DNA-PK as a target for radiosensitization in high-risk Myc-Driven Medulloblastoma.

E.L. Hawkins[1]

[1] Curie Institute, Paris, France.

Abstract

Medulloblastoma (MB) is the most common pediatric malignant brain tumour. This malignancy arises in the cerebellum and has an overall survival rate of ~70%. MB is treated with a multimodal regimen of surgical resection, chemotherapy, and radiotherapy. Four molecular subtypes with different transcriptomic profiles have been identified, of which Group 3 (G3), driven by MYC overexpression, has the worst prognosis. Aggressive treatment, in which radiotherapy is essential, allows a ~50% survival rate in G3 MB, but induces strong side effects. Despite this intensive treatment, relapse is common and almost always fatal, with relapsed MB accounting for ~10% of all cancer-related deaths in children.

Herein, we propose DNA-PK as a target for radiosensitization in G3 MB. Indeed, DNA-PK was identified as a target in an in vitro screen where its inhibition was shown to radiosensitive more G3 MB as compared to the other MB groups. Accordingly, database analysis revealed high expression of DNA-PK in G3 MB, as well as a strong correlation with MYC expression and prognosis. Pharmacological inhibition or shRNA-mediated knockdown (KD) of DNA-PK in vitro increases the radiosensitivity of G3 cells by inducing apoptosis. In vivo, KD of DNA-PK sensitized MB tumors to irradiation in orthotopic grafted G3 mouse models, resulting in a significant survival benefit. Current work focuses on identifying the underlying mechanisms and the radiosensitizating activity of a pharmacological DNA-PK inhibitors in vivo on G3 MB to assess its potential clinical utility.

Overall, our results suggest the potential of DNA-PK as a target of radiosensitization in high-risk Group 3 Medulloblastoma.