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THE ROLE OF PROTEOLYTIC ENZYMES IN TUMOR GROWTH CONTROL: A Review

Proteolytic enzymes have been used for years as therapeutic agents. The medical documentation of exogenous enzyme application in the treatment of cancer and other diseases goes back to the early 1900s when Beard used crude enzyme extracts from pancreatic tissues on cancer patients. However, the use of enzymes has been only occasional within the conventional medical practice. Due to their protein nature, exogenous enzymes were initially thought to have little, if any, replacement or therapeutic value when administered orally.

Some of the main arguments against the use of oral enzymes were that they (1) are hydrolyzed in the stomach, (2) cannot be absorbed as a whole functional protein, and (3) may induce allergic reactions. However, several studies have focused on these points and have in fact shown that some enzymes can sustain the gastric environment and are absorbed into the blood stream where they maintain their catalytic function (Seifert, et al., 1995; Castell, 1995; Pirotta, et al., 1978; Steffen and Menzel, 1987). Additionally, more and more data are pointing to the use and benefits of exogenous proteolytic enzymes as therapeutic agents or as adjuvant to therapy.

For instance, bromelain, a protease derived from the pineapple plant, has been used as a digestive aid, an anti-inflammatory, and a burn debridement agent as well as for prevention of swelling/edema, smooth muscle relaxation, inhibition of platelet aggregation, enhancement of antibiotic absorption, cancer treatment, ulcer prevention, sinusitis relief, appetite inhibition, and shortening of labor (Taussig, et al., 1975, 1988; Gerald, 1972). In addition, Batkin, et al., (1988a,b) showed that bromelain reduced lung cancer metastasis in mice. Maurer, et al., (1988) used bromelain to induce differentiation of leukemic cells. Moser (1957) reported on the thrombolytic and anti-inflammatory role of trypsin.

Since the 1960s, it has been postulated and later demonstrated that cancer cells are sticky and that the stickiness resulted from an excess of fibrin covering the cells. This increased presence of fibrin may be due to poor plasma fibrinolytic and thrombolytic activity. In fact, many studies have correlated the metastatic ability of cancer cells to fibrinolysis and thrombolysis. With less thrombolytic activity, there is more prevalence of cancer cells that invade and metastase within the body (O'Meara, 1958;

Kojima and Sakai, 1964; Clifton and Agostino, 1964). The fact that oral enzymes enhance thrombolytic and fibrinolytic activities may help attenuate and/or prevent further tumor cell growth (Kokron, et al., 1976; Thornes, 1968; 1975; Steckerl, et al., 1961).

Wald, et al., (1998) investigated the effects of hydrolytic proteases on solid tumors in mice. They used C57Bl6 inbred mice that were inoculated with Bl6 melanoma cells. The mice were given the enzyme preparation rectally and the dosage was chosen to be proportional to human dosage. Ten days after inoculation, the growing tumors were removed. The results indicated that 30% of the test animals survived for 100 days. The other 70% survived on average about 58.3% longer than the animals in the control group.

Histological and immunocytochemical observations indicated that metastasis was more pronounced in the control animals than in the test animals that were given proteolytic enzymes. In similar studies, Wald, et al., showed that proteolytic enzymes administered orally improved (1) the survival time as well as the hematological parameters of spontaneous lymphoblastic leukemia in rats and (2) the metastasis and survival time of mice with Lewis lung carcinoma.

Using proteolytic enzymes as adjuvant to 5-FU and levamisole hydrochloride in the treatment of patients with solid and metastatic adenocarcinomas of the colon, Sakalova, et al., (1993) reported a 64% survival rate in the 6-30 month observation period. Bessing (1994) obtained similar success with colon cancer patients. Garbin, et al., (1994) inhibited the growth of various tumor cells in-vitro using bromelain. Wessenbacher (1993) reported on the role of oral enzymes as biological response modifiers.

Shibata, et al., (1970) showed that oral enzymes help reduce the adverse side effects of chemotherapeutic agents in cancer patients. Intensive pain, weight loss, anorexia, nausea, and emesis are substantially reduced in cancer patients taking oral enzymes compared to those not taking the enzymes. Furthermore, oral enzymes were shown to enhance the benefits of chemotherapy, prolong general health, and reduce cancer therapeutic costs.

