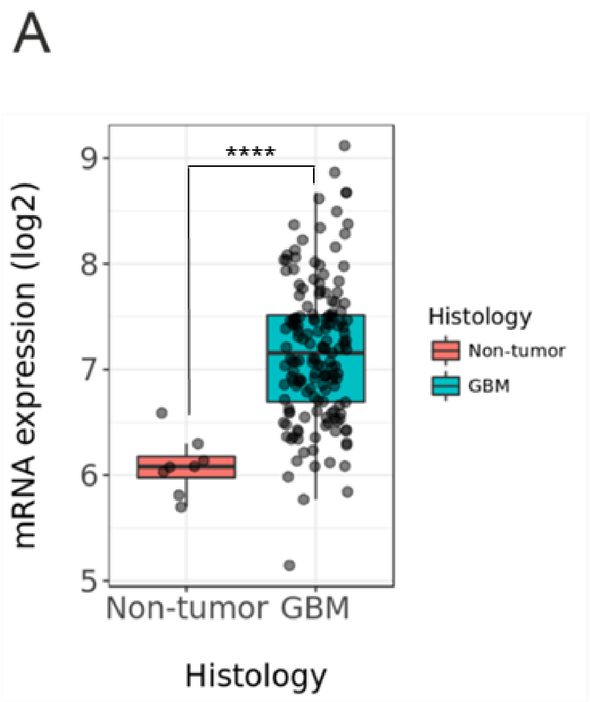
- Glioma stem-like cells (GSCs)
  - Originate from neuronal stem cells or de-differentiate from normal brain cells
  - Expression of stemness markers
  - High resistance to radio- and chemotherapy

