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NUTRITIONAL MANIPULATION: EPIGENETIC EFFECT IN CANCER

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Absract – *We discuss the role of nutritional science in cancer and summarize the need for this perspective. It is now clear that bio-behavioral factors not only affect cellular immunity but both directly and indirectly modulate fundamental processes in cancer growth, including inflammation, angiogenesis, invasion, and metastasis. It is wrong and simplistic to think that nutrition in cancer patients consists only in some food exclusions. The ultimate goal, therefore, is to restore or enhance the physiological intracellular metabolic pathways, which can be altered in numerous situations. In case of neoplastic disease, the targets are: 1: androgens and insulin-like growth factors (IGF) levels; 2: immunological tolerance; 3: extracellular acid-base balance. The "diet" then should become a real manipulation to promote nutritional therapies, by modulating hormonal parameters, cytokine, as well as acid/base balance.*

KEY WORDS: *Nutraceutic, Acid/base imbalance, Cancer diet.*

INTRODUCTION

In the last twenty years we have seen a gradual change in medicine. From a simple approach cause/effect, it has been slowly growing a new vision, which inextricably links the patient, taken as a whole, the disease that afflicts him, and the environment in which he lives[1]. This is undeniably happening in the world of research and cancer therapy, where are increasingly developing new models of Integrated Medicine (such as the Center for Integrated Medicine Local Health Unit 19 Hospital Pitigliano, Grosseto) and more effective intervention strategies, not only as cell target, (between good cells and bad cells), but to a specific attempt to influence the microenvironment in which these cells live, proliferate and die. This is now possible even modulating nutrition, the environmental component in which we live easier and at the same time more complex to use. In recent years, we are experiencing a boom of new anticancer molecules and methods; anyway, every system should be validated scientifically, and should not interfere with conventional therapies. Every day we are dealing with patients who are cured through the Internet by integrating conventional therapy with vitamin C, Essiac, Gerson, etc. without the knowledge of pharmacokinetics and pharmacodynamics of these molecules which sometimes interfere with the therapy itself. This is not integrated medicine. Integrated Medicine consists rather in the integration of a team of professionals who interact individually, according to their expertise towards a common goal, without illusions but with extremely significant results. The nutrition and integration thus understood, in association with the usual protocols chemo and radiation, are called "Nutritional Manipulation".

The ultimate purpose of this new discipline, is to make the extracellular matrices inhospitable

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and unsuited to the neoplastic cell, (making it more difficult to proliferate), intervening on the expression of oncogenes directly involved in the pathogenesis or in the maintenance of cancer. In this way, the body will be prepared to face chemotherapy/radiotherapy treatment, and will preserve or improve body lean mass.

The ultimate goal, therefore, is to restore or enhance the physiological intracellular metabolic pathways, which can be altered in numerous situations. In case of neoplastic disease, the targets we are going to focus our attention are 1: the level of androgens, and insulin-like growth factors (IGF); 2: the immunological tolerance; and 3: the balance of matrices buffer system.

Consequently, the relationship between overweight/obesity and oncologic pathology is made clear: in fact, we now know that body fat is an important endocrine organ, producing sex hormones, cytokines, and many inflammatory mediators, all molecules involved in the pathogenesis and progression of neoplastic disease.

PROJECTS DIANA: INSULIN AND GROWTH FACTORS

Projects DIANA are still in progress, under the guidance of Dr. Franco Berrino (Istituto Europeo di Oncologia 2, Milano). Aim of the study is to assess the impact of food strategies on recurrence of breast cancer. The name comes from diet and androgens, because the first DIANA projects were primarily intended to lower the blood concentration of male sex hormones (androgens), which more than others contribute to development of breast tumors and metastases. But Diana is also the name of the goddess who protects women, maternity and breastfeeding[2].

The diet is based on the reduction of simple sugars, fats and animal products, and the increase of unrefined grains, legumes and vegetables. The results were and are extremely significant.

Whatever the type of malignancy (except perhaps a few exceptions) due to an inherited mutation, acquired or supervening, cancer starts from a DNA damage, or from control mechanisms failure, which may affect oncogenes or tumor suppressor genes. Any somatic cell can lose differentiation if accumulates along its life a sufficient number of unrepaired damages. It is actually believed that there are biological niches of stem cells that somehow acquire differentiation, and could affect virtually every organ. Cancer is therefore definitely a systemic disease, and should be treated as such. On the other hands cell proliferation, as well distance migration (metastasis), is closely linked to hormones or hormone-like substances, such as sex hormones, insulin and growth factors (IGF-1). If a mutated cell does not receive any stimulus for growth and proliferation, it simply will stay, and sooner or later it will die or will be destroyed; if it is in a fertile environment, it will multiply indiscriminately, giving rise eventually to the tumor mass itself. A food such as milk for example, manages to multiply the weight of a calf in a few months, and not because it is particularly nutritious, but because the impact that the high content of lactose and casein have on insulin and factors growth. The same thing is said for the red meat and animal proteins in general[3]. It's wrong and simplistic, however, to think that nutrition in cancer patients is simply a diet of exclusion of certain foods. Milk and red meat in fact could be used when stimulation of cellular hypertrophy is needed. Nutritional and integrative protocols in cancer should be managed by a highly qualified and trained team, coordinated by the oncologist, including necessarily the figure of a nutritionist specialist in Nutrition Science with specific expertise in nutraceuticals.

