Chapter 34

Immunomodulation by Nutrition: A New Challenge for Milk-Derived Proteins and Peptides

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ABSTRACT

Immunomodulation by nutrition is a novel strategy emerging from research on mucosal immunity as regarded to the gastrointestinal tract and its role in the continuous activation of lymphocytes in the mucosal environment. The intestine and the naso-oro-pharyngeral cavity in humans represent the largest immune organ, with a surface area of about $400m^2$, lined by a single layer of epithelium that is persistently exposed to myriads of dietary antigens and pathogens. Evidence continues to accumulate that many whey-derived products provide a variety of health benefits including anti-microbial, anti-inflammatory, anti-carcinogenic, hypocholesterolemic or hypertension controlling effects. These principles emphasize the prevention of many age-related disorders by timely utilization of such clinical nutrition, including both whey concentrate and its highly purified components. The key benefit from this strategy is a substantial reduction in the cost of the health care management with minimal training of medical personnel.

Keywords: Immunomodulation; Lactoferrin; Milk-derived proteins; Beta-lactoglobulin, Alpha-lactalbumin; Oxidative stress

INTRODUCTION

The immune system plays a central role in protection against microbial infections and neoplasia, as well as many age-related disorders. The mucosal surface of the gastrointestinal tract is one of the first important interfaces between pathogens or various dietary antigens and the host. Thus, the intestine is the site of intense immunologic activities and the challenge is to maintain a disease-free state in the face of chronic antigen exposure. Normal immune homeostasis depends on coordinated interactions among the various lymphoid, phagocytic and somatic cells that comprise the immune system. In general, these interactions are tightly regulated to obtain a balance between the need to eliminate harmful insults and the need to avoid damaging autoimmune response.[1]

One of the greatest advances of modern immunology is the recognition that this balance is achieved largely through intercellular communication mediated by a diverse group of molecules known as cytokines. Cytokines produce a wide array of immunologic and non-immunologic effects, which together shape the state and the duration of any insult-induced metabolic imbalance.[1-3] Through coordinated interactions, cytokines activate target cells to release other mediators of the inflammatory response to any specific insult.[4-6] The maintenance of homeostasis is essential for cellular integrity and depends on the ability of our body to induce proper inflammatory responses. The ultimate goal of inflammation is to dispose of both the initial cause of injury and its consequence. In the intestine of a normal healthy individual however, inflammation has its own “physiologically justified” chronic character. Again, this is a reflection of continuous exposure of epithelium to myriads of dietary antigens and pathogens.[7] In fact, this constitutes for oral tolerance, which is defined as the immunologic mechanism by which the mucosal immune system maintains unresponsiveness to many antigens.

An increasing body of evidence suggests that dietary supplements, particularly milk-derived components, can systemically modulate both acute and chronic metabolic imbalances.[8-11] The nutritional value and functional properties of milk-derived products have recently been addressed in various monographs.[12, 13]

HEALTH-ENHANCING PROPERTIES OF MILK-DERIVED INGREDIENTS

Bovine milk contains a large number of bioactive compounds including proteins, carbohydrates, and minerals. Whey in particular becomes a reliable source for a number of high quality factors capable of improving health and preventing disease. Whey proteins are easily digested and contain an amino acid profile that meets the daily dietary requirements for all essential amino acids. The major whey proteins are beta-lactoglobulin, alpha-lactalbumin, immunoglobulins, and bovine serum albumin. The minor whey proteins are lactoferrin, lactoperoxidase, glycomacropeptides, lysozyme, and Proline-Rich Polypeptide.

The percentage of these proteins is fairly consistent in mature milk and is shown in Table 1 as a percentage of total whey proteins.

Table 1. Whey proteins, as a percentage of total whey proteins (%)

Beta-lactoglobulin	52.5
Alpha-lactalbumin	22.5
Immunoglobulins	12.5
Bovine serum albumin	7.5
Lactoferrin	1.5
Lactoperoxidase	0.5
Glycomacropeptide	3.0
Lysozyme	<0.1
Proline-Rich Polypeptides	<0.1

The following individual whey components are potential candidates for ingredients in clinical nