Hypothesis
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A Potential Concept In The Management of Tumors With Modulation of Prostaglandin, Nitric Oxide and Antioxidants

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Prostaglandins (PGs), nitric oxide (NO), free radicals and chronic inflammation play a major role in tumorogenesis. We have found *in vivo* that PGs suppress antibody production; reduce serum iron, and modulate bone marrow function. Tumors are associated with immunosuppression and anemia. We have hypothesized that the over-production of PGs is responsible for immunosuppression and anemia in conditions associated with increased production of PG such as tumor, and that PG inhibitors might help reversing immunosuppression and anemia, and play a role in eradication and prevention of tumors. This is supported by reports that demonstrate the immunosuppressive effects of PGs in tumors. PG inhibitors have also been shown to be crucial in the prevention of tumors such as esophageal and colon cancers. Others and we have found that high NO production was encountered in patients with cancer while antioxidants are decreased. Evidence supports the efficacy of PG inhibition in malignancies, and the concept of PG inhibition, NO modulation, anti-oxidants, immunotherapy with antibody or immune cells, and anti-inflammatory agents when used in the prevention and management of malignancies are discussed.

KEY WORDS: prostaglandins, nitric oxide, cancer, NSAIDs, anemia, immunity, inflammation

INTRODUCTION

In-vitro studies have shown that the addition of malignant cells synthesizing large amounts of PGs to spleen cells stimulated with sheep red blood cell (RBC) caused a marked suppression of antibody production in the sheep RBC. The introduction of a PG inhibitor prevented this suppression[1,2]. In 1977, it was proposed that the soluble mediator responsible for such immunosuppression might be PGs. We studied the effects of PGA1 on antibody production against thymus-dependent antigen (Ag) (Sheep RBC) and thymus-independent Ag (*E. coli*) in rabbits. The results had shown that PGA1 causes a marked suppression of antibody production during primary and secondary immune response[3,4]. It was hypothesized that PG's might be responsible for immunosuppression encountered in conditions associated with increased PG production (Figure 1). We also studied effects of PGs on hematological and biochemical parameters under various stresses to further understand how the release of large amounts of

PG is involved in the pathogenesis and alteration of these parameters in malignancies. The effect of PG's on serum protein, albumin and globulin during antigenic stimulation was studied[5]. PGA1 causes a significant reduction in serum albumin and changes in serum total protein. It was postulated that the low serum albumin associated with various chronic or acute illnesses might be related to the high PG synthesis associated with these conditions, and inhibition of PGs might be useful in treatment and prevention of malignancies[5,6].

