4 - 54 Inhibiting Autophagy Enhances the Anti-tumor Effect of High-LET Carbon Ions via Promoting ER Stress-related Apoptosis

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Autophagy is an evolutionarily conserved catabolic process directly related to human health and various diseases. Autophagy helps cells under stress to cope with severe metabolic demand by degradation of basic cellular components. Diverse physiological or pathological changes may lead to endoplasmic reticulum (ER) stress. In response to ER stress, BiP disassociates from sensor proteins PERK, ATF6, and IRE1 and then the unfolded protein response (UPR) is activated. The UPR essentially aims at reestablishing proper ER homeostasis and eventually induces autophagy and apoptosis during acute or persistent ER stress.

In this work, by using the S180 mouse sarcoma cell line, combined *in vitro* and *in vivo* experiments after irradiation with high linear energy transfer (LET) carbon ions (CI) or low-LET X-rays, we examined how inhibition of autophagy induced by ER stress enhances apoptosis and increases the anti-tumor effect of ionizing radiation. We obtained the following results:

The combination of ionizing radiation and chloroquine (CQ) could inhibit the proliferation of S180 cells, promote cell apoptosis, and inhibit the growth of transplanted tumor. ER stress induced by ionizing radiation elicited autophagy via the IRE1/JNK/p-Bcl-2/Beclin-1 pathway, which can alleviate ER stress and maintain the proliferation of tumor cells and tumor growth. After the inhibition of autophagy by CQ, intracellular unfolded or misfolded proteins cannot be cleaned quickly and effectively, leading to apoptosis of tumor cells and enhancement of the radiosensitivity of tumor cells and xenografts. CI radiation could induce UPR signaling, and IRE1 upregulated the expression of pro-apoptotic protein CHOP, which led to the down-regulation of the anti-apoptotic mitochondrial protein Bcl-2 and increased the expression of apoptotic protein Bax. Meanwhile, X-rays exerted no effect on CHOP expression, which may be one of the reasons CI provides a greater advantage in tumor suppression, compared with X-rays. CI radiation combined with continuous administration of CQ could more effectively suppress tumor.

In summary, this work showed that high-LET CI combined with CQ could enhance the anti-tumor effect of CI radiation via the aggravation of ER stress-related apoptosis, thereby increasing the radiosensitivity of tumor cells.

4 - 55 Biological Effects of Iron Ion Radiation in Mice*

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Cosmic radiation and microgravity are the two main factors of the space environment affecting the health of astronauts[1]. The high background level of ionizing radiation is particularly dangerous during missions of long duration[2], since exposure to cosmic radiation causes oxidative damage that induces DNA lesions, cancer, cell death[3] and other adverse effects[4]. Protons and ions of high atomic number and energy (HZE) particles are the main source of radiation that astronauts are exposed to[5], and the high ionization density of heavy ions in particular causes complex DNA damage that is more difficult to repair than conventional radiation-induced damage from X-rays and γ-rays[6]. Heavy ion radiation (HIR) kills cells by a combination of direct and indirect actions. Direct actions involve a direct hit on a biologically important target by a particle or beam, and this causes more damage than indirect actions that involve water-derived free radicals[7]. Therefore, heavy ion radiation is effective at killing cells with minimal dependence on cell-cycle or oxygen levels[6], and can trigger cell death via multiple mechanisms including apoptosis, necrosis, autophagy, premature senescence, accelerated differentiation and/or delayed reproductive cell death[8]. Iron ions are of special interest in space radiation research[9], and ^{56}Fe is probably the most important ion regarding radiation exposure[10], while carbon ions are the preferred heavy ion for cancer radiotherapy[11].

As the development of manned space flight continues, the duration and distance of shuttle missions extend from those in past years. However, it has also increased the risks of central nervous system (CNS) damage which is attributed to exposure to solar particles and cosmic rays. In general, these solar particles and cosmic rays mainly consist of high linear energy transfer (LET) ions such as protons and high (H) atomic number (Z) and high-energy (E) ions[12]. Although HZE particles are a small part of cosmic rays, these highly diverse charged ions contribute a dominant share of the effective dose and they also possess a strong ability for oxidative damage which induces impairment of DNA and some other biological molecules[13]. It is known that whole-body exposure of mice to HZE particles may induce significant deficits in the CNS. Although the CNS is the most important system in the