Radiation induced senescence in diffuse intrinsic pontine glioma cells reveals selective vulnerability to Bcl-XL inhibition

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BACKGROUND

DIPG is in urgent need of novel therapeutic strategies

Diffuse Intrinsic Pontine Glioma (DIPG) is a devastating paediatric diffuse midline glioma (DMG). Currently radiotherapy is offered in the palliative setting, with a median overall survival of 9 months. Anti-cancer treatments such as exposure to ionising radiation, can result in cellular senescence induction in a process termed therapy induced senescence (TIS). Senescent cells also secrete an array of factors termed the senescence-associated secretory phenotype (SASP).

AIMS & METHOD

Radiation induced senescence in DIPG

Three primary human DIPG cell lines (HSJD-DIPG007, ICR-B117 and SU-DIPGIV) harboring the histone mutations [HIST1H3B and H3F3A] are subjected to single doses of 137Cs γ-ray irradiation. The following schema will be used to identify senescence following radiation.

RESULTS

Radiation increases SA-β-gal staining in primary human DIPG cell lines

Treatment of primary human DIPG cell lines with single doses of radiation (12, 24 and 36 Gy) increases senescence associated beta galactosidase staining when compared to control (P<0.0001) after 5 days.

Radiation induces senescence and SASP in primary human DIPG cell lines

qRT-PCR of primary human DIPG cell lines treated with single doses of radiation (6 and 24 Gy) show mRNA upregulation of CDK inhibitor CDKN2A, and SASP factors CCL2 and IL1B, in a dose and time dependent manner. RNA-sequencing of these cell lines reveals upregulation of senescence associated genes IL1B, CCL2 and IL6 and downregulation of LMNB1, MYBL2 and EZH2. Gene set enrichment analysis was carried out revealing significant enrichment with senescence and SASP gene sets (FDR q values <0.0001).

Senescent DIPG cells are vulnerable to Bcl-xL inhibition using Navitoclax

Cell viability of non-senescent and senescent DIPG cells was measured using CellTitre-Glo viability (CellTitre-Glo, Promega) assay. Senescent DIPG cells are more sensitive to pan-antiproliferative Bcl-2 family inhibitor, using Navitoclax, however are not sensitive to selective Bcl-2 inhibitor Venetoclax.

CONCLUSION

This data provides strong evidence of the role of radiation induced senescence in DIPG. Further in vitro and in vivo work is required to understand the role of ablation senescent DIPG cells using Navitoclax as shown in the data here. This highlights previously unknown therapeutic vulnerabilities in DIPG.