

## 4 - 52 Control of Alternative Splicing of Caspase-9 Enhances the Radiosensitivity of Cancer Cells to Ionizing Radiations

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The splicing of *caspase-9* gene generates two isoforms such as *caspase-9a* and *caspase-9b/9S*, which can be generated by the inclusion or exclusion of a 4-exon cassette including exon 3, 4, 5, and 6 in the mature *caspase-9* mRNA<sup>[1]</sup>. To investigate whether artificial increase of *caspase-9a/9b* mRNA ratio could enhance the sensitivity of non-small cell lung cancer (NSCLC) cells to low linear energy transfer (LET) X-rays and high-LET carbon ions, clonogenic survival assays were performed to detect the radiosensitivity of NSCLC A549 cells following *caspase-9b* knockdown and ionizing radiations. The results revealed that high-LET carbon ions enhanced the alternative splicing-mediated radiosensitivity within the exposure dose limits, but low-LET X-rays could increase the radiosensitivity in a dose-dependent manner.

### Reference

[1] D. W. Seol, T. R. Billiar, J. Biol. Chem., 274(4)(1999)2072.

## 4 - 53 Metformin Enhances the Different Radiosensitivity of Human NSCLC Cancer Cells to X-rays

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Metformin(MET), which is a biguanide commonly used as first line of treatment for type II diabetes, has recently sparked interest as a potential anticancer agent. But in previous studies, we found that metformin could induce great differences of growth inhibition in different cancer cells. To explore the radiosensitivity effect of MET in different NSCLC genotypes, we used lines that represent common histologies and mutation profile of NSCLC (A549 adenocarcinoma: LKB1-deficient (nonsense mutation of codon 37 leading to stop codon), K-Ras G12S-activating mutant, p53-WT; H1299 adenocarcinoma: LKB1-WT, p53-deficient (TP53 partial deletion) and H1650 adenocarcinoma: LKB1-WT, p53-WT,EGFR-mutation(the  $\Delta$ E746-E750 deletion mutant).

Parts of the results are shown in Figs. 1 and 2. The results showed that MET could cause discrepant radiosensitivity in different NSCLC genotypes. MET markedly enhanced and also prolonged radiation-induced  $\gamma$ H2AX formation such that a significant amount of  $\gamma$ H2AX was still present even at 24 h after irradiation in H1299 and H1650. Consistent with this data, MET treatment also enhanced the apoptosis and cell block after radiation in both H1299 and H1650.

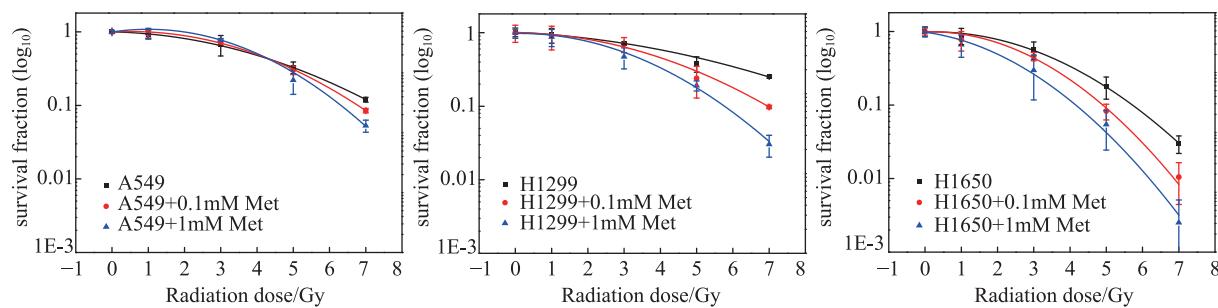


Fig. 1 Surviving fraction of A549, H1299 and H1650 cells with and without metformin after X-ray.

In recent reports, the AMPK/mTOR pathway may be the target of the anti-proliferative effects of metformin in combination with ionizing radiation. We also analyzed the autophagy in above cell lines. The result showed in Fig. 3, is consistent with previous findings. Next, we will explore the different activation level of the AMPK/mTOR/Akt signaling pathway in those NSCLC cells combine metformin and radiation.