



Gateway to Improved Cancer Treatment

Scientific Program and Abstracts

Adam's Mark Hotel • April 20-24, 2004 • St. Louis, Missouri USA

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Hyperthermia is one of the most potent cellular radiosensitizers known. Hyperthermia is known to alter protein folding and alter protein-protein associations in the cell. In contrast, the lethal effects of radiation exposure are believed to result from damage to DNA, specifically DNA double-strand breaks and clustered lesions involving double-strand breaks. Thus, it is commonly believed that heat effects on the proteins involved in DNA repair pathways are responsible for heat-induced radiosensitization. Our previous studies have shown that after a radiosensitizing thermal exposure in human colon adenocarcinoma NSY cells 1) about 60% of the total amount of the DNA repair protein, Mre11, was delocalized from the nucleus into the cytoplasm; 2) much of the remaining nuclear Mre11 formed aggregates with the nuclear matrix; 3) Mre11 was disassociated from its functional partner and 4) there was an induced association between Hsp70 and Mre11. Therefore, we hypothesize that reduced availability of DNA repair protein Mre11 for the repair of damaged DNA is a basis for thermal radiosensitization induced by moderate hyperthermia. To test this hypothesis we measured the total amount of Mre11 DNA repair protein and its heat-induced alterations in four human tumor cell lines requiring different heating times at 41°C to induce measurable radiosensitization. The results show that the larger the amount of Mre11 protein in cells, the longer the heating time at 41°C required to induce radiosensitization and the heat doses required for delocalization of Mre11 protein from the nucleus are correlated with that needed to induce significant thermal radiosensitization in the four human tumor cell lines. Further, the extent of radiosensitization correlates with the extent and association between Hsp70 and Mre11. These observations are consistent with the possibility that the heat effects on Mre11 are necessary for cells to be radiosensitized. Support CA 07555605S1 and CA7163807.

Electrochemical Treatment Induces Apoptosis in Each Tumor of Mice

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Purpose:

Electrochemical treatment (ECT), called low level direct current treatment is known to one of therapeutic potentials to many diseases in the field of cancer treatment. This study was basically designed to elucidate the relationship between ECT and the prevalence of apoptosis in tumor cells using histopathology.

Methods and Materials:

For the experiment, squamous cell carcinoma (SCC)-7 strain was transplanted into right upper thigh of C3H mice, and the considerable growth of the tumor was confirmed. ECT was done to the tumors and cellular changes were observed microscopically to examine the effect of the ECT with different direct current doses. In situ nick end labeling method was employed for the analysis of apoptosis.

Results:

A significant difference was found between the above 5 Coulomb treatment groups and the control group ($p < 0.05$). In terms of tumor necrosis scores, there were significant differences between the 5 Coulomb treatment group and the 10 Coulomb treatment group, and the control group 24 hours after ECT ($p < 0.05$, $p < 0.05$). In the 5 Coulomb or the 10 Coulomb-treated group, there were noticeable increases in the number of apoptosis comparing the control group ($p < 0.01$, $p < 0.01$; $p < 0.01$, $p < 0.01$). Twenty-four hours after ECT, apoptosis of all treatment groups were significantly decreased more than in the control group ($p < 0.05$, $p < 0.01$, $p < 0.01$).

Conclusion:

These results showed that the ECT could delay tumor growth of SCC-7. Particularly in the groups treated with 5 and 10 Coulomb of ECT, the number of apoptosis in tumor mass was significantly increased more than in the control group during the period of experiment; and it suggests that the apoptosis is directly related with the histopathologically destructive changes of tumor cells after ECT.

Evaluation of Quality of Life (QOL) in concurrent hyperthermia therapy for Head and Neck cancer using a EF-2001 Lactic Acid Bacteria (BeRMKAIN)

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Purpose:

Hyperthermia therapy for head and neck cancer may make some normal tissue toxicity and affecting quality of life of patients during and after treatment. This prospective clinical trial evaluated the normal tissue toxicity and the change of the quality of life of patients in head and neck cancer patients with hyperthermia treatment alone and hyperthermia treatment plus EF-2001 as nutritional supplement.

Method:

We prospectively studied 40 patients (mean age 57, range 35-78 years) with advanced head and neck cancers who were received concurrent chemoradiotherapy. Patients were divided into two groups consecutively: BRK group (experimental group: 20 patients) received concurrent chemoradiotherapy with 1000 mg of EF-2001 three times per day during whole treatment schedule of concurrent hyperthermia therapy. NBRK group (control group: 20 patients) received concurrent chemoradiotherapy without 1000 mg of EF-2001. Quality of life (QOL) score were obtained from each patient during the treatment.

Results:

33 patients were evaluated (18 patents in BRK group, 15 patients in NBRK group). There was no statistical difference comparing BRK group against NBRK group at first treatment week. However a tendency of remarkable improvement of quality of life after first week treatment in BRK group, compare to NBRK group was observed. All score of QOL in NBRK group did not significantly change during the treatment period. Although not significantly, the pain score slight improved during the treatment in NBRK group. There was a significant improvement in all QOL score in BRK group between QOL scoring measured at first week period and four week period of treatment, but did not change compare the score measure at four week period and the end day of treatment. The most remarkable change during the treatment is QOL score of the gastrointestinal symptom and the appetite in BRK group was reported.

Conclusion:

The use of EF-2001 as nutritional supplement may be proposed as a means of improving the worsening in quality of life for head and neck cancer patients during hyperthermia treatment.

Fever-Range Thermal Exposure can Substitute for CD28 Co-Signaling to Promote IL-2 Secretion and Lipid Raft Reorganization

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Mild (Fever-range) whole body hyperthermia has been confirmed to delay or slow tumor growth in several mouse models including those of metastatic tumor growth, and is being evaluated in clinical trials for patients with cancer. The exact mechanism by which mild hyperthermia helps to control tumor growth is not well established. One potential possibility is that a fever-like state can help activate the anti-tumor immune response. In this project, we have been testing whether mild thermal stress alters the activation potential of T cells, and/or the organization of their lipid rafts. It is generally accepted that two signals are needed to fully activate resting T cells: the first involves T cell receptor (TCR) ligation while the second signal is mediated through engagement of a "co-stimulatory" receptor, such as CD28. A dramatic reorganization of lipid "rafts" within the plasma membrane is also a hallmark of productive T cell activation. For this study, we are using cells of the Jurkat T cell line, which require two receptor-mediated signals to become activated (as measured by IL-2 secretion) and are also known to undergo lipid raft reorganization upon TCR ligation. Following mild thermal exposure (39.5°C for 6 hrs), we observed that Jurkat T cells could be activated to secrete IL-2 following TCR ligation in the absence of CD28 co-engagement. On the other hand, thermal exposure did not lead to activation when followed by only CD28-ligation. We also observed that fever-range hyperthermia promotes lipid raft aggregation in the absence of any receptor ligation; 80-85% Jurkat T cells were observed to have aggregated lipid rafts after thermal exposure alone. These data suggest that mild thermal stress may lower the activation threshold of T lymphocytes by its ability to selectively regulate membrane events (e.g., organization of membrane rafts) associated with activation. This research is being supported by NIH CA71599 and CA94045 grants.

Differential Sensitivity of Several Tumor Lines to a Doxorubicin Containing Low Temperature Sensitive Liposome: Microenvironmental Effects

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