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The impact of IR radiation on the induction of bystander killing by genetically engineered ovarian tumor cells: implications for clinical use of cancer vaccines - Jehad Zweiri, University of Liverpool School of Medicine

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Cellular based therapeutic approaches for cancer rely on careful consideration of finding the optimal cell to execute the cellular goal of cancer treatment. Cell lines and primary cell cultures have been used in some studies to compare the in vitro and in vivo efficacy of autologous vs. allogeneic tumour cell vaccines. This study examines the effect of □-irradiation on a range of tumor cell lines in conjunction with suicide gene therapy of cancer. To determine the efficacy of this modality, a series of in vitro and in vivo experiments were conducted using genetically modified and unmodified tumor cell lines. Following co-culture of herpes simplex virus thymidine kinase (HSV-TK) modified tumor cells and unmodified tumor cells both in vitro and in vivo we observed that the PA-STK ovarian tumor cells were sensitive to □-irradiation, completely abolishing their ability to induce bystander killing of unmodified tumor cells. In contrast, TK-modified human and mouse mesothelioma cells were found to retain their in vitro and in vivo bystander killing effect after □-irradiation. Characterisation of tumor cell death showed that PA-STK cells underwent pyknosis (necrosis) after □-irradiation. These results suggest that PA-STK cells are not suitable for clinical application of suicide gene therapy of cancer, as lethal □-irradiation (100Gy) interferes with their bystander killing activity. However, the human mesothelioma cell line CRL-5830-TK retained its bystander killing potential after exposure to similarly lethal □-irradiation (100Gy). CRL-5830 may therefore be a suitable vehicle for HSV-TK suicide gene therapy. This study highlights the diversity among tumor cell lines and the careful considerations needed to find the optimal tumor cell line for this type of suicide gene therapy of cancer.

The focal target in disease treatment is to slaughter the dangerous cells while making close to nothing or ideally no inadvertent blow-back solid cells. Self-destruction quality treatment, as applied to the therapy of malignancy, holds the possibility to accomplish only that. A model is the addition of the herpes simplex infection thymidine kinase (HSV-TK) quality into disease cells which are therefore initiated to "end it all" when within the sight of in any case non-poisonous portions of ganciclovir (GCV). This specific harmful impact of the purine simple ganciclovir is on the grounds that HSV-TK phosphorylates ganciclovir, changing over it at last to ganciclovir-triphosphate, a poisonous compound when embedded into the DNA of these transfected cells. Similarly as with some other quality treatment procedure, and any enemy of malignancy treatment approach, its principle constraint is the particular focusing on and transduction of all tumor cells in vivo. In any case, it may not be important to transduce each tumor cell in vivo to achieve a clinically-significant enemy of tumor impact. For sure, it has been exhibited that two kinds of "onlooker tumor cell murdering" components are interceded by this methodology: (a) a "immediate" spectator impact, because of the exchange of ganciclovir triphosphate from HSV-TK-positive tumor cells into untransfected adjoining cells, (b) a fundamental immunologically-intervened observer impact because of the in vivo safe introduction of tumor-explicit/related antigens following the slaughtering of HSV-TK—communicating cells.

The hereditarily adjusted HSV-TK human ovarian disease cell line, PA1-STK, has been utilized for the therapy of strong tumors (directed intraperitoneally in patients with ovarian malignant growth). The in vitro culture of these cells within the sight of ganciclovir incited onlooker slaughtering, yet with restricted cytotoxic action in vivo. The reasoning for this technique was that PA-STK cells, infused in the region of the patient's tumor mass, could connect with, and seed themselves onto, the patient's tumor cells in vivo and, after treatment with ganciclovir, could end it all and slaughter the patient's tumor cells by a "immediate" spectator system (for example hole intersection interceded move of the phosphorylated ganciclovir from the HSV-TK positive cells to the TK negative cells. This immediate cytotoxicity could then initiate a more foundational immunological onlooker tumor-executing impact.

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