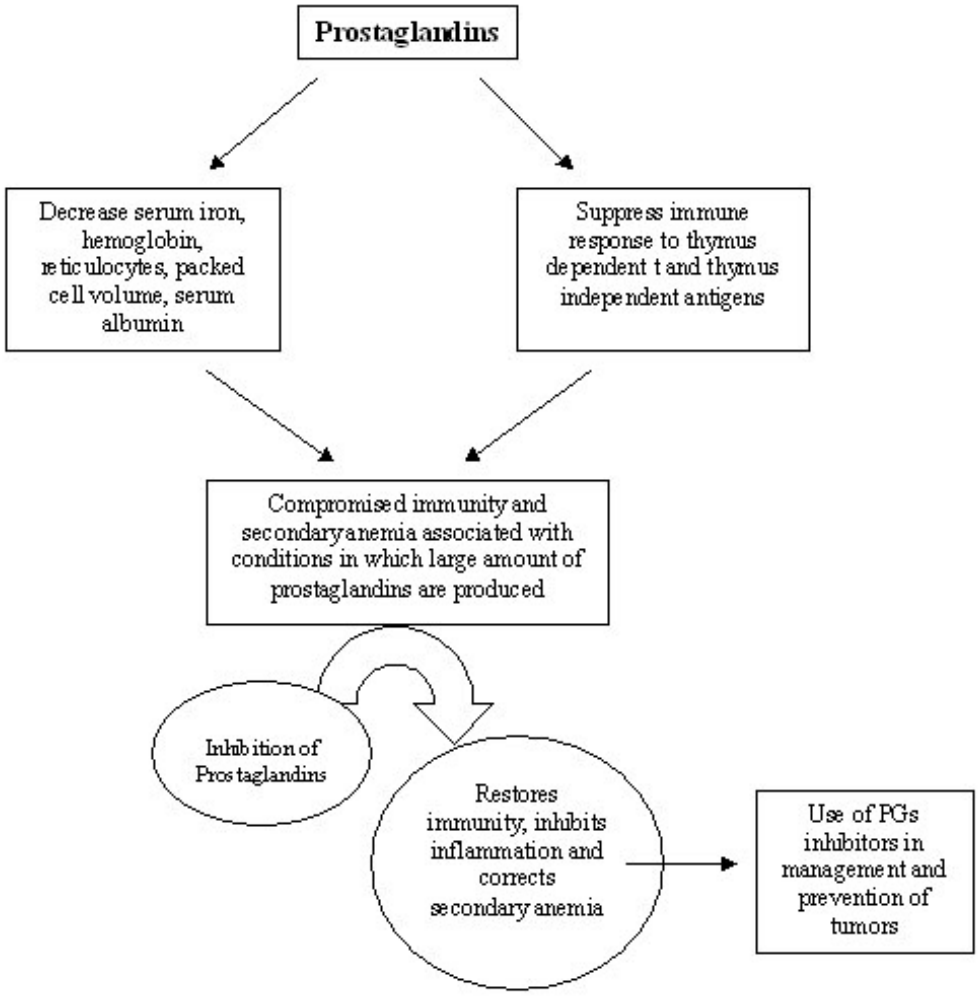

Figure 1: Proposed concept for etiology of immunosuppression and secondary anemia and their possible correction with use of prostaglandin inhibitors

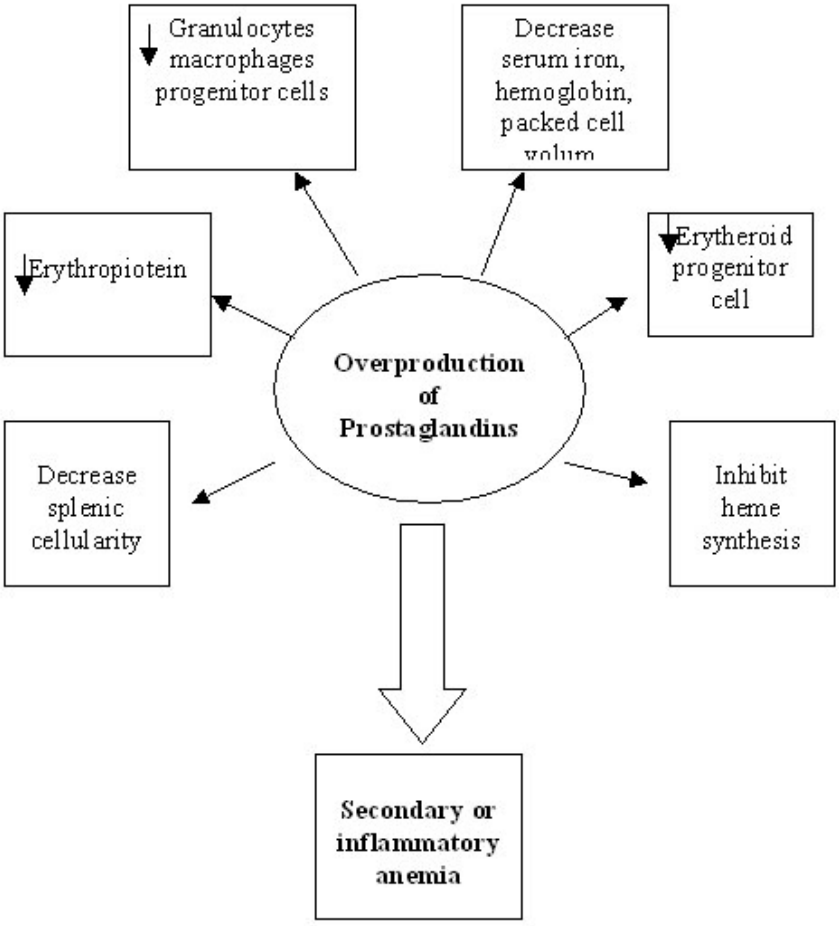

Figure 2- The concept for secondary anemia caused by overproduction of prostaglandins

