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Research Article

Is it Possible to induce the “Spontaneous Regression” of Cancer? A Mechanism of Activation for the Innate Immune Response

Józef Oleksyszyn*

Division of Medicinal Chemistry and Microbiology, Wrocław University of Technology, Poland

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Abstract

The article deals with a theoretical model of the mechanism of the spontaneous regression of tumor, involving the activation of innate immune response. After stimulation the cells of the immune system, use glycolysis for ATP synthesis. Lactic acid, the final product of glycolysis, acts as inhibitor of such activation. Therefore, highly glycolytic cancerous cells form the environment (hypoglycemia with high level of lactic acid), which is strongly inhibitory to immune cells activation. Starvation, KD (ketogenic diet) and Coley's toxin induce hypoglycemia and in the long term should also lower lactic acid level. After a few days of such treatment the glucose level could increase naturally due to gluconeogenesis or by the application of significant dose of glucose. Such procedure should induce activation of immune cells response (high glucose and low lactic acid levels) and a spontaneous regression of cancer. If lactic acid concentration remained still too high and thus inhibit the activation of immune cells, the organism would require alkalization because sodium lactate is not inhibitory to the activation of immune cells. The model explains the cases of spontaneous regression described in literature and could be easily verified experimentally.

Introduction

Spontaneous regression of cancer is well known for a long time. It is a very rare phenomena, estimated to occur an one per 100 000 cancer cases [1,2]. Regression is commonly associated with the strong acute infection or vaccine therapy [3,4]. Dr William Coley introduced, so called Coley's toxins, to the clinic at the end of XIX century [5]. It was a mixture of heat-killed *Streptococcus pyrogene* and *Serratia*

marcescens. In Coley's experiments, it was observed that regression occurred within hours of injection the toxin. Sometimes, the dosing needed to be repeated for a long time, up to 6 to 12 months, to see therapeutic effect. Clearly, the data indicated the involvement of innate, nonspecific immune response [4]. In 2012, Karbach et al. [6] reported results of Phase I Clinical trial of Mixed Bacterial Vaccine (Coley's Toxins) in cancer patients. This time, a new biochemically well-defined, and current good manufacturing practice-compliant mixed bacterial vaccine preparation (Coley's toxins) was investigated, and very promising results was generated. Spontaneous regression, however can also happen without any bacterial vaccination [7-9].

***Correspondence:** Józef Oleksyszyn, Division of Medicinal Chemistry and Microbiology, Wrocław University of Technology, Poland, E-mail: jozef.oleksyszyn@pwr.wroc.pl

The Hypothesis

In 2010, Nikan [10] reported analysis of the more than one thousand cases of spontaneous regression of cancer, and concluded that the regression are accompanied by hypoglycemia and hypoxia. When low glucose levels should impair the erythrocyte activity it is not surprise to noticed hypoxia under hypoglycemic conditions. A large solid tumor tissue with increased glucose consumption induces sometimes systemic hypoglycemia. However there is doubtful that hypoglycemia itself will induce spontaneous regression of cancer [11]. Starvation, ketogenic diet, calorically restricted ketogenic diet all of these slow down the tumor growth [12] and are intensively investigated as the alternative approach for the cancer treatment, that is able to induce tumor cell necrosis (see the recent progress in the review [13]). What is intriguing, repeated application of the Coley's vaccine, should induce the deep hypoglycemia also, because the bacterial infection commonly induce hypoglycemia [11,14]. It seems there is a strong connection between hypoglycemia and spontaneous regression of cancer but the nature of this is not clear. At present we need to review recent studies regarding the activation of immune cells that are the part of the innate immune system. It seems that all these cells utilize the glycolysis for ATP synthesis, after the activation [15-18]. Tumor tissue environment due to an extensive glycolytic metabolism of cancerous cells are highly hypoglycemic therefore activation of innate immune cells system is deeply inhibited. This is only one part of the problem because the final product of glycolysis, lactic acid need to be transported outside of the cells to assure the continuation of glycolysis. The specific transport system is the proton-linked monocarboxylate transporter, which cotransport protons and lactate anions following the concentration gradient [16]. Such transporter is competitively inhibited by the large extracellular concentration of lactic acid. In tumor tissue a large accumulation of lactic acid was observed even up to 40 mM [19]. Thus metabolism of tumors cells at least at two points inhibit activation of immune cells – by depleting of glucose and increasing extracellular concentration of lactic acid. Actually we have no idea what concentration of glucose is required for the immune cells activation and at which lactic acid

concentration the inhibition of such activation really happens. This need to be subject of future investigation. However, we easily could reach the therapeutic window (glucose level needed for activation of the T cells at lactic acid level that is not inhibitory for such activation) by initiation of the dynamic change in the glucose level. We would like to hypothesize that these happen during observed cases of spontaneous regression (Figure 1).

Starvation, calorically restricted diet, ketogenic diet, calorically restricted ketogenic diet, repeated vaccination with Coley's toxin, all of these will induce hypoglycemia. If we keep such conditions for duration of several days, depleted glucose level, should lower concentration of lactic acid in tumor tissue also (we have no idea how much time such process might take). The signal of hypoglycemia will switch on the gluconeogenesis and glucose level will slowly start to grow. Low lactic acid concentration in tumor tissue (because of recent hypoglycemia), and the growing concentration of glucose could trigger activation of the cells of the innate immune system. The result will be observed as the spontaneous regression of cancer.

The large concentration of lactic acid in tumor tissue (up to 40 mM [19]) could be not easy to remove. However, it was noticed by Fischer et al. [16] that sodium lactate has no inhibitory effect on the T lymphocyte activation. The acidic pH of the organism could be easily brought up by the oral application of the sodium bicarbonate. Bicarbonate inhibits metastases of tumor cells and is being investigated as the potential drug [20]. The Figure 1 clearly illustrated how difficult is to reach the “therapeutic window” and, explain why spontaneous regression is very rare, but possible.

Evaluation of the Hypothesis

The potential treatment should include the application of ketogenic diet, calorically restricted ketogenic diet or simple starvation, lasting several days, together with the alkalization of the organism by the application of sodium bicarbonate (e.g. a few glasses of water with ½ teaspoon of baking soda and 2 teaspoon of lemon juice). After several days, (probably 2-3 days of starvation or 4-6 days of calorically restricted ketogenic diet) the

Figure 1: Hypothetical changes in glucose and lactic acid concentrations during spontaneous regression of cancer. Line A – concentration of lactic acid inhibitory for the activation of immune cells. Line B – concentration of glucose required for the activation of immune cells.

level of the glucose needs to rapidly be brought up (e.g. glass of water with 30-60 g of sugar). The procedure needs to be repeated a few times until a positive sign i.e., spontaneous regression of tumor is observed. The experiments on animal models of human cancer are in progress.

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Conflicts of Interest

The authors do not declare the conflict of interest.

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