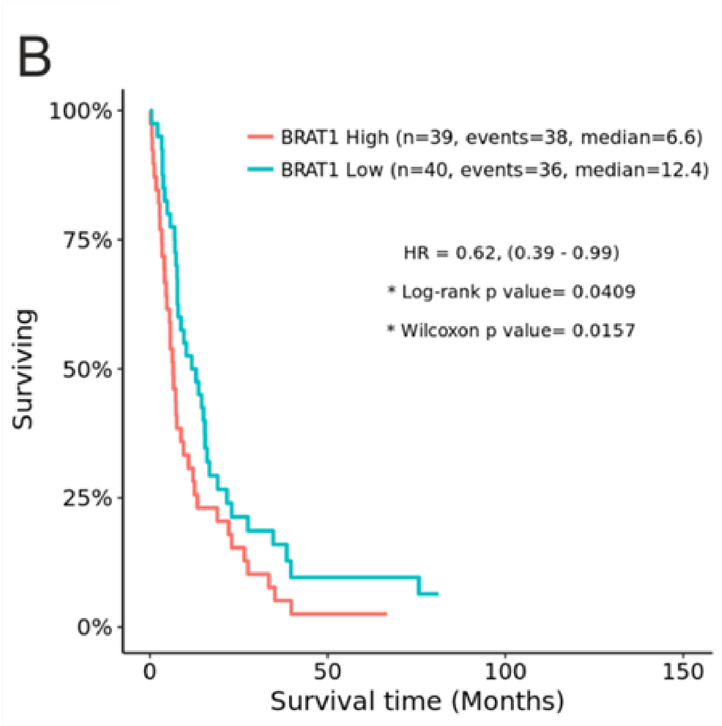
The potential role of BRAT1 in DDR



BRAT1 expression is increased in GBM





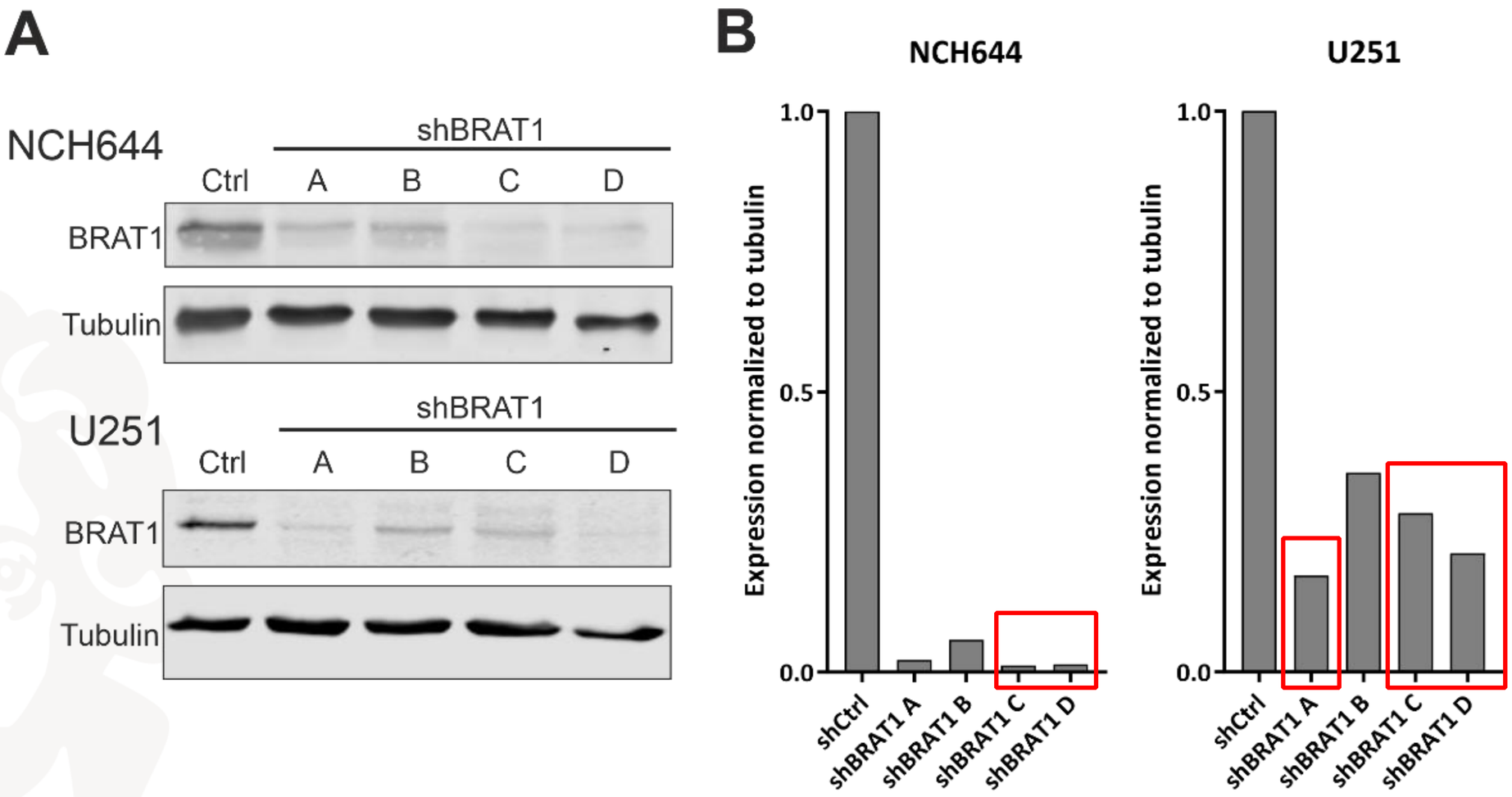


