TRANSFORMATION

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CELLULAR INJURY, part 2: Inflammation Control and Oral Enzymes

As a result of cellular injuries, infections, and other pathologies, there is an inflammatory process that takes place in the body (Mamadou, 2003). Inflammation, in general terms, may be defined as the body's response to and return from an imbalanced, injurious state to homeostasis.

There are various steps in the inflammatory process. The basic steps of any inflammatory process include:

- the signal of a disruption in cellular structural and/or functional integrity
- the setting up of a defense mechanism against further damage
- the initiation of a process that will lead to the reparation of the cell's structural and/or functional disorders

However, these basic steps can be further subdivided in order to illustrate the extent of the often intricate biochemical processes that take place. Some of the biochemical and cellular reactions that could be noted in an inflammatory process are:

- impact of the causative agent on the tissue/cells, leading to the expression of the injurious state
- secretion of the neurotransmitters epinephrine and norepinephrine as well as the humoral mediators histamine, serotonin, and bradykinin
- vascular reactions characterized by vasoconstriction and/or vasodilatation
- increased blood pressure at the microcirculatory network near the affected tissue
- increased permeability of the vessels around the site of injury
- outward movement of plasma from blood vessels into the surrounding tissues, resulting in the formation of exudate and a raised plasma protein concentration within the interstitial tissues
- increased protein concentration in the tissues, which counterbalances the osmotic pressure in the blood and results in more water being retained in the tissues
- loss of plasma in the blood vessels, resulting in increasing packing of the red cells and reduced flow and rheology of the blood

- poor blood flow, which reduces oxygen supply to the tissues and increases carbon dioxide-loaded red cells in the blood, thus lowering blood pH and resulting in the acidification of the injured tissues
- increased hydrolysis of the endothelial blood vessel lining by elastase and collagenase from the neutrophils
- increased formation of edema and exudates, which could be serous, purulent, and fibrinous and which contributes in identifying the site as a focus of inflammation
- dissemination of excess bacteria found in exudates to tissues and lymphatic vessels during drainage, creating further inflammatory reactions
- potential inflammation of the lymph nodes (i.e., lymphadenitis)
- onset of fever, leukocytosis, and other health complications
- pressure of the exudate on pain receptors and nerve endings, leading to a feeling of pain and increased secretion of substance P, bradykinin, histamine, and prostaglandins
- immune response
- proliferation and migration of fibroblasts to the injured site
- synthesis of connective tissue, resulting in scar formation and healing of the damaged tissues
- formation of necrotic tissue
- degradation of scar tissue

The intensity and duration of these various stages in the inflammatory process may vary according to the causative agents as well as the state of overall wellness. More specifically, *the effectiveness of the various biochemical reactions depends to a great extent on the availability of nutrients and the delivery of those nutrients, mediator molecules, and immune cells to the injured tissues as well as the overall health environment within the body*. It should also be noted that, as the inflammatory process takes place and becomes more generalized within the body due to persistent cellular injuries, some of the biochemical reactions cited above overlap and further weaken the body's ability to respond properly.

One of the key sets of molecules involved in mediating the inflammatory process is the class of cytokines. Cytokines are short-acting small soluble polypeptides that are involved in the induction and regulation of the many interactions and effector functions of the immune system (i.e., lymphocytes, monocytes, neutrophils, endothelial cells). There are several types of cytokines and more are continuously being isolated and characterized. Presently, five categories of cytokines are known and characterized. These include cytokines involved in:

- the mediation of natural immunity, including protection against viral infections and initiation of inflammatory responses (IL-1, IL-6, TNF-α)
- the regulation of lymphocyte growth, activation, and differentiation (IL-2, IL-4, IL-5, IL-12, IL-15, TGF-β)
- the activation of inflammatory cells and nonspecific effector cells (IFN-γ, TNF-α, TNF-β)
- the movement of leukocytes (IL-8)
- hematopoiesis stimulation

As a group, cytokines are produced by various types of cells, and are pleitropic (i.e., they act on many types of cells). According to LaMarre et al. (1991), many inflammatory and proliferative disease processes are associated with inappropriate or excess cytokine activity. For instance, studies have shown that excess TGF-β is associated with experimental glomerulonephritis (Border et al., 1990) and hepatic fibrosis (Czaja et al., 1989). Additionally, pulmonary fibrosis was associated with excess TNF-α (Piguet et al., 1990) and endotoxic shock both to excess TNF-α (Beutler et al., 1985; Tracey et al., 1986) and to excess IL-1 (Okusawa et al., 1988).