IMMUNOLOGICAL TOLERANCE: IMMUNOLOGY OF PREGNANCY AND CANCER

Pregnancy is a physiological phenomenon unique in nature, consisting of the symbiosis between different organisms; in fact the fetus carries a genetic paternal half derivation[3]. This type of coexistence requires a refined regulation of the maternal and fetal immune system, to ensure an efficient protection against infections, and allows the embryonic "stranger" tissue invasion process, avoiding those immune maternal reactions, that are harmful to the embryo.

Years of studies and research have only partially clarified the ways in which this immunological reorganization is accomplished. To date, fetus tolerance by the maternal immune system remains an enigma and, in some respects a real immunological paradox[3].

The major subset of immune cells present in the maternal decidua, with an important role in the immune response of pregnancy (in addition to the Natural Killer cells which are not discussed here) is represented by T lymphocytes. These cells are in contact with the trophoblast, but not recognizing as foreign cells the trophoblastic MHC- (Ia) - negative, they do not attack it. As it is known, there are two main subsets of T helper CD4+: Th1 and Th2, characterized by a different cytokine secretion profile and different functions within the immune response.

Th1 cells secrete IFN-γ, TNF-β, IL-2 and TNF-α (type pattern 1). Th1 cytokines activate macrophages and are involved in cell-mediated responses (cellular immunity), important in infection resistance by intracellular pathogens and in the reactions of cytotoxicity and delayed hypersensitivity. Th2 cells secrete IL-4, IL-5, IL-6, IL-10 and IL-13 (pattern type 2) and are more involved in antibody production (humoral immunity) and resistance to extracellular pathogens. Th1 cells and Th2 are mutually inhibitory. In particular, IL-10, produced by Th2 cells, inhibits the development of Th1 cells by acting on antigen-presenting cells, while IFN-γ produced by Th1 cells, prevents the activation of Th2 cells. This polarization of the immune response is actually an oversimplification, since there are other patterns of cytokine secretion not covered in this model[5]. Depending on the prevalence of one of secretory pattern (type 1 or type 2) and the time sequence with which it is realized, the immune response results differently modulated. During pregnancy humoral response (type 2) is enhanced, while the cell-mediated is attenuated (type 1)[6].

Several lines of evidence have shown that cytokines Th1 have a negative effect on pregnancy. In decidua they promote abortion inhibiting the trophoblast invasion; in particular TNF-α stimulates apoptosis of human trophoblast and IFN-γ enhances TNF-α-mediated trophoblast killing. These cytokines also stimulate decidual macrophage activity level, inducing production of potentially embryotoxic factors[7]. In contrast, Th2 cytokines stimulate growth and invasion trophoblast favoring the development of pregnancy[8].

The currently most accepted hypothesis, with some exceptions, is based on the fact that both in decidual that in peripheral blood, during pregnancy, Th2 cells predominate, as a result of a Th1-Th2 shift under the influence prevalent, but not exclusive, of cytokines[9].

For the successful outcome of pregnancy, what appears more relevant seems to be the ratio between the relative levels of the different cytokines, their receptors and antagonists, rather than their absolute concentrations[10]. Once induced, Th2 shift is maintained throughout pregnancy until the final stages. The conclusion is that the phenomenon of pregnancy, understood as an explosion extremely controlled growth of blasts, is tolerated by the immune system, through the rearrangement of a complex communication system, mediated by cytokines. The same thing happens in the phenomenology of cancer: somehow the tumor mass in growth is also tolerated by the immune system, which, though predominantly Th2-oriented, can lose much of its immunological surveillance, intended as cytotoxicity. The same explosion of allergic diseases, could be related statistically to this phenomenon. It would be interesting develop studies that correlate cancer incidence in a cohort of subjects allergic/atopic.

The immune system, anyway, resides for 4/5 in the gut: it is not wrong to pay attention on how to maintain balance in this complex organ, through the choice of foods and / or supplements.