The effects of PG's on hemopoiesis and hematological indices have been studied during acute and chronic blood loss[7,8,9]. PGE2 caused significant lowering of serum iron and a greater reduction in hemoglobin, RBC and packed cell volume, and decreased reticulocyte counts after acute or chronic blood loss. PGE2 decreased leukoid series after acute blood loss[8]. Following chronic blood loss, PGE2 caused a marked depression of promelocyte, myelocyte, metamyelocyte, segmented cells and total myeloid in

bone marrow in comparison to normal and chronically bled animals[9]. It was postulated that PG's might be involved in pathogenesis of secondary anemia, and that PG inhibition might be of value in the management of anemia resulting from malignancies (Figure 2)[10].

The effect of PGF2 alpha on blood sugar was studied; PGF2 alpha causes significant lowering of fasting blood sugar in normal rabbits (11). PGE2 ameliorates hyperglycemia that followed bleeding and ether anesthesia[12]. Similar results were obtained with use of PGE2[13]. PGE2 causes significant suppression of hyperglycemia and elevation in alkaline phosphates following bleeding; and inorganic phosphorous was mildly lowered by PGE2[14]. Therefore, it was postulated that changes in calcium, inorganic phosphorous or blood sugar might be related to increased PG by cancer cells. Clinically, we showed the beneficial effects of PG inhibitor, indomethacin, in the management of chorionic carcinoma and basal cell carcinoma[10,15].

PGs have considerable effects on immune response. In late 1970's and early 80's, *in-vitro* studies demonstrated the immunosuppressive effect of PGs[16,17,18,19]. PGE inhibits human T-cell proliferation and lymphokine production, and suppresses IL-2 production[20,21]. PGE2 exerts selective regulatory effects on human B-cell responses[22]. PG's stimulate suppressor cells to release suppressor lymphokines[23]. PG's inhibit the murine natural killer-cell activity[24]. PGE2 has many immunoregulatory functions including the inhibition of Ia expression, IL1 and TNF production by Mphils and Ag induced T-cell proliferation, the promotion of suppressor T-cell differentiation, and immunoglobulin secreting cells[25]. PGE2 reduces expression of type 1 immune responses such as a contact hypersensitivity reaction[26]. PGE2 has significant immunosuppressive effects on cell-mediated immunity[27]. PGE1 and E2 have immunosuppressive effects on T-cell and Mphil functions. PGE2 enhances the cellular spread of herpes virus probably by suppressing natural killer-cell activity[28].

Prostaglandins, immunity and Cancer

Evidence from clinical and preclinical studies indicates that PGs participates in carcinogenesis, inflammation, immune response suppression, apoptosis inhibition, angiogenesis, and tumor cell invasion and metastasis[29]. Studies demonstrate defective Ag presentation, T-cell defects, and premature thymic atrophy in cancer patients and tumor-bearing animals (30). Recent review showed that tumor cells inhibit the physiological function of immune cells, and that NSAIDs restore the immune function[31].

Reports showed that PG's are produced in excess from malignancies and are implicated in the growth and spread of tumors[32,33]**.** The addition of MC16 tumor cells to cultures of cells inhibits immune response in sheep RBC; PG synthetase inhibitors block this inhibition[34]. Findings indicated that probably all tumor cells possess immunosuppressive factor(s), which may account for their apparent lack of immunogenicity and the failure of proper immune responses in the tumor-bearing hosts[35]. PG's can modulate a variety of immunological responses and thereby play an important role in host antitumor immunity[36]. Elevated tumor COX-2 and PGE2 levels have been implicated in angiogenesis, tumor invasion, resistance to apoptosis, and suppression of antitumor immunity[37]. Studies suggest that COX-2 assists in determining and defining the metastatic signaling pathways that promote the breast cancer progression to metastasis[38].

