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Combined inhibition of the Fanconi anaemia (FA) pathway and ATR promotes R-loop generation and profound radiosensitisation in glioblastoma

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Glioblastoma is a deadly cancer in which treatment resistance is mediated through extensive intratumoural heterogeneity including difficult-to-treat glioblastoma stem cell (GSC) subpopulations. GSC eradication represents an attractive therapeutic goal, but these cells possess upregulated DNA damage response (DDR) processes, resulting in a chemo- and radioresistant phenotype. However, recent studies have demonstrated that elevated replication stress in GSCs may partially explain DDR upregulation and resistance, thus highlighting a potential therapeutically exploitable vulnerability. ATR and the FA-pathway are both fundamental to cellular DNA replication stress responses and maintaining replication fork stability. Since we have previously shown the FA-pathway is inactive in normal brain, but is re-activated in glioblastoma with potential to provide a cancer-specific foundation for combination DDR therapies, we explored the therapeutic potential of simultaneous inhibition of the FA-pathway (FAPi) and ATR (ATRi), in addition to other FA-pathway-based DDR inhibitor (DDRi) combinations. We find that compared with single agent treatments, combined inhibition of the FA-pathway and ATR in both 2D and 3D GSC ex vivo models promotes a substantial increase in conflicts between DNA replication and transcription (R-loops) which is further exacerbated by ionising radiation (IR). Molecular analyses of DNA damage indicate that FAPi+ATRi increases peak DNA damage post- IR treatments, with sustained elevation of DNA damage even at 24 hours post-treatment. In conclusion, simultaneously targeting the FA-pathway and ATR represents an appealing therapeutic strategy for glioblastoma. This approach promotes substantial R-loop generation, likely through exacerbating constitutively high levels of DNA replication stress previously observed in GSCs, with deleterious effects in these treatment resistant cells. Our findings underline the value of developing clinical FA pathway inhibitors and also support the application of current ATR inhibitors to molecularly-selected subsets of glioblastoma, namely, those with defects in one of 22 currently known FA-pathway genes which include BRCA1/FANCS and BRCA2/FANCD1.

Keywords: glioblastoma; DNA damage response; Fanconi; ATR; BRCA1/BRCA2