Hamilton, et al., (1969) showed that the proteolytic enzyme papain protected rodents against the side effects of radioactive exposure. Barth (1963) and Graebner (1964) obtained similar results. In a clinical study involving patients with epithelial tumors in the neck and head area, Schedler, et al., (1990) found that the patients receiving oral enzymes in addition to the chemotherapeutic agent bleomycin did not exhibit the characteristic side effects of pneumotoxicity. However, the patients receiving only the chemotherapeutic agent bleomycin without enzymes exhibited the characteristic side effects (including fatalities). Moreover, their study indicated that the dose of bleomycin could be increased when enzymes are included in the treatment to effect beneficial results in patients.

Several hypotheses have been put forth as to the mechanisms by which proteolytic enzymes modulate the immune system as well as control and eliminate tumors. Studies have shown that the toxicity of chemotherapeutic agents such as bleomycin results from the over-expression of TNF and adhesion molecules. Bleomycin was shown to induce the over-secretion of these molecules. Other studies have independently indicated that one of the effects of the oral enzymes is to control the expression of TNF and also to selectively remove adhesion molecules from the surface of tumor cells.

Recent research data indicated that proteolytic enzymes selectively remove some adhesion molecules such as CD4, CD44, B7-1, ICAM-1, B7-2, CD45RA, CD6, CD7, E2/MIC2, and Leu81/LAM 1 from cell surfaces (Kiessling and Gordon, 1998; Targoni, et al., 1999, Harrach, et al., 1994; Hale, et al., 1992). According to Hale, et

al., (1992) the removal of these surface molecules has markedly enhanced CD2 mediated T-cell activity.

CD44 is a glycoprotein adhesion molecule that has been shown in several studies to play a major role in tumor growth and metastasis (Herrlich, et al., 1993; Underhill, 1992; Lesley, et al., 1993; Sy, et al., 1997; Gebauer, et al., 1997). According to Mulder, et al., (1994) a variant of CD44, is expressed in higher copies as colorectal cancer progresses. However, other studies indicated that CD44 does not appear to be a good marker of tumor growth in all types of cells (Terris, et al., 1996; Friedrichs, et al., 1995).

The above studies implied that by removing CD44, some proteases help control the tumor growth of certain types of cells. This selective removal of some mediator proteins and the regulation of cytokines (Desser, et al., 1993, 1994, 1997; LaMarre, et al., 1991; Zavadora, et al., 1995) constitute some factors by which proteolytic enzymes are thought to modulate the immune system and act as biological response modifiers. Although the exact mechanism of oral protease impact on tumor cells is not understood, several studies indicate that some orally administered proteolytic enzymes stop and/or down-regulate tumor growth and/or progression. Further studies may need to determine the specific significance of selective hydrolysis of CD44 on some tumor cells by orally administered proteolytic enzymes.

Other possibilities include the scavenging of oxidized proteins. Oxidized proteins are proteins that have been attacked by free radicals. As a result, they loose their functions in the body. In cancer therapy, some of the main causes of oxidized proteins formation are chemotherapy and radiation. The persistent presence of these oxidized proteins not only overwhelms the system, but also perpetuates the free radical damage, along with the destruction of normal cells, enzymes, and hormones. The orally administered enzymes shown to be absorbed in the blood stream (Castell, 1995) can hydrolyze these oxidized proteins and remove necrotic tissues from the circulation. Additionally, as stated above, the proteolytic enzymes enhance the fibrinolytic and thrombolytic activities within the circulatory system. The capacity of tumor cells to attach to the endothelium lining of the blood vessels is a necessary step in tumor cell invasion and dissemination to other tissues. The enhanced blood rheology resulting from proteolytic enzymes will impede on this attachment. The lysis of fibrin covering the tumor cells will also help expose the cancer cells and promote their removal by the immune system and apoptosis.

Oral enzymes have been specifically used in clinical studies involving several forms of cancer and treatments. These have included brain tumors, respiratory cancer, melanoma, multiple myeloma, leukemia and lymphomas, stomach cancer, colon cancer, pancreatic cancer, cervix, breast and uterus tumors, and prostate cancer (Argyropoulos and Tritthart, 1977; Kesztele, et al., 1976; Alth, et al., 1973; Kokron, et al., 1976; Wrba, et al., 1995; Sakalova, et al., 1993, 1995; Kim, et al., 1980, 1981, 1982; Ahumada, 1994; Wolf and Ransberger, 1970; Seifert, 1983).

In addition to these tumors, oral enzymes have also been used with various metabolic and infectious diseases. In most of the documented and studied cases, the orally (and sometime rectally or intra-tumor) administered enzymes are considered as adjuvant to the main conventional therapy.

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