

871 **IRRADIATION POTENTIATES NK CELLS FOR SURVEILLANCE AGAINST PARENTAL AND CANCER STEM CELLS OF HEPATOCELLULAR CARCINOMA THROUGH LFA-1/ICAM-1 AXIS**

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Background Radiation therapy (RT) is considered an effective local treatment for downstage or definitive therapy of inoperable localized hepatocellular carcinoma (HCC). However, the potential synergistic effect of RT in combination with local tumor irradiation, immune cytokines, and allogeneic NK cells has not been explored in metastatic liver cancer. In this study, we evaluated the efficacy of combination therapy in both localized and metastatic human liver cancer models.

Methods *Ex vivo* expansion of NK cells from human peripheral blood mononuclear cells was performed by co-culture with irradiated K562 cells. HepG2/HepG2-Luciferase and Hep3B cells were injected into the right lobe of the liver or intraperitoneally injected into NOD-SCID IL2 receptor gamma chain knockout (NSG) mice. A 2 Gy RT was delivered to the peritoneum or liver tumor of NSG mice. A 12 Gy local RT was applied to the HCC subcutaneous tumor. HCC tumor spheres were generated to evaluate the function of combination treatment against liver cancer stem cells (CSCs). Finally, HepG2 and Hep3B ICAM-1 knockout (KO) cells were generated using CRISPR/CAS9 to clarify the role of the LFA-1/ICAM-1 axis in combination therapy.

Results Allogeneic NK cells enhanced recognition and conjugation of irradiated liver cancer cells through the LFA-1(lymphocyte function-associated antigen 1)/ICAM-1(intercellular adhesion molecule-1) axis. In addition, combination with RT and IL-15 also increased allogeneic NK cells' degranulation ability against ICAM-1 positive HCC cell lines. Knock-out ICAM-1 in HepG2 cells significantly reduced the lysis and cytokine release ability of NK cells. The combination therapy significantly improved therapeutic efficacy over the monotherapies against localized liver tumors in subcutaneous (HepG2) and orthotopic (HepG2 and Hep3B) mice models. Interestingly, expanded NK cells pretreated with LFA-1 inhibitor before infusion failed to enhance the therapeutic efficacy against Hep3B tumors compared to RT treatment alone. Knockout ICAM-1 in HepG2 also prevented the combination therapy in controlling tumor growth in the xenografted model. In the metastasis model, the combination therapy enhanced the recognition and lysis of EPCAM+CD133+CD24 + CSCs by NK cells, which led to the improving survival of the mice. Moreover, the deficiency of ICAM-1 in the HepG2 and Hep3B tumor spheres also reduced the cytolysis ability of expanded NK cells. The LFA-1/ICAM-1 axis also correlated with better prognosis in patients with metastasis from the PANCAN database.

Conclusions Our data suggested that combination therapy enhances the ability of allogeneic NK cells to recognize and eliminate both parental and liver CSCs through LFA-1/ICAM-1.

Ethics Approval All animal procedures and experiments were approved by the Institutional Animal Care and Use Committee of Chonnam National University (CNU IACUC-H-2019-7).

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