Linder et al. (2019)
Unpublished work

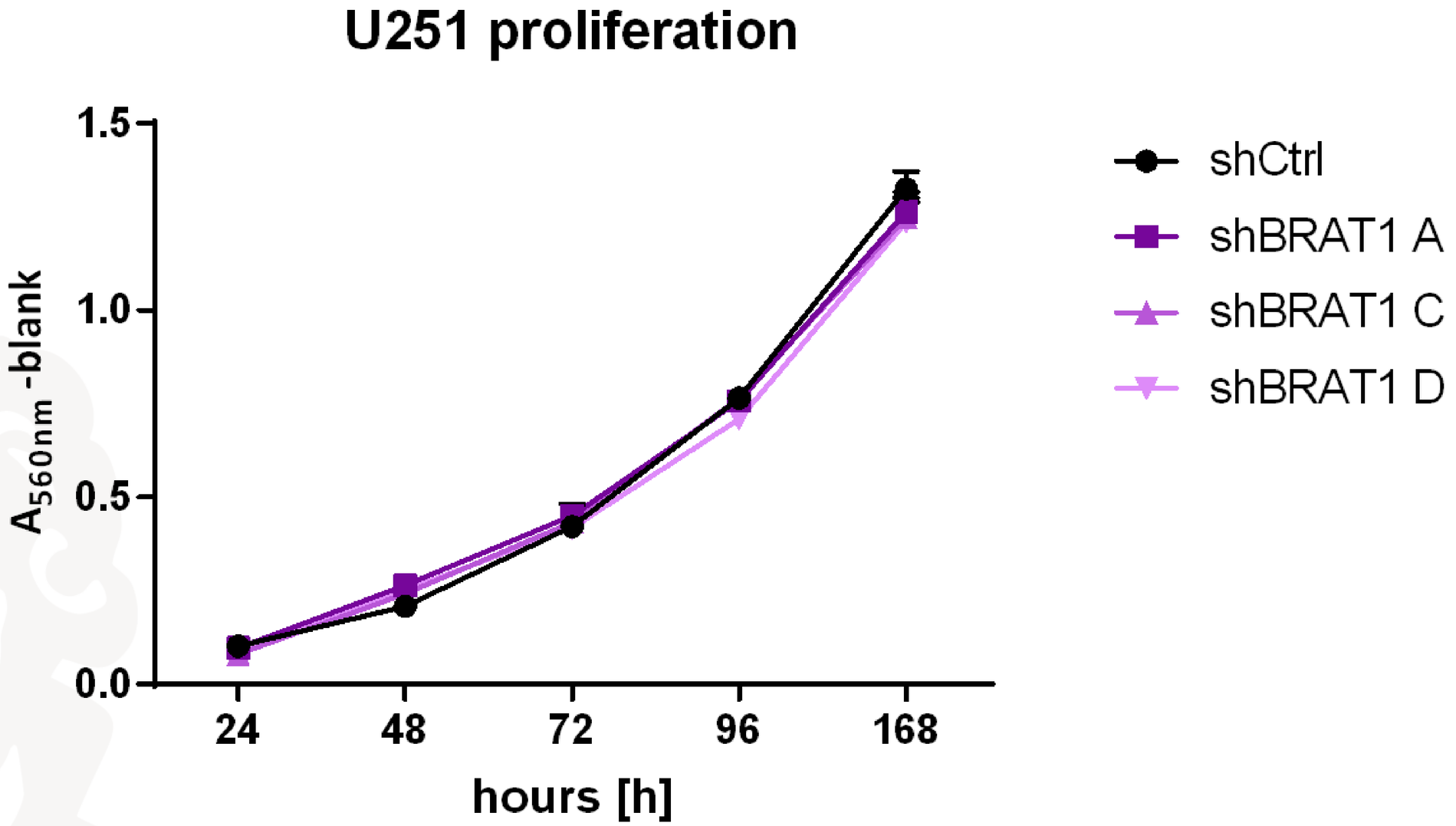
Hypothesis

BRAT1 is a key protein for glioblastoma radio-resistance.

