Modeling Childhood Brain Tumor Mutations in Fruit Flies: Testing Therapeutics for H3.3 K27M Mutant Glioblastoma in Drosophila melanogaster

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The K27M mutation in histone H3.3 drives incurable glioblastomas in children called Diffuse Intrinsic Pontine Gliomas (DIPG). Research in human cells shows that a deficiency in H3.3 protein levels or the presence of the H3.3K27M mutation leads to sensitivity to DNA damaging agents and the cancer drug Olaparib that blocks certain types of DNA repair. However, obtaining samples from children with DIPG or performing research on patients is fraught with difficulties and this has hindered the development of treatments for H3.3 mutant cancers. Fruit flies (Drosophila melanogaster) also have two copies of histone H3.3 genes that encode proteins that are identical to humans and this study aims to determine if flies are a good model organism for studies on the roles of histone H3.3 and its mutations. Unlike mammals including humans, flies can survive without any copies of H3.3. To determine whether flies are a good model organism to study histone H3.3 functions, we tested larvae from wild type (WT) and H3.3 deficient flies for their ability to hatch into adult flies following DNA damage. The larvae were either left untreated or treated with varying amounts of Olaparib and radiation to cause DNA damage. My results show a reduction in the number of H3.3 deficient fly larvae that hatch into adults compared to WT larvae following treatment with Olaparib or radiation, mimicking the findings in human cells. This suggests that flies can be used as a convenient model system for studying H3.3 and to test potential therapeutic drugs.

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