IMMUNOLOGIC ASPECTS IN CANCER TREATMENT BY MICROWAVE HYPERTHERMIA

By

[redacted]

Abstract

Whole-body and local microwave hyperthermia as applied in cancer treatment changes reactivity of the cell-mediated immunity, although the mechanisms of the phenomenon are still virtually unknown. Still more, the reaction of macrophages and lymphocytes differs significantly at 39-41°C /stimulation/ and at 42-44°C /inhibition/. Thus, the reaction of cell-mediated immunity to whole-body heating or local hyperthermia of tumorous tissues in vivo may differ significantly.

The following subjects will be presented and discussed:

I. Whole-body microwave /2450 MHz/ hyperthermia in mice /rectal temperature 41°C/:

1. Damage to cell membranes /inhibition of potassium transport and increased membrane permeability for labelled compounds/ in different subpopulations of lymphocytes /splenic, lymph-node and thymic/ and in macrophages heated to 40 or 43°C;

2. Increased intracellular level of cyclic AMP in heated lymphocytes;

3. Inhibition of lymphocyte reaction to non-specific mitogens after repeated sessions of microwave hyperthermia.

II. Local microwave hyperthermia of tumorous tissues /43°C/:

1. Regression of Guerin carcinoma in rats after local hyperthermia and enhancement of the tumor-inhibiting effect by bacterial immunostimulators /Propionibacteriae/;

2. Stimulation of cell-mediated immunity in vivo /increased reaction of spleen lymphocytes to non-specific mitogens, increased cytotoxicity of spleen lymphocytes for 51-Cr-labelled primary culture tumor cells/;

3. Increased antigenicity of heated tumor cells as measured by cancer lung colony assay in healthy animals.

Summary

Microwave hyperthermia leads to inhibition of tumor growth both after whole-body or local heating of tumorous tissues, although it was proved that the mechanism of tumor inhibition differ in both cases significantly.

Thermotolerance of mammalian cells limits the whole-body hyperthermia to a value of about 42°C, while higher temperatures /43-44°C/ may be used only for local heating of selected parts of the body.

It was demonstrated that cell temperature elevation to 39-41°C results in stimulation of glycolysis, oxygen consumption, protein synthesis and proliferation. On the other side, temperature 42-44°C leads to quick inhibition of cell metabolism, increased membrane permeability and finally to cell death. In this range of temperature the significantly higher sensitivity of cancer cells as comared to normal cells was found. It is believed that cells involved in immune reactions /lymphocytes and macrophages/ are extremely sensitive to increased temperatures both in the stimulatory /39-41°C/ and inhibitory /42-44°C/ range.

It was demonstrated recently that thermal death of cancer cells cannot exclusively account for the inhibitory effect of microwave hyperthermia on tumor growth and some other mechanisms must be involved. It is believed that reactions of the immune system play an important role in this phenomenon.

The present paper will present the summary of the results obtained in our laboratory from 1975 to 1978 and discussion in view of the most recent literature:

I. Whole-body hyperthermia.

The majority of information about the influence of the whole-body hyperthermia upon immunological status comes from experiments performed on tumor-bearing animals or patients with advanced neoplastic process. The existance of the tumor in the body changes the balance of the immune system towards its suppression. As the present concepts on mechanisms involved in this immunosuppression are not uniform, the results of experiments on the influence of hyperthermia on the immune status of tumor-bearing animals must be viewed with caution. All things considered, we wanted to evaluate the effects of hyperthermia on healthy organisms' immune responses and on immune cells from healthy donors. Some membrane properties of lymphocytes, thymocytes and macrophages exposed to moderate and intensive hyperthermia were examined. We found pronounced differences

in sensitivity of these cells to elevated temperatures. Moreover, we observed different sensitivity of different lymphocyte subpopulations /splenic, lymph-node and thymic/. Results indicated also the increased permeability of cell membranes to ions and elevation of cyclic AMP level during and after exposition to hyperthermia. This would explain the findings of other authors postulating changes in lymphocyte membranes on the basis of indirect observations.

The inhibitory effect of hyperthermia on lymphocytes' and macrophages' functions, such as transformation induced by T- and B-mitogens and phagocytosis of labelled bacteria, will be presented. It is worth to mention that some of these functions can be markedly enhanced by moderate hyperthermia. Nevertheless, antineoplastic activity of microwave treatment is not diminished by the observed immunosuppressive side effects. On the other hand, we found that hyperthermia treatment of healthy animals significantly decrease their natural resistance to cancer. This observation may be of particular value in view of the possibility of applications of whole-body hyperthermia treatments in fields other than cancer therapy.

II. Local microwave hyperthermia.

Despite the well known cell-inhibiting effects of local hyperthermia there exists evidence that cancer cells exposed to elevated temperatures in vitro increase their antigenicity in vivo. The tumor-inhibiting effect of local hyperthermia may be significantly enhanced by combination with substances stimulating cell-mediated immunity and non-specific cytotoxicity of macrophages and lymphocytes for neoplastic cells /e.g. bacterial toxins and products such as Streptolysin S, Corynebacterium parvum, interferon and interferon-inducers/. More attention should be paid to the reaction of cell-mediated immunity to local hyperthermia of tumors.

Monitoring of the immune system in tumor-bearing animals revealed stimulation of both specific and non-specific immune mechanisms by local microwave hyperthermia of tumorous tissue. Local hyperthermia, at least in some systems, acts at the same time as cancer-cell killer and immunopotentiator. The mechanism of the stimulation and its role in the inhibition of cancer cell growth remains an open question.