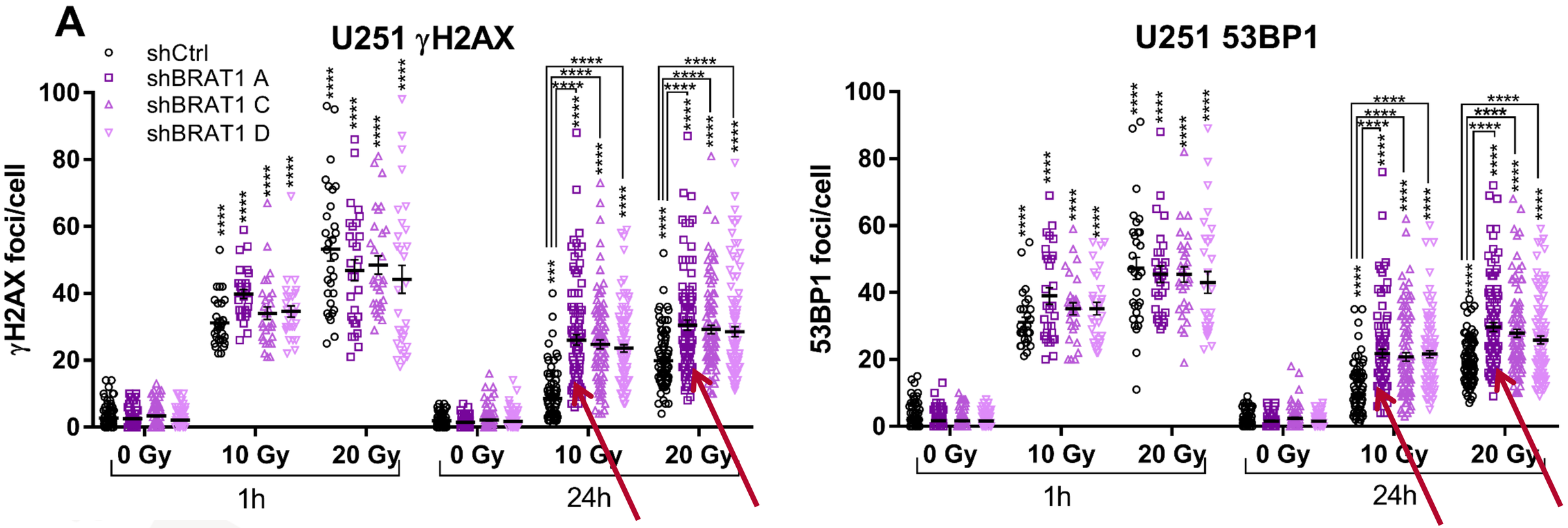
1 | Validation of BRAT1 knockdown cells



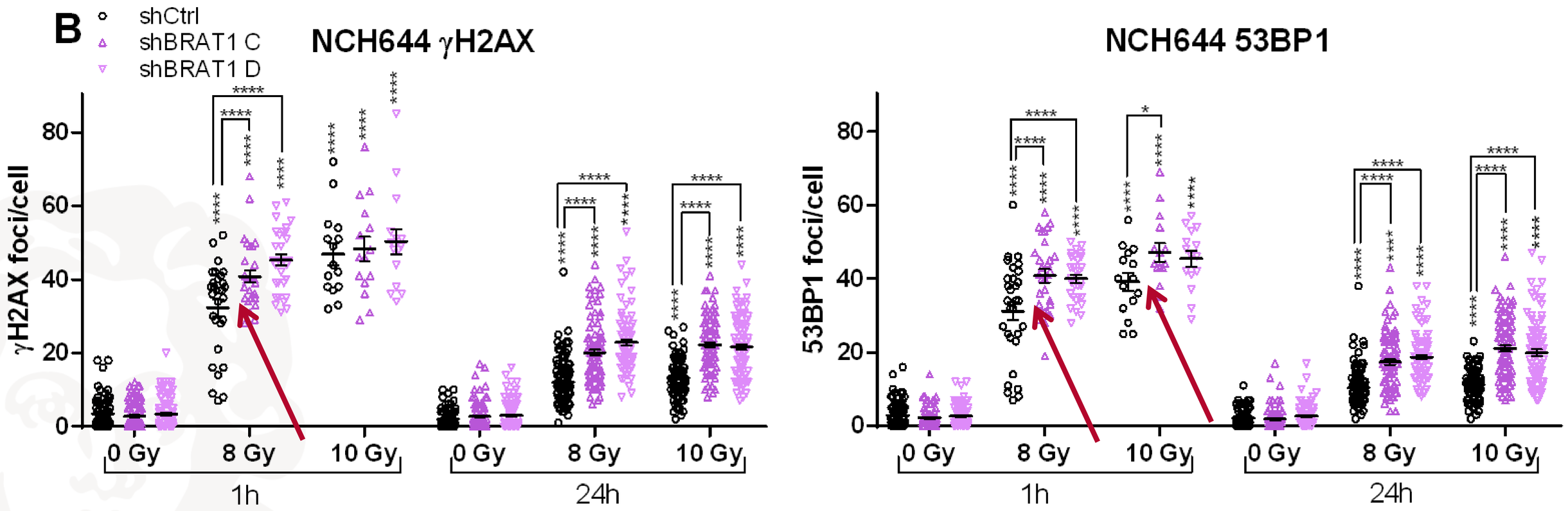
2 | GBM cell proliferation is not affected by BRAT1 downregulation



