9 Manipulation of Physiological Parameters During Hyperthermia

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9.1 Introduction

Thermal sensitivity of tumors depends on a number of physiological parameters such as tumor pH and metabolic status. Therefore, efforts to improve the efficacy of hyperthermia treatments have led to attempts to manipulate these various physiological factors either directly or indirectly. The parameters most often studied have been tumor pH and tumor blood flow. Tumor blood flow will influence tumor temperatures achieved during the treatment, as well as oxygen and nutrient delivery to the tumor and waste by-product removal from the tumor that can ultimately impact on tumor pH. Thus, manipulation of tumor blood flow can affect many physiological parameters in the tumor. This chapter will cover some of the methods and results used to manipulate these physiological parameters.

Murines with transplantable tumors have been used in the majority of in vivo studies investigating the manipulation of physiological parameters to enhance tumor thermal sensitivity. It is very important to remember the large step necessary to get these experimental techniques which appear to work in rodents into the human cancer clinic. Although spontaneous tumors in privately owned dogs appear to be a useful intermediate animal model between murines and humans, the ultimate validation of the efficacy of any method must be achieved in the human clinic, and information from human studies is currently very limited to nonexistent.

9.2 Tumor pH

In the mid 1970s, several investigators showed that decreasing extracellular pH enhanced cellular thermal sensitivity and inhibited thermotolerance development for in vitro preparations, particularly for pH values <7.0 (Gerweck and Rottinger 1976; Gerweck 1977; Nielsen and Overgaard 1979). However, cells allowed to chronically adapt to the acidic extracellular pH are not as sensitive to hyperthermia as cells acutely exposed to low extracellular pH conditions (Hahn and Shi 1986; Chu and Dewey 1988; Cook and Fox 1988). Cells chronically exposed to low extracellular pH conditions are able to adjust their intracellular pH back to a normal range (Cook and Fox 1988; Chu et al. 1990; Griffiths 1991). Acute decreases in intracellular rather than extracellular pH are better at enhancing thermal responses (Hofer and Mivechi 1980; Chu et al. 1990). Therefore, methods to acutely decrease tumor pH, and in particular intracellular pH, immediately before or during hyperthermia treatments have been investigated. These techniques include induction of hyperglycemia, use of various ion channel blockers, and inhibition of mitochondrial respiration. Although partial or complete obstruction of blood flow will also result in acidification of tumors indirectly, this technique will be discussed in Sect. 9.3, addressing tumor blood flow.
9.2.1 Cellular pH Regulation

The major mechanisms by which mammalian cells regulate intracellular pH are: (a) the sodium-hydrogen (Na\(^+\)/H\(^+\)) exchange system, (b) the Na\(^+\)-dependent chloride-bicarbonate (Cl\(^-\)/HCO\(_3\)^-) exchange system, and (c) the Na\(^+\)-independent Cl\(^-\)/HCO\(_3\)^- exchange system (for reviews see Roos and Boron 1981; Mahnensmith and Aronson 1985; Tannock and Rotin 1989).

The first two mechanisms involve primarily the removal of excess H\(^+\) in acid-loaded cells while the last mechanism participates in decreasing the intracellular pH in alkaline-loaded cells. The Na\(^+\)/H\(^+\) exchanger uses the energy of the Na\(^+\) gradient that exists across the cell membrane to transport H\(^+\) out of the cells. The Na\(^+\)-dependent Cl\(^-\)/HCO\(_3\)^- exchanger moves HCO\(_3\)^- into the cell to prevent intracellular pH from severe acidification. The Na\(^+\)/H\(^+\) exchange system has been detected in every mammalian cell line examined but the activity of the Na\(^+\)-dependent Cl\(^-\)/HCO\(_3\)^- exchanger differs considerably in different cell lines. The Na\(^+\)/H\(^+\) exchange system and the Cl\(^-\)/HCO\(_3\)^- exchange system clearly account for almost all the intracellular pH regulating ability in mammalian cells (Roos and Boron 1981).

To acidify intracellular tumor pH, the mechanisms by which a cell regulates its intracellular pH must be overcome. This may sound like an easy task but cells have a tremendous ability to maintain homeostasis (i.e., pH neutrality) in their environment.

9.2.2 Hyperglycemia

Since tumor cells have a high glycolytic capacity, stimulation of glycolysis with glucose administration to increase production of acidic metabolites is one way of reducing pH in the tumor tissue. Therefore, hyperglycemia has been studied extensively to decrease tumor pH. Figure 9.1 is a

![Diagram](Fig. 9.1. Proposed mechanisms responsible for decreases in tumor blood flow and tumor pH following induction of hyperglycemia. (Modified from Vaupe and Okunieff 1988))