심포지움 1-5

Combination of Gene Therapy with Radiation Therapy

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Therapeutic Effect of Oncolytic Herpes Simplex Virus(NV1066) on Radioresistant Head and Neck Squamous Cell Carcinoma

The sensitivity of tumor cells to radiotherapy is a critical determinant of local control and potential cure in advanced head and neck squamous cell carcinoma (HNSCC). The emergence of radioresistant tumor cells is an obstacle to cancer therapy. Most radioresistant cells have a higher proportion of cells in the S-phase of the cell cycle and a lower apoptotic fraction than radiosensitive cells. HSV replication is increased in cells that have higher S-phase and lower apoptotic fractions. NV1066 is an oncolytic herpes simplex virus type-1 mutant. We hypothesized that NV1066 replication and cytotoxicity are increased in radioresistant cells. The purpose of this study is to evaluate the antitumor efficacy of NV1066 to treat radioresistant HNSCC. Radioresistant cells were selected by treating five HNSCC cell lines with repeated conventional fractionated doses of radiation (2Gy/day), using a Cs-137 irradiator, up to a cumulative dose of 70Gy. Clonogenic cell survival, apoptosis, and S-phase fractions were compared between radioresistant and parental radiosensitive cells. The two cell populations were then treated with NV1066 to examine viral replication, by the viral plaque assay and real-time RT-PCR, and viral cytotoxicity. Fractionated irradiation resulted in the selection of radioresistant cells. Clonogenic cell survival after irradiation correlated with a reduced apoptotic fraction ($P< 0.01$). Radioresistant cells had a higher S-phase fraction (42.9%) compared to parental cells (26.2%). NV1066 replication in radioresistant cells was 7.4 times higher than in parental cells ($p<0.01$). Treatment with NV1066 resulted in increased cytotoxicity of 24.5% in radioresistant cells compared to parental cells ($p<0.05$). NV1066 showed increased viral replication and cytotoxicity in radioresistant HNSCC cell lines. These findings suggest a potential clinical application for this oncolytic viral therapy as treatment for radioresistant head and neck cancers

Combination of Mutated Herpes Simplex Virus Type 1(G207 Virus) with Radiation for the Treatment of Squamous Cell Carcinoma of the Head and Neck

G207 is an oncolytic herpes simplex virus (HSV) with deletions at both (134.5 loci and a LacZ gene insertion inactivating the HSV ribonucleotide reductase gene. Ionizing radiation induces the growth arrest-inducible gene GADD34 and ribonucleotide reductase. GADD34 is a protein that correlates with apoptosis following radiation and has homology with the G207 $\gamma_1$134.5 gene. We hypothesized that the combination of radiotherapy with G207 may have a potentiating effect on viral replication and anti-tumor efficacy. The purpose of this study is to evaluate the combination of G207 with radiation therapy to treat head and neck tumors. Cytotoxicity of G207 was tested in six head and neck squamous carcinoma cell lines in the presence or absence of irradiation. For *in vivo* experiments, flank tumors in C3H/HeJ mice or in nude mice were treated with direct injection of G207 with or without radiation. All head and neck squamous cancer cell lines tested demonstrated significantly increased antitumor effect with the combination of G207 virus with radiation therapy as compared to the each single modality ($P<0.01$). Furthermore, the combination treatment effect was better than the expected additive effect of the two therapies in combination. Even the radiation resistant cell lines (SCC25, MSKQLL2, SCCVII)

were susceptible to the combination therapy. The combination of direct G207 injection with radiation therapy suppressed human and murine squamous cell carcinoma growth significantly ($p<0.05$ and $p<0.001$) as compared with control or single modality therapy. G207 enhanced the effectiveness of radiation therapy and low-dose radiation potentiated the effectiveness of G207 viral therapy in head and neck cancer. These findings suggest a potential clinical application for this combined therapy as treatment for radiation-resistant head and neck cancers