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Therapeutic Effects of Toll Like Receptor 9 Ligand CpG-ODN on Radiation Injury

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Abstract : Exposure to ionizing radiation causes severe damage to human body and an safe and effective radioprotector is urgently required for alleviating radiation damage. In 2008, flagellin, an agonist of TLR5, was found to exert radioprotective effects on radiation injury through activating NF-kB signaling pathway. From then, the radioprotective effects of TLR ligands has shed new lights on radiation protection. CpG-ODN is an unmethylated oligonucleotide which activates TLR9 signaling pathway. In this study, we demonstrated that CpG-ODN has therapeutic effects on radiation injuries induced by γ ray and 12C6+ heavy ion particles. Our data showed that CpG-ODN increased the survival rate of mice after whole body irradiation and increased the number of leukocytes as well as the bone marrow cells. CpG-ODN also alleviated radiation damage on intestinal crypt through regulating apoptosis signaling pathway including bcl2, bax, and caspase 3 etc. By using a radiation-induced pulmonary fibrosis model, we found that CpG-ODN could alleviate structural damage, within 20 week after whole–thorax 15Gy irradiation. In this model, Th1/Th2 imbalance induced by irradiation was also reversed by CpG-ODN. We also found that TGFβ-Smad signaling pathway was regulated by CpG-ODN, which accounts for the therapeutic effects of CpG-ODN in radiation-induced pulmonary injury. On another hand, for high LET radiation protection, we investigated protective effects of CpG-ODN against 12C6+ heavy ion irradiation and found that after CpG-ODN treatment, the apoptosis and cell cycle arrest induced by 12C6+ irradiation was reduced. CpG-ODN also reduced the expression of Bax and caspase 3, while increased the level of bcl2. Then we detected the effect of CpG-ODN on heavy ion induced immune dysfunction. Our data showed that CpG-ODN increased the survival rate of mice and also the leukocytes after 12C6+ irradiation. Besides, the structural damage of immune organ such as thymus and spleen was also alleviated by CpG-ODN treatment. In conclusion, we found that TLR9 ligand, CpG-ODN reduced radiation injuries in response to γ ray and 12C6+ heavy ion irradiation. On one hand, CpG-ODN inhibited the activation of apoptosis induced by radiation through regulating bcl2, bax and caspase 3. On another hand, through activating TLR9, CpG-ODN recruit MyD88-IRAK-TRAF6 complex, activating TAK1, IRF5 and NF-kB pathway, and thus alleviates radiation damage. This study provides novel insights into protection and therapy of radiation damages.

Keywords : TLR9, CpG-ODN, radiation injury, high LET radiation
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