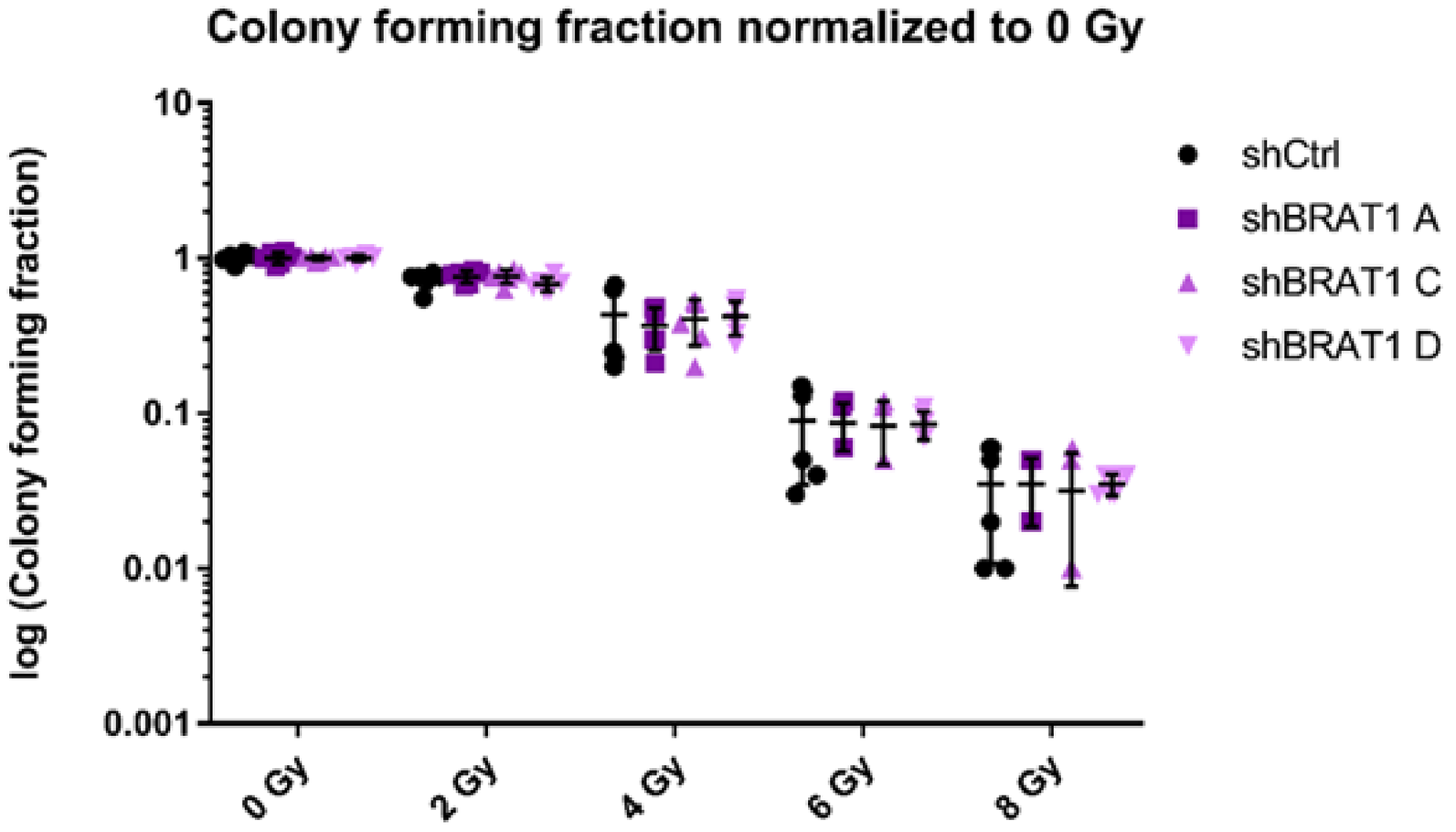
3a | BRAT1 is essential for an efficient and timely DNA repair: GBM cells



