3 - 58 Telomerase Activity Inhibition Block DNA Damage Repair*

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Previous studies in malignant cells have shown that irradiation-induced upregulation of telomerase activity, not only protected damaged telomeres, but also contributed to DNA damage repair by chromosomal healing and increased resistance to irradiation[1,2].

To investigate the radiosensitizing mechanism of telomerase inhibition, the influence of telomerase inhibitor (MST-312) combined with X-ray irradiation on γ-H2AX foci were determined. As shown in Fig. 1(a), the combined treatment resulted in retention of γ-H2AX nuclear foci and significant decrease of DNA damage repair. This result was validated by flow cytometry. Compared with irradiation alone, the sub-G1 fraction of the MST-312 pretreatment group was greater, at 24 h after irradiation. The presence of a sub-G1 peak is often interpreted as a loss of DNA due to its fragmentation associated with apoptosis[3]. Therefore, the results shown in Fig. 1(b) suggested that MST-312 pretreatment, followed by X-ray irradiation caused apoptosis. Classical theories hypothesize that cell cycle arrest is a mechanism of self-protection, to enable sufficient time to repair DNA damage. If cells are efficiently repaired, they will reenter the cell cycle. Once the DNA damage is too severe to be repaired, the cells will ultimately die. Our results were consistent with the theories that the majority of the damaged cells could not be efficiently repaired during the post-irradiation time period, resulting in apoptosis which might be due to impaired DNA repair.

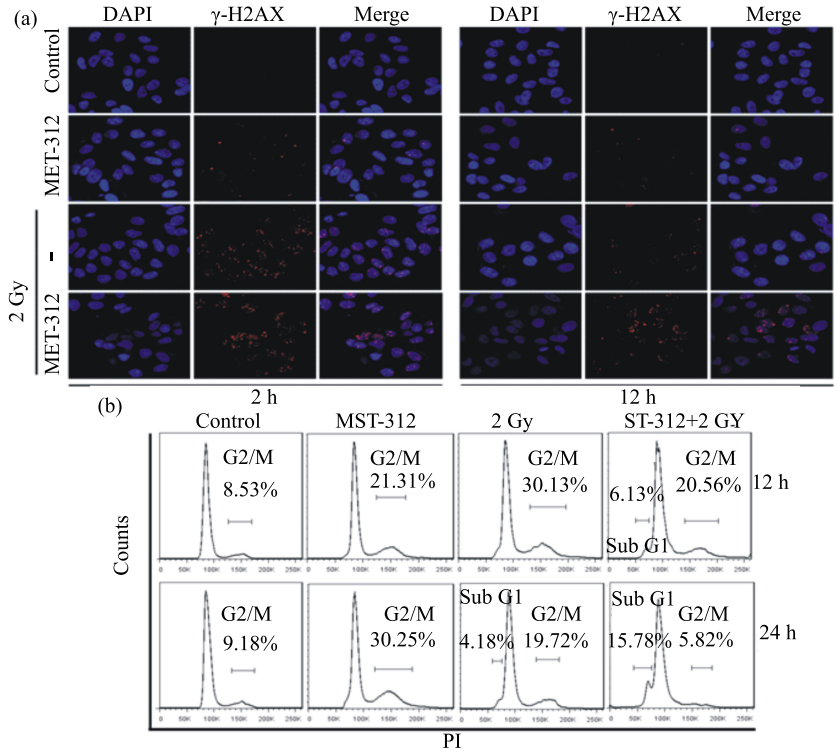

Fig. 1 (color online) Effects of MST-312 pretreatment followed by X-ray irradiation on cell cycle distribution and DNA damage in HepG2 cells. (a) Nuclear staining was done with (DAPI). (b) Sub-G1 peaks of HepG2 cells were detected by flow cytometry after propidium iodide (PI)staining. after irradiation.

References

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