By regulating cytokine synthesis, activity, and clearance, it is possible to therapeutically manage the harmful effects of inflammation as well as the various forms of tissue damages induced by excessive immune response. There are several important mechanisms by which the regulation of cytokines may be achieved. Some of the methods proposed consist in down-regulating the synthesis of cytokines, accelerating the process of their inactivation, and promoting their clearance from the system.

It should be noted that the early phase in immune response triggering is mediated by cytokines. In order to optimize the effect of cytokines on the immune system, they need to be synthesized locally and act on target tissues and cells on a timely manner. *A key role in supplemental oral enzymes as an adjuvant in therapy is their effect on the regulation of cytokines*. For instance, proteolytic enzymes taken orally have been shown to act on the cytokines.

Several studies have been conducted to determine the effect of oral therapeutic enzymes on cytokines. Desser et al. (1993), studied the effect of oral hydrolytic enzymes on cytokine synthesis. Their study showed that peripheral blood mononuclear cells from human volunteers who were given oral hydrolytic enzymes synthesized higher levels of TNF-α, IL1β, and IL-6 than the control subjects. The importance of this finding relates to the fact that TNF-α has been shown to play a major role in host defense against tumor cells (Arai et al., 1990).

In order to therapeutically exploit the benefits of TNF-α, recombinant human TNF-α (rh-TNF-α) has been used in some trials, but with severe side effects (Crum, 1989; Bocci, 1988; Nakatsuji, et al., 1990). However, as hydrolytic enzymes could mediate the synthesis of TNF-α along with IL1β and IL-6, they could constitute a safe alternative. In fact, the physiologically induced TNF-α secretion after oral ingestion of hydrolytic enzymes does not appear to have the severe side effects observed with rh-TNF-α.

Furthermore, Desser et al. (1993; 1994), showed that if the enzymes are inactivated, then they loose their ability to induce TNF-α synthesis. Thus, active enzymes capable of sustaining the gastrointestinal conditions and reaching the blood stream are necessary for therapeutic application. Furthermore, their studies indicated that hydrolytic enzymes are more efficient than phorbol-12-myristate-13-acetate in inducing the synthesis of TNF-α from peripheral blood mononuclear cells.

Additionally, Zavadora et al. (1995), showed that oral hydrolytic enzymes stimulate higher production of reactive oxygen species in polymorphonuclear neutrophils obtained from human volunteers between the ages of 19 and 45 who received oral enzymes when compared to control subjects. The importance of the reactive oxygen species relates to their action as tumoricidal and cytotoxic.

It may even be speculated that the effects of oral hydrolytic enzymes on cytokines may be multiple. For instance, as shown by Desser et al (1993; 1994), oral enzymes promote the synthesis of TNF and may possibly be involved in the process of shedding cell surface molecules. This latter activity is an important factor in cell regulation as well as in future therapeutic strategies (Kiessling and Gordon, 1998).

TNF is a proinflammatory cytokine needed very early at the onset of injury to initiate the inflammation process. However, as its concentrations are elevated and its molecules are distributed throughout the system, TNF will continuously trigger the onset of inflammation, leading to various side effects seen along with its administration. *A possible role of oral proteases and perhaps glycosidases is to simultaneously cleave and shed off cell membrane molecules and the receptors that may be involved in transducing the effects of TNF*.

As the receptors are removed, the side effects will not be observed. Furthermore, the receptors that are now soluble and circulating in the blood stream will bind to the released TNF and enhance its clearance. This dual function of enhancing synthesis and shedding cell surface receptors may explain the various observations resulting from the ingestion of oral hydrolytic enzymes, namely, the alleviation of pain and other inflammatory symptoms.