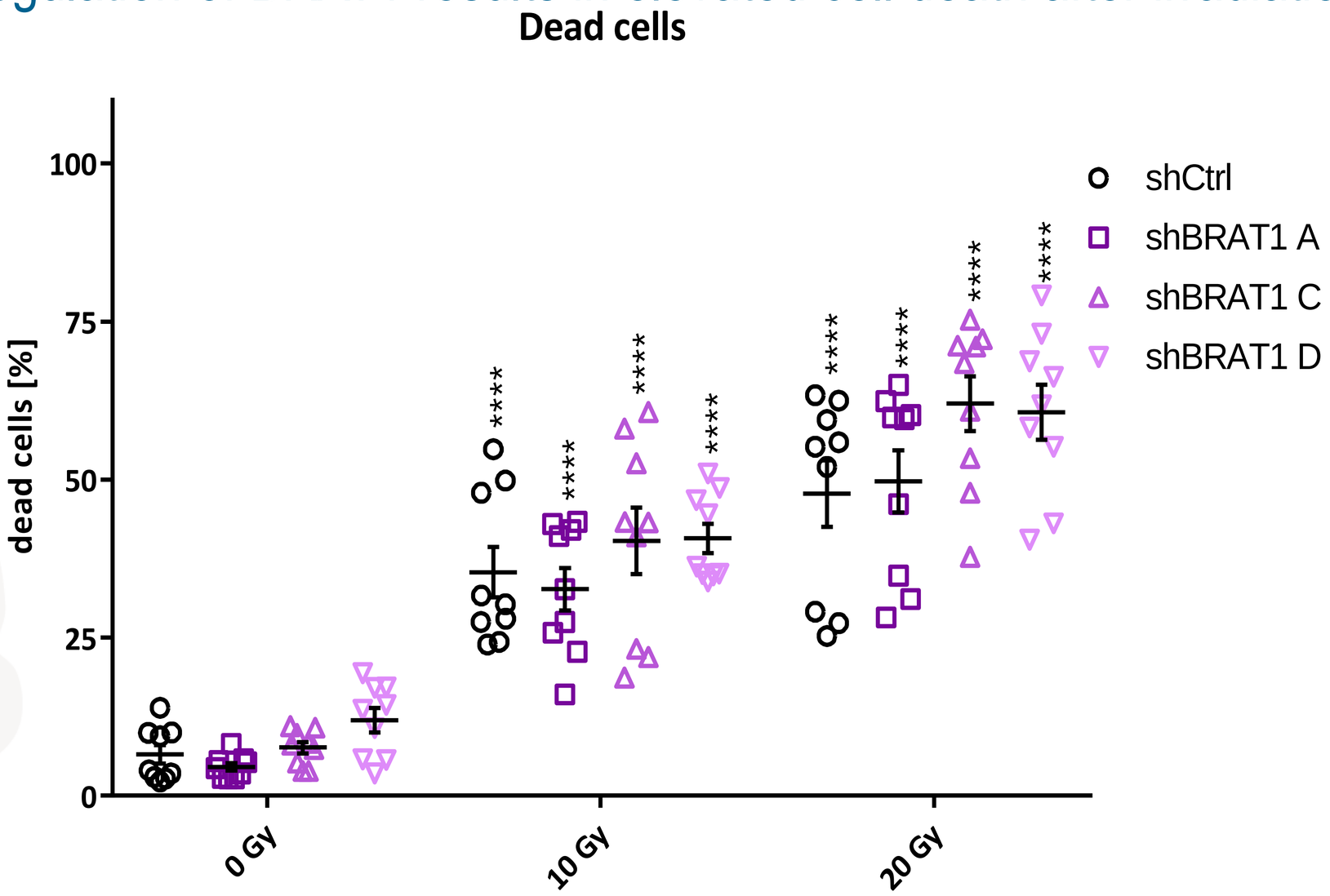
3b | BRAT1 is essential for an efficient and timely DNA repair: GSCs



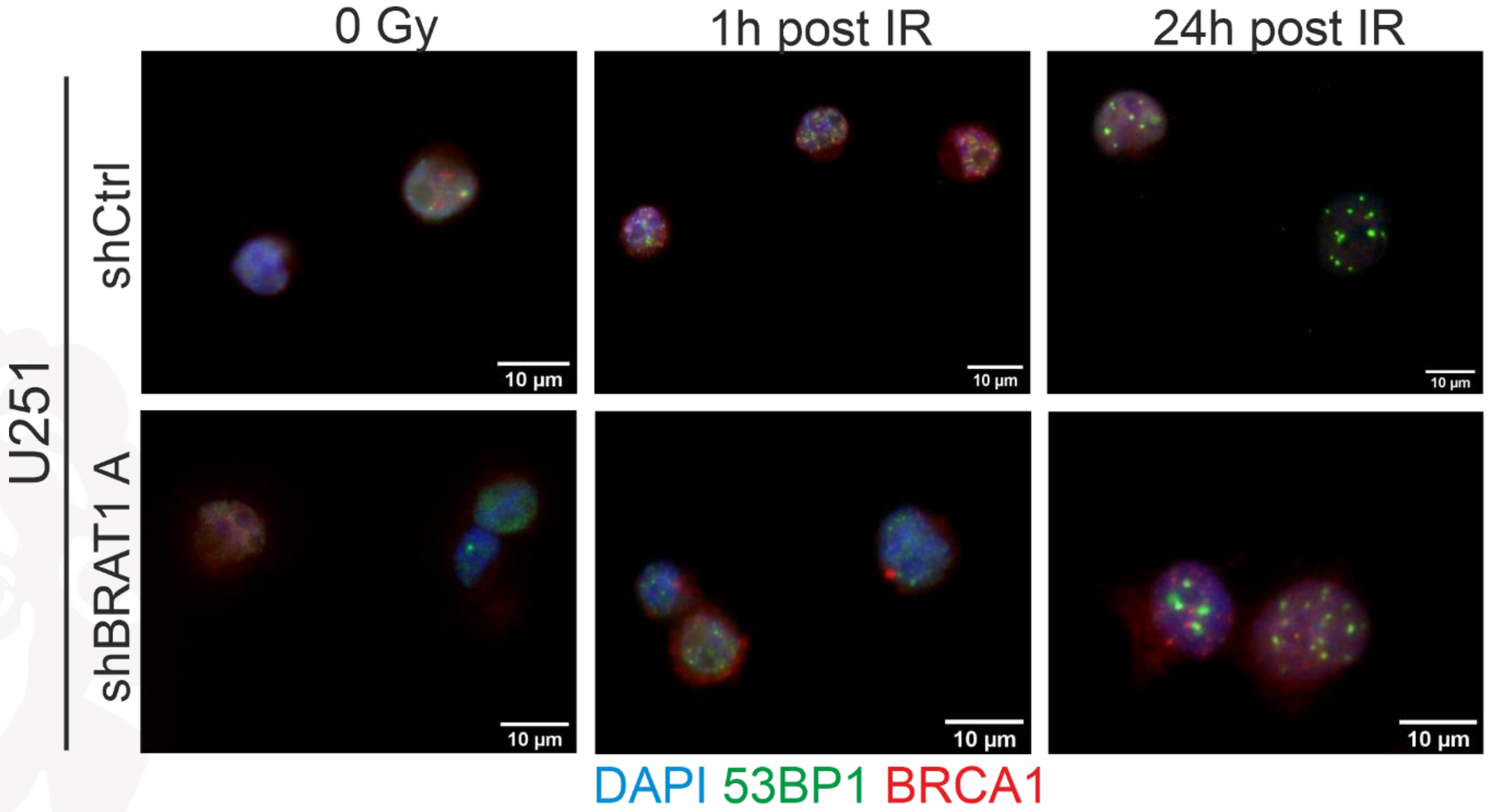
4 | BRAT1 deficiency does not affect colony formation ability