PGE2 can act as a feedback inhibitor for cellular immune processes[39]. COX-2 expression is associated with development of aggressive breast cancer[40]. PGE receptors EP1 are associated with breast cancer development, and selective PGE receptor EP_1 antagonists may possess chemo-preventive effects through the induction of apoptosis[41]. The mechanisms of carcinogenesis related to COX and PG include oncogene synthesis and expression, upregulation of COX, accelerated cell replication, failed apoptosis, viral activation, and disruption of signaling pathways, autoimmunity, immunosuppression, angiogenesis and metastasis[42]. Recent review shows that studies indicate that COX-2 produced in breast cancer cells may be vital to the development of osteolytic bone metastases in patients with breast cancer, and that COX-2 inhibitors may be useful in halting this process[43]. Other review discussed impact of overexpression of COX-2 in tumors leading to an increase in PG levels, which affect

angiogenesis, inhibition of apoptosis, stimulation of cell growth as well as the invasiveness and metastatic potential of malignant cells[44].

Prostaglandin inhibitors in cancer and Immunity

It was found that indomethacin blocks IFN-gamma-induced suppression in tumor bearing host Mphils -T cell cultures, blocks the immunosuppression in renal cell carcinoma-bearing mice, and restores normal lymphokine-activated killer cell activity for patients with malignant mesothelioma[45,46,47]**.** Indomethacin increases in Th/Ts cell ratio and an improvement in delayed type hypersensitivity response[48]. Indomethacin can increase tumor cell killing by the reversal of the suppression for many immune functions by PGE2[49]. PG inhibitors enhance mitogen responses both before and after breast cancer radiation therapy[50]. Data showed that indomethacin might be of use in immunotherapy of bladder cancer[51]. Piroxicam, nonselective PG inhibitor and widely used for treatment of inflammatory arthritis, stimulates cellular immune function[52].

Indomethacin stimulates immune response o sheep RBC, as well as on the formation and functional activity of the antigen-induced (by the tolerogenous dose of RBC) T-suppressors[53]. Indomethacin enhances the secondary but not the primary humoral immune response[54]. Aspirin and indomethacin have proven immunomodulatory and anti-angiogenic[55]. Indomethacin treatment could partially restore depressed host defense parameters after cardiopulmonary bypass[56].

Epidemiological evidence has shown a decreased incidence of lung cancer in patients who use NSAIDs[57]. NSAIDs inhibit activity of phosphodiesterases and cyclic GMP-AMP protein kinases, which may be central to cancer initiation and promotion. Flurbiprofen enhances tumor response to radiotherapy and chemotherapy, and prolong survival time after excision of primary tumor[58]. COX-2 inhibitors, Rofecoxib and celecoxib, and nonselective NSAIDs protect against the development of colorectal neoplasia and esophageal cancer[59,60]. Sulindac, PG synthesis inhibitor, causes dramatic regression of colonic adenomas in patients with Familial Polyposis[61]. Further, sulindac and its metabolites induce apoptosis in colonic adenomas *in vivo*[62]. Chronic use of aspirin and NSAIDs might be associated with a reduced risk of gastrointestinal cancers[63,64]. Aspirin and COX-2 inhibition is effective for prevention and treatment of experimental breast cancers[65,66]. NO- NSAIDs showed a more efficient anti-tumor-cell effect and chemoprevention effect than standard NSAIDs[67,68]. Recent review supports that NO-NSADs hold the promise of being safe and effective chemopreventive agents against colon cancer[69]. The recent reports of cardiovascular adverse events in patients treated with selective COX-2 inhibitors has been reviewed and outline for using them with minimized side effects are discussed[70].

Prostaglandin and Prostaglandin Inhibition in Anemia

PGE inhibits the proliferation of normal colony-forming cells[71]. Both COX isoforms are present and active during human erythropoiesis, and COX-derived prostanoids may play a role in erythroid maturation[72]. PG's mediate the suppression of early and late erythroid progenitor cells in patients with chronic renal failure[73]. PGF2 alpha inhibits extrarenal erythropoietin production[74]. Intravenous injection of native PGE2, or 16,16 dimethyl-PGE2 suppressed absolute number of detectable granulocyte-Miph progenitor cells per femur or spleen[75,76]. Myeloid suppressor cells from tumor bearing mice produce suppressive levels of PGE[77]. Co-culture of Ehrlich ascites carcinoma and Sarcoma (S-180) cells with normal mouse bone marrow cells profoundly suppresses formation of MSC colonies[78].

