

# Enzyme Therapy in Oncology

The use of oral and injected enzymes in oncology, either as an adjuvant or as an additive therapy, has been disputed. In the past, supporters of classical chemotherapy have paid little attention to this additional treatment option due to the absence of convincing clinical data. But that has changed in the previous decade. In an age, in which medical science is increasingly specialized, one should remind himself that many approved drugs are based on naturally occurring compounds.

Enzymes are molecular saboteurs. They extend their effects by gumming up the works of key proteins in the organism. They drop their wrenches selectively, slotting seamless onto binding domains of their target proteins, cleaving them into peptide fragments and leaving other proteins untouched. It was in 1926, when Sumner crystallized the enzyme urease from jack bean meal and identified it unequivocally as a protein. He ultimately was awarded a Nobel Prize for his efforts and at present, enzymology occupies a very important position in medical, biological and industrial research.

Enzyme therapy modalities have found their way into oncology, e.g. asparaginase which cleaves asparagines into aspartic acid and ammonia disrupts the supply to lymphatic leukemia cells of the essential amino acid, and hyaluronidase, which may improve the transport of cytotoxic drugs to, or facilitate the oxygen level in, tumor tissue by degradation of the extracellular matrix or alteration of the central tumor interstitial fluid pressure, respectively.

Therapies with enzymes and proteinases, like Bromelain, play an increasing role in the treatment of oncological patients. Proteinases like Bromelain, increase immunocyto-toxicity of lymphocytes, activate immunocytotoxicity of monocytes, regulate the adhesion and signal transduction of lymphocytes, which makes adhesion and metastases far more difficult, and increase the production of several cytokines (IL-2, TNF-alpha, and IL-1-beta) through which their anti-tumor activity can be explained (7, 8).

## **11.a Research and Clinical Evidence**

Lauer *et al.* (1) showed that oral application of enzymes triggers the formation of TGF-beta binding species of activated alpha-2-macroglobulin by converting this clearance protein from the so-called slow form into the fast form. High concentrations of TGF-beta, chemokines and cytokines, as reported by other researchers, are preferentially bound leading to increased clearance in the form of the alpha-2-macroglobulin-cytokine complex. Thus, proteinase therapy, using trypsin, chymotrypsin, papain or bromelain may prove beneficial in patients with certain cancers by reducing the level of growth factors, which are known to be elevated in such patients.

Desser *et al.* (2) have shown, that oral therapy with proteolytic enzymes decreases elevated levels of TGF-beta in blood of healthy volunteers, given orally low dosages of a cocktail of active proteinases over a period of seven days.

Wald *et al* (3) could demonstrate that a mixture of enzymes could reduce the formation of metastases of melanoma B16 cells and extend the survival time significantly. They also reported a decreased expression of CD44 and CD54 molecules in tumors exposed to proteolytic enzymes and conclude, that serine and cysteine proteinases are able to inhibit metastatogenesis.

Batkin *et al.* found anti-metastatic effects of bromelain and other proteolytic enzymes in cancer patients (4).

Further evidence of surface protein modulation by proteolytic enzymes is given by the work of Zavadova and Freedman (in press: Chemotherapy Pharmacology Vol. 48, issue 3) using **dendritic cells** from the peritoneal cavity and peripheral blood of ovarian cancer patients. They cultured these antigen-presenting cells in the presence of poly-enzyme preparations and were able to induce enhanced maturation.

Gujral *et al.* (5) and Dale *et al.* (5) could demonstrate alleviation of side effects of radiotherapy treatment like mucositis, skin reactions and dysphagia in patients with cancer of the head and neck, and in uterine cervix cancer, when patients received oral enzymes.

Grabowska *et al.* (9) found that Bromelain proteinases suppress growth, invasion and lung metastasis of melanoma cells in a mouse model.

There is no doubt that that further advances in molecular biology in the field of cancer treatment will allow to understand more fully how and why a drug works., and this holds true in the clinical use of enzymes as well. In experimental settings, it has been shown that proteolytic enzymes are active substances in the fight against malignant cells, and in addition successful animal models have been established to elucidate the mode of action of enzymes in the process of metastasis formation.

The trial and error approach, by which medicines have been discovered and developed over the past 100 years is still ongoing at the beginning of the 21<sup>st</sup> century. However, the more one is armed with the blueprints for genes of enzymes of interest, the more one can develop individual designed enzymes. Experimental research with such designer enzymes is currently underway focusing on ways in which tumor cells may be compromised through the cleavage of key proteins, essential for cell proliferation and invasion.

When appropriate, in the **Cologne Model** enzymes are used to enhance the biological defense mechanism against cancer. Great care is put into the choice of the enzymes and their pharmacological preparation.

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## 11. 2. Enzyme Therapy in Chronic Inflammatory Diseases and Chronic Fatigue Syndrome

In Western Europe, proteases are widely prescribed drugs for treating immune-related inflammatory conditions, tissue damage from radiotherapy and sports injuries of athletes (1-4). Current clinical trials test the efficacy of protease to ameliorate immune-mediated diseases like multiple sclerosis (MS) and rheumatoid arthritis (RA). Our clinical experience in the **Cologne Model** show also impressive activity in **Chronic Fatigue Syndrome** (CFS). Orally administered proteases, such as bromelain, are absorbed in a non-degradable bioactive form, resulting in increased proteolytic serum activity (2).

Bromelain is a mixture of various, closely related proteinases from pineapple, demonstrating, *in vitro* and *in vivo*, anti-edematous, anti-phlogistic, anti-thrombotic and fibrinolytic activities.

Prevention of murine experimental allergic encephalomyelitis (EAE) and autoimmune diabetes by oral hydrolytic enzyme treatment has been shown (5, 6). Pilot and phase-II trials in humans have strongly suggested that proteases have ameliorating effects for MS and RA without any side-effects (7). However, the mechanism of their action is not clear, whilst no molecular basis exists to use mixtures of different proteases.

Type-I (insulin-dependent) diabetes mellitus results from a T-cell-dependent immune-mediated destruction of the insulin producing pancreatic beta cells. In first degree relatives, the development of the disease can be predicted by the detection of islet-reactive auto-antibodies to islets of Langerhans, insulin, GAD and IA-2 (8, 9, 14).

The quality of immune activation plays an important role during chronic autoimmunity. The ratio of Th-1 and Th-2 cytokine expression regulates disease activity (10, 11).

Th-1 cytokines cause increased vascular permeability and edema (12, 13), whereas IL-10 inhibits cytokine production, vascular leakage and swelling during Th-1 induced delayed-type hypersensitivity (13).

Very interesting observations have been documented where in chronic inflammatory bowel disease (Morbus Crohn, Colitis ulcerosa) proteases would inhibit chronic inflammation on an autoimmune basis (15).

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