様式３

学 位 論 文 要 旨

研究題目

Carbon-ion irradiation together with autophagy inhibition and immune checkpoint inhibitors protect against pancreatic cancer development in mouse model（炭素イオン照射とオートファジー阻害および免疫チェックポイント阻害剤の併用は、マウスモデルにおける膵癌の発生を抑制する）

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Background: Pancreatic cancer remains fatal because of resistance to chemo-, radio-, and immunotherapies. Carbon-ion radiotherapy (CIRT) has been beneficial for patients with pancreatic cancer. The purpose of this study was to identify the mechanism by which CIRT exerts its anticancer activity, particularly in combination with immunotherapy.

Methods: We implanted murine pancreatic cancer cells treated with CIRT and autophagy inhibitor, hydroxychloroquine (HCQ) (CIRT+ HCQ) into syngeneic mice, followed by the application of a regulatory T (Treg) cell blockade using immune-checkpoint inhibitors. We compared CIRT+HCQ-treated tumors with those implanted without any treatment. Further, we also implanted CIRT+HCQ-treated pancreatic tumors into CD8+ T cell-depleted mice. To characterize immunological alterations, we conducted immunohistology and flow cytometry of implanted tumors.

Results: CIRT+HCQ-treated tumors exhibited reduced growth, higher numbers of CD8+ T cells, and lower numbers of Treg cells compared with control tumors. CD8+ T cell depletion restored growth in CIRT+HCQ-treated tumors. A Treg blockade resulted in greater tumor growth remission and elevated levels of intratumor CD8+ T cells in mice bearing CIRT+HCQ-treated tumors but not in mice bearing control tumors.

Conclusions: Treg cell-targeted therapy exerted an anticancer effect in mice bearing CIRT+HCQ-treated tumors but not in those bearing untreated pancreatic tumors by activating cancer-specific CD8+ T cells.