Inhibition of PG with indomethacin increases granulocyte-Mphil progenitors and splenic erythropoiesis[79]. Indomethacin facilitates hematopoietic recovery following 5-FU administration, and enhances the rate of extrarenal erythropoietin production by reducing the PGF2 alpha titer in the liver. Indomethacin dminishes the myelopoietic suppressive effects associated with IL-1 administration and

optimizes its myelopoietic stimulatory capacity[80]. PG inhibitors may have a role in combination with hematopoietic growth factors in accelerating hematopoietic recovery following cytoreductive chemotherapy[81].

Nitric Oxide, Antioxidants and Cancer

NO plays a central role in the physiology and pathology of diverse tissues including the immune system. Like PG and other biological substance, the levels of NO must be carefully regulated to maintain homeostasis. Appropriate levels of NO derived from iNOS help building effective defense against pathogens. In addition, overproduction of NO has been associated with the pathogenesis of many disorders, including atherosclerosis, inflammatory diseases, neurodegenerative diseases, and cancer. Therefore, depending upon the levels of NO generated, NO could be harmful or beneficial. Despite the apparently conflicting observations, it is evident that NO is involved in cancer pathogenesis.

It was found that NO synthesis represents a significant Miph antitumor mechanism[82]. Very low doses of an NO mimetic can produce significant reduction in this resistance phenotype and, therefore, may have a potential therapeutic role. However, it was found that plasma as well as erythrocyte malondialdehyde and plasma NO level was higher in cervical cancer as compared to healthy controls, while antioxidant enzymes activities were decreased[83]. I have found that NO end product increased markedly in patients with breast cancer, and this elevation was correlated with stage of the disease and whether the patients treated or not[84]. Further, antioxidants are decreased in patients with cancer. Leukocyte nitrate and nitrite level was increased and superoxide dismutase activity was decreased in patients with gastric cancer[85]. Lipid peroxidation products, including lipid hydroperoxide and malondialdehyde, NO products, were significantly elevated with a concomitant depletion of antioxidants in head and neck squamous cell carcinoma[86].

Cells are endowed with an antioxidative defense system, which when compromise will lead to pathogenesis of disease including cancer[87]. Therefore, the imbalance between free radicals and antioxidants is the key. Studies suggest that there is a link between the initial involvement of oxidative stress and subsequent induction of the COX mediated inflammatory process. Free radicals are generated in the course of PG synthesis and inhibitors of PG synthesis are free radical scavengers. COX inhibitors decrease superoxide anion production[88]. PGH synthase-dependent co-oxidation of chemicals can result in the intracellular formation of free radical metabolites[89]. Therefore, PG and free radicals potentiate each other, and they involve in malignancies.

Antioxidants neutralize free radicals as the natural by-product of normal cell processes. The oxidative damage can affect the DNA and cell membranes, making the cells more vulnerable to cancer. In both laboratory and animal studies, antioxidants have been shown to protect against this damage.

Cancer and Inflammation

Oxidative stress and inflammation contribute to carcinogenesis. Angiogenesis is demand for tumor growth and dissemination; inflammation can promote tumor angiogenesis. Studied showed that PGs produced by COX-2 promote tumor development by stimulating cell proliferation and angiogenesis and by suppressing programmed cell death and immune defense[90]. Recent review showed that population-based studies examining individuals with chronic inflammation revealed that suppressed cellular immunity, in combination with enhanced humoral immunity and humoral immunity-associated cytokines, suppress anti-tumor immune responses while simultaneously enhancing angiogenesis and presumably overall cancer risk in afflicted tissue[91]. Accumulation of free radicals leads to inflammation[92]. Chronic inflammation may cause cancers of different organs including stomach, colon, breast, skin, prostate, and pancreas[93,94,95]. A proinflammatory mediators, such as cytokines, chemokines, PGs, NO,

and leukotrienes, promote neoplastic transformation of cells by altering normal cellular signaling cascades[96]. Laboratory and epidemiological studies suggest that prolonged use of NSAIDs reduces the risk of malignancies that frequently occur in persistently inflamed tissues[97,98].

POTENTIAL APPROACH FOR CANCER ETIOLOGY AND THERAPY

Every substance works in coordination with others. Therefore, every biological substance must be within limit to allow it to work with other substances as one unit (Surely we have created everything according to a measure, *Holy Quran, Surat Moon, version 49*). Lord created every thing in a measure and in purpose. Any sustained changes out of biological balance will cause disturbance and disease. PG and NO are very active substances with wide variety of biological influences, and their disturbed measure could affect tremendously the biological systems.

