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DNA DOUBLE-STRAND BREAK HOMOLOGOUS RECOMBINATION REPAIR MEDIATED BY PHOSPHORYLATION OF PKM2 IN GLIOBALSTOMA

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With high risk of recurrence and therapeutic resistance, glioblastoma is considered to be the most malignant and lethal subtype brain tumours. Our previous studies have indicated that DNA double-strand breaks repair played a central role in the recurrences of gliobastoma after radiotherapy. We also revealed several key regulators, such as GSK3β and 53BP1, played critical role in DNA repair signalling pathway. Emerging evidence has shown that pyruvate kinase M2 (PKM2), which played essential role in tumour metabolisms, could mediate DNA- damage repair. However, there exists two main repair pathways, which are homologous recombination (HR) and non-homologous end joining (NHEJ). Currently, no studies have shown by which pathway PKM2 mediated DNA-damage repair. Therefore firstly, this study aimed to reveal the significance of PKM2 in DNA double-strand break repair. Then we showed whether PKM2 was phosphorylated and translocated into the nuclear. Lastly, we aimed to demonstrate by which pathway PKM2 mediate DNA damage repair. Predominantly PKM2 resides in the cytoplasm, which functions as the main regulator in tumour metabolism. In the present study, we observed the PKM2 translocation from cytoplasm to nuclear under the treatment of ionizing radiation, and thus it played the function of the initiation of HR repair in the nucleus of glioblastoma cells. In addition, by CRISPR/Cas9 technology, DNA double-strand breaks HR repair was observed to be abrogated in PKM2 null cells. Furthermore, we explored the phosphorylation site of PKM2. More importantly, our in vivo and in vitro data clearly indicated that inhibition of PKM2 could not only abolish the tumour metabolism, but also enhance the radio-sensitivity after ionizing radiation therapy. Based on these results, we concluded that the phosphorylation of PKM2 was indispensable for DNA double-strand breaks HR repair. Therefore, PKM2 may be the potential targets for improving radiation sensitivity of glioblastoma.

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