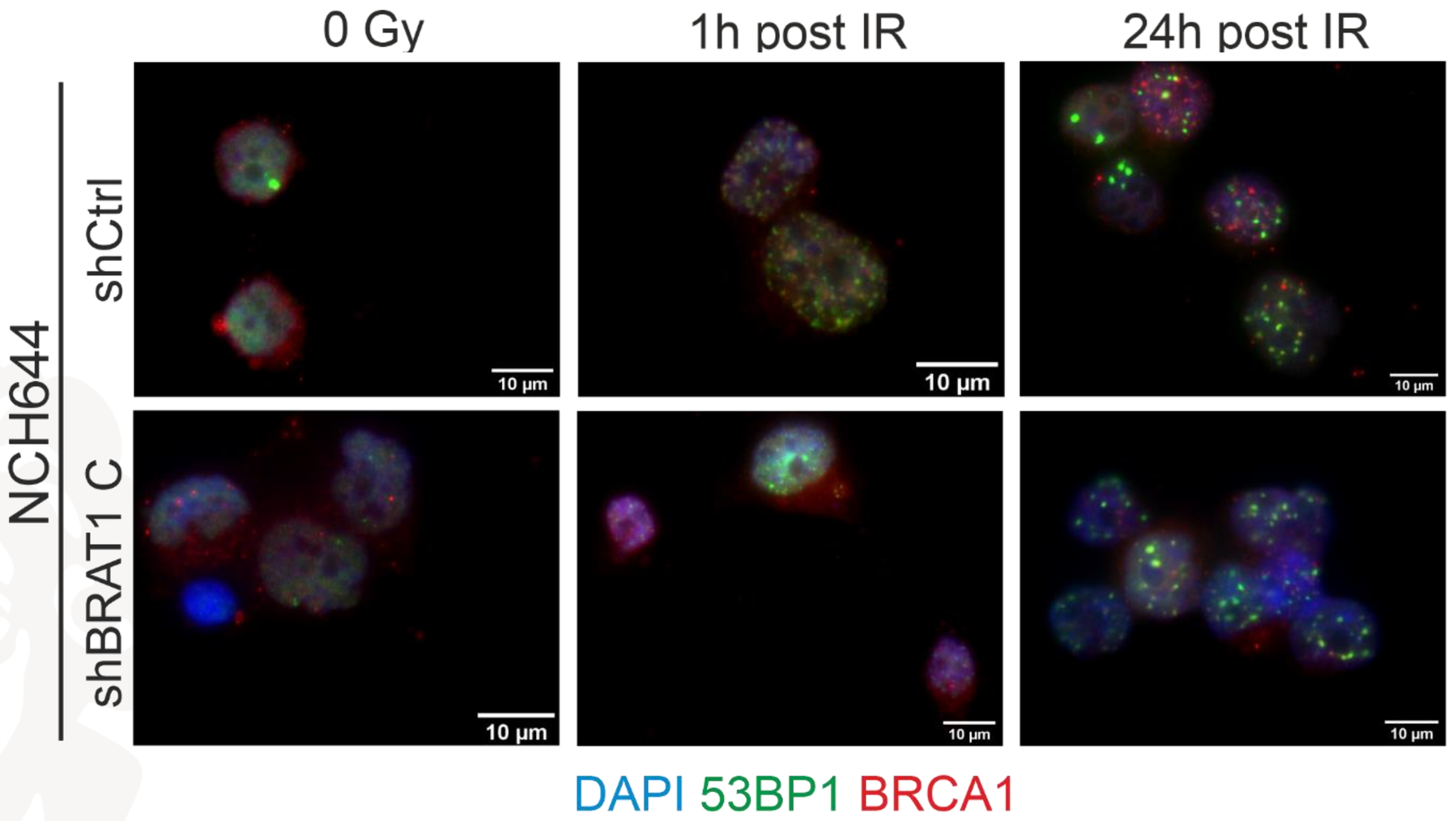
5 | Downregulation of BRAT1 results in elevated cell death after irradiation