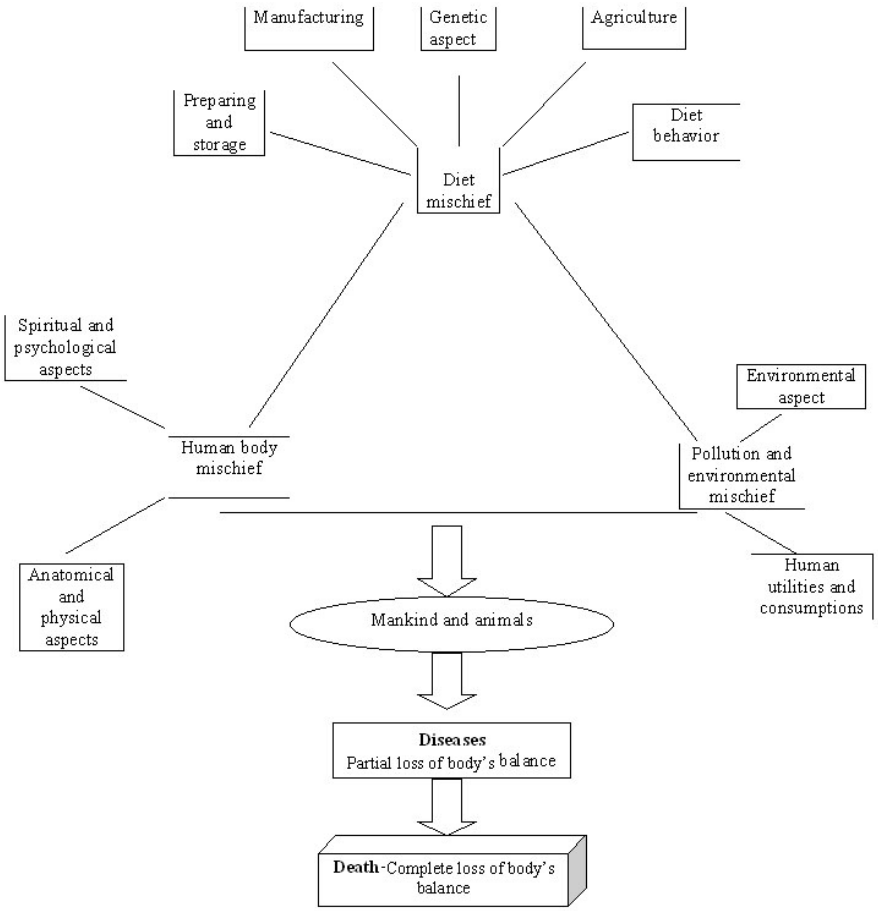

Figure 3: Al-Waili' Disease's Triangle (Basic etiology of illnesses as malignancies)

When immunity, such as humoral immunity, cellular immunity, hormonal balance, enzymatic activity, spiritual attitude, and antioxidants, is disturbed, dividing cells become out of the biological balance and begin to divide and develop into more and more cells, and will cluster into tumors. Defects in the balanced biological functions, caused by the aspects mentioned in Disease's Triangle (Figure 3),

should take place before the development of cancer[99,100]. Cancer cells will not grow and spread in healthy body with a balanced biological function. Many mechanisms are proposed for initiation and growing of cancer, but I think that all proposed mechanisms rose as a result of impaired body immunity. Immunity is not humoral or cellular, innate or acquired tools against biological invaders, but it means the power of body that designed to repair imbalance and impairment[12]. Understanding the mechanisms and discovering the mediators that enable these cells to thrive is crucial in learning how to deal with them by activating the immune system.

We found that PGs suppress the lymphoid system, and reduce blood indices, serum iron and serum albumin, and modulate blood glucose, and calcium and phosphorus blood level. Therefore, it was hypothesized that PG's are involved in the immunosuppression and secondary anemia encountered in conditions in which large quantities of PG's are released such as tumors, and PG inhibitors may reverse the immunosuppression and enhance the immune response to tumor growth. This concept allowed using PGs inhibitors for treatment and prevention of cancer. This has been supported by many studies showing that PG's are potent immunosuppressive and administration of PG inhibitors could improve immune function. Long-term use of PG inhibitors decreases the incidence of certain malignancies, including colorectal, esophageal, breast, lung, and bladder cancers. Piroxicam, indomethacin, aspirin and ibuprofen could stimulate immune response or restore immuno-deficiency in certain pathological conditions[27,49,53,54,55,56].