MAINTAINING THE ACID-BASE BALANCE, DOES NOT MEAN THAT BICARBONATE CURES CANCER

In the early last century Otto Warburg postulated that tumor masses were acidic because of the high production lactic acid rate[11]. Subsequently, measurements made in many solid tumors using microelectrodes have confirmed this hypothesis[12]. In the following years many studies have finally revealed that generally solid tumors, although keeping an acid extracellular pH (pHe), have an intracellular pH (pHi) neutral/alkaline, thus generating a pH gradient intra/extra cellular[13]. Among other things, the grading of acid correlates with lower efficacy of chemotherapy in general, especially those weakly basic (e.g. Doxorubicin), since chemotherapics slowly enter in cells relatively alkaline and are partly seized by acidic matrices peritumoral[14,15]. The increase in pHi involves, ultimately, alteration of a whole series of processes pH related, such as glycolysis, synthesis, transcription and repair of DNA, as well as generally compromises genetic stability, increasing the competitiveness and growth capacity of cancer cells, compared to healthy cells[16,17]. The tumor microenvironment is also characterized by a marked depletion of oxygen (hypoxia), and high levels of lactate and extracellular acidosis (which from now will be called acidemia, very different by acidosis)[18]. These changes are caused by a combination of factors: poor tissue perfusion, uncontrolled proliferation and intracellular metabolic dysregulation[19]. The levels of most marked abnormalities relate primarily to glucose metabolism. In physiological conditions, the pyruvate produced at the end of the anaerobic glycolysis is further processed in the Krebs cycle, with subsequent oxidative phosphorylation; otherwise in hypoxic condition, it is fermented to lactic acid; it follows that more glucose molecules are used, the excess of lactic acid is generated and placed in the connective tissue or extracellular matrix. This explains why the tumor peripheral tissues are more acidic than normal; it also adds the fact that the chemotherapy, although well directed and used for their mechanism of action, induces cellular

damage with further production of acid radicals: this process gradually leads to a state of latent connective acidemia, increasing the grading. When, for lack of adequate information or gluttony, that patient should also eat foods that leave acidic ashes (e.g. Pasta and bread made with white flour, industrial cakes, cow's milk and dairy products, red meat, acidic water, etc.), the level of acidemia increases further; in some foods, also, there are micronutrients such as IGF1 or profiline representing a delicacy for the cancerous cells; not everyone is aware of how these foods, although very common and known, are a true ally of the tumor cell and therefore should be strictly excluded from diet. Is also important to consider the adipose tissue as a producer of cytokines, which promote the growth of tumor cells; often it happens that patients eat more thinking to face general asthenia induced by chemotherapy. In a renowned 1995 work, 40 patients with tumors of different histological types, locations and dimensions have been studied: the results have shown that all patients develop intracellular generalized acidosis, which could be modified with the use of alkalizing foods and with the result of reducing the cellular degeneration[20]. In any case, although the situation is in many ways still controversial, it is certain that the pHe of solid malignant tumors is moved down (pH 6.5-6.9 against a range of 7.2-7.5 of healthy tissue)[21] due to the massive export of acid in the extracellular matrix by the tumor itself, and that by acidifying the tumor cells increases their rate of metastasis[22]. These observations has led to the so-called "hypothesis of aggressiveness acid-mediated", in which the tumor-derived acidic molecules promote the aggressiveness and the ability to metastasize. On the other hand in the last few years new prognostic genetic tests (pharmacogenomics) are slowly growing, which are based on the ability of the genotype to prefer more or less anaerobic lactate-metabolism[23,24]. In this regard it is interesting to consider the work of the group of Arizona Cancer Center, where researchers have shown, in vitro and especially in vivo, interesting results in the treatment of metastatic breast cancer: through administration of $NaHCO_3$ orally. They have found, together with a tumor pHe rise (but not in the healthy tissue), reductions in spontaneous metastasis and infiltration rate. The researchers conclude that although many mechanisms have yet to understand, low pHe are related to the release of active cathepsin B, a major protease involved in the process of matrix remodeling. In fact, low-pHe and hypoxia greatly affect the effectiveness of anticancer therapy: hypoxia confers radio-resistance; the acid extracellular gradient can confer resistance to chemo instead hypoxia probably falls into an effective defense mechanism of cancer cell to keep the hyperacidity[25]. Even in acidemia treating we should be very careful, and remember to start from the cell physiology, which in this case is governed by well-defined cycles and rhythms. The collagen and extracellular matrices in fact, is subject to a phase change from sol to gel in the course of the day, where in the morning prevail catabolic and inflammation phenomena, subsequently arises the reconstructive phase. So, it is appropriate to use mixtures of carbonates and bicarbonates to increase alcalemia exclusively in the afternoon hours. Indeed oxidative stress with the consequent acidemia is absolutely necessary during the phases of aggression with chemotherapy for more effective treatments. It is not always correct, therefore, to "alkalinize". The restoration of the physiological circadian rhythm is mainly important, as pulsatile secretions of the pineal gland, largely depends on the release of other hormones. In addition, a food, a nutraceutical, as well as a drug (in this case an antineoplastic) can act or be absorbed in a different manner depending on the extracellular matrices phase state.

CONCLUSIONS

The neoplastic disease is definitely a priority of our time. Its growth is linked to longer life expectancy and a significant change in lifestyle[26].

Among the factors identified in this study, in addition to cigarette smoke, viruses and radiation, it appears, clearly and unequivocally, the diet. The real risk of getting cancer is a combination of several factors; for this reason, new treatment strategies no longer are concerned exclusively on single cancer cell, but on the complex peritumoral environment[27].

Furthermore, it is understood that the preventive measures are not only limited to the stages that precede the onset of the disease (primary prevention), but can also be applied when the disease is already present (secondary and tertiary prevention).

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The Authors declare that they have no conflict of interests.

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