When cytokines persist in the system and are disseminated throughout the body, they may pose serious health problems. In fact, the persistent action of cytokines is thought to contribute to the debilitating impact of chronic inflammation, including the onset of several degenerative diseases. Thus, a controlled inactivation and/or clearance of cytokines upon completion of the desired function is critical. Similarly to proteolytic enzymes, cytokines have been shown to preferentially or randomly bind activated alpha 2-macroglobulin, resulting in their accelerated clearance from the system. This may constitute one form of biological control of cytokine levels in the blood stream (LaMarre et al., 1991).

Besides the various mediator molecules and cells involved in inflammation, it is important to consider the function of blood. In its role of delivering oxygen and nutrients as well as removing waste materials from the cellular environment, blood needs to flow freely through a closed network of arteries and veins of varying sizes. One of the consequences of inflammation is reduced blood flow, often created by the packing of blood cells and ultimately resulting in the formation of blood clots or thrombus. This condition of poor blood flow impedes healing and wellness. Thus, cellular injuries that perpetuate inflammation create conditions favorable to chronic fatigue, pain, immune inefficiencies, diseases, and various disease syndromes. Thrombus formation as well as other clots within the blood vessels are not predictable and could occur at any time as based on chronic inflammatory processes, poor diet, excess free radicals, and xenobiotics.

As a general rule, any factor that impedes blood flow will stimulate acidosis and coagulation. Acidosis is the result of reduced or lack of oxygen supply and accumulation of carbon dioxide. Blood coagulation is also a very controlled and regulated process. Although it is necessary under conditions of bleeding in order to control blood loss, blood coagulation within the vessels can be fatal. Some factors that induce thrombus within the vessels are more prevalent in cases of cancer and autoimmune diseases.

Fibrin is a glycoprotein formed from fibrinogen by the action of a thrombin. The clot is basically a network of fibrin molecules formed in the presence of calcium ions and Factor XIII (Hageman factor). Under normal conditions and with regular blood flow, the fibrin that forms the clot is hydrolyzed by the protease plasmin. Therefore, any action that hydrolyzes or dissolves the fibrin network will contribute in enhancing the blood flow and protect the blood vessels from any endothelial damage.

Proteolytic enzymes have been used therapeutically to correct just such fibrin formations and thereby ensure thrombus prevention. Oral proteases, once in the blood stream, enhance blood rheology (i.e., the flowing properties of blood). Some of the oral proteases that have been investigated include substilisin, bromelain, fungal proteases, papain, trypsin, and chymotrypsin.

In addition to their fibrinolytic activity, oral proteases help break aggregated thrombocytes. Thrombocytes are blood cells that aggregate under certain conditions to "seal" leaks in blood vessels. An uncontrolled aggregation of these cells can also lead to poor blood flow and damage of blood vessels.

Still another area of major health impact where oral proteases promise possible relief is cardiac arrest due to plaques in the blood vessels. As plaques form in vessels and are continuously "bumped" by flowing blood cells, they create injuries along the endothelial lining of the blood vessels, thus setting an inflammatory site. Sometimes, the dislodged plaque debris will travel along the vessels and potentially clog arterioles or venules. This will result in hypoxia, ischemia, or even death. However, *supplemental protease helps prevent plaque formation in vessels and can therefore be used therapeutically to lower the risk of cardiovascular disease*.

Another inflammation characteristic cited above relates to the formation of exudates and edema, which results in swelling, fibrin clots, and the aggregation of molecular and cellular debris, pain, and excessive connective tissues. Under normal conditions, the healing process controls the extent of tissue damage as well as repairs the inflamed site. Proteolytic enzymes have been specifically beneficial in alleviating pain and hydrolyzing the various plasma protein molecules that have migrated out of the vascular system as well as the debris from the leukocytes. Proteolytic enzymes are also involved in the remodeling of collagen to heal the wound and reduce scar tissues. These hydrolytic activities result in the resolution of swelling and pressure on the nerve endings.

Cellular injuries occur frequently in the body and repairing them so as to offset any chronic inflammation is very important in maintaining wellness and preventing debilitation of the body and the onset of degenerative diseases. It could therefore be concluded that *oral supplemental enzymes that sustain the gastric environment and are effectively absorbed into the blood stream to modulate inflammation-induced molecules such as cytokines constitute good alternative therapeutic adjuvants*.

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