6a | BRAT1 is necessary for BRCA1-recruitment to DNA damage sites



6b | BRAT1 is necessary for BRCA1-recruitment to DNA damage sites



BRAT1…

- Is essential for efficient DNA repair.
- Does not affect cell proliferation and colony formation ability.
- Depletion might reduce radio-resistance.
- Is necessary for BRCA1 recruitment to the DNA damage site.

Thank you for your attention!

Sources

Bradshaw A, Wickremsekera A,Tan ST, Peng L, Davis PF and Itinteang T (2016) Cancer Stem Cell Hierarchy in Glioblastoma Multiforme. Front. Surg. 3:21. doi: 10.3389/fsurg.2016.00021

Linder B, Wehle A, Hehlgans S, Bonn F, Dikic I, Rödel F, Seifert V and Kögel D (2019) Arsenic Trioxide and (-)-Gossypol Synergistically Target Glioma Stem-Like Cells via Inhibition of Hedgehog and Notch Signaling. Cancers 11, 350. doi:10.3390/cancers11030350

Linder B (2018) Novel strategies for the targeted elimination of glioblastoma stem-like cells. DFG form 53.01– 03/18

Kinner A, Wu W, Staudt C and Iliakis G (2008) γ-H2AX in recognition and signaling of DNA double-strand breaks in the context of chromatin. Nucleic Acids Research, Vol. 36, No. 17, doi:10.1093/nar/gkn550

Aglipay JA, Martin SA, Tawara H, Lee SW and Ouchi T (2007) ATM Activation by Ionizing Radiation Requires BRCA1-associated BAAT1. JBC Vol. 281, No. 14, pp. 9710-9718, doi: 10.1074/jbc.M510332200

So EY and Ouchi T (2011) Functional interaction of BRCA1/ATM-associated BAAT1 with the DNA-PK catalytic subunit. Experimental and therapeutic medicine 2: 443-447, doi: 10.3892/etm.2011.232

Bao S, Wu Q, McLendon RE, Hao Y, Shi Q, Hjelmeland AB, Dewhirst MW, Bigner DD and Rich JN (2006) Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. Nature 444 (7120): 756-760, doi: 10.1038/nature05236

Gupta A, Hunt CR, Chakraborty S, Pandita RK, Yordy J, Ramnarain DB, Horikoshi N and Pandita TK (2014) Role of 53BP1 in the Regulation of DNA Double-Strand Break Repair Pathway Choice. Radiat Res. 181 (1): 1-8. doi:10.1667/RR13572.1.

So, E.Y.; Ouchi, T. (2014) BRAT1 deficiency causes increased glucose metabolism and mitochondrial malfunction. BMC Cancer, 14, 548, doi:10.1186/1471-2407-14-548

Pictures

Bradshaw A, Wickremsekera A,Tan ST, Peng L, Davis PF and Itinteang T (2016) Cancer Stem Cell Hierarchy in Glioblastoma Multiforme. Front. Surg. 3:21. doi: 10.3389/fsurg.2016.00021

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