Others and we have found that NO is increased markedly in malignancies and could prompt cancer development. NO-NSAIDs, has have been developed to reduce side effects of NSAIDS, cause cell cycle perturbations and induce apoptosis in cell lines from different tumors[101,102]. Many natural products, such as honey, could lower PGs and increase moderately NO, and therefore they may represent alternative and safer interventions[103,104,105,106]. Chronic inflammation has been associated with increased risk of human cancer[107]. Inflammation facilitates the initiation of normal cells and their growth and progression to malignancy[108]. Free radicals are involved in the pathogenesis of malignancies too.

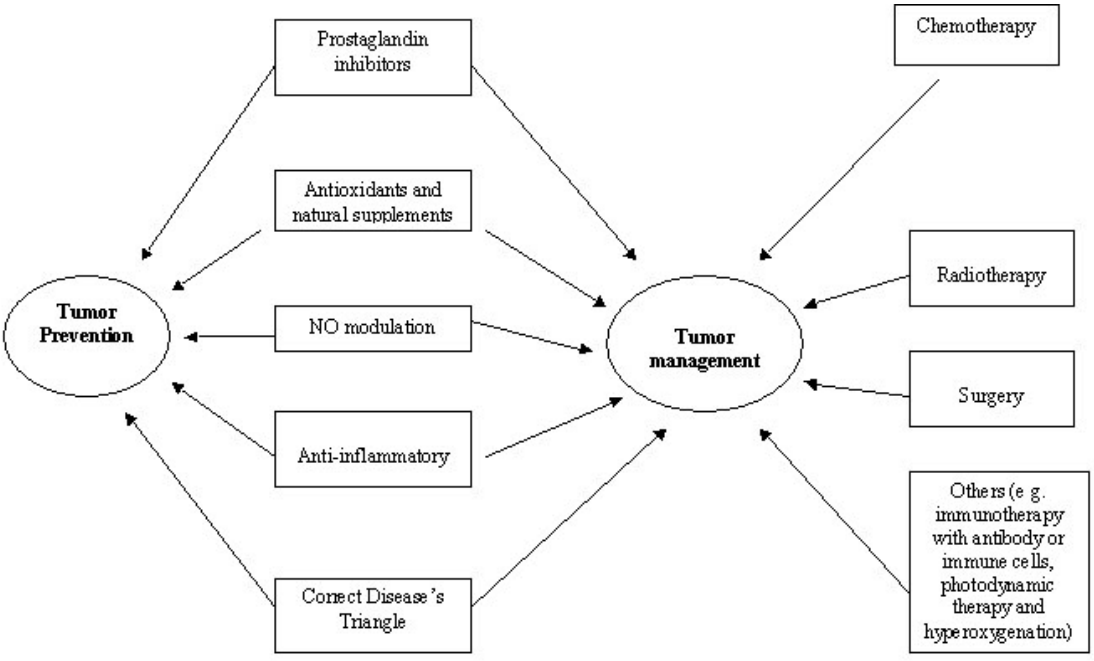

Figure 4: Proposed concept for management of tumors

A recent review discussed the potential use of immunostimulatory monoclonal antibodies directed to immune-receptor molecules in cancer therapy[109]. Gene therapy of targeting specific genetic defects found in certain tumors need extensive work before reaching final conclusion. Using immune cells, such as Miphs, to combat tumor cells and their dissemination warrants further studies and consideration. In this regard we have found that peritoneal cells including Miphs could be transferred intravenously and can combat bacterial infections[110,111,112,113]; these finding pave the way to examining the potential therapeutic effect of peritoneal cells and Miphs for treatment of tumors as well as inflammatory conditions. I believe that the main strategy to prevent and manage malignancies should include inhibition of PG over-production, modulating NO production, use of antioxidant and anti-inflammatory agents, immunotherapy, and improvement of life styles according to the Disease Triangle. These issues could be used alone to help prevent malignancies or, in combination with chemotherapy, radiotherapy and surgical intervention, to manage diagnosed cases of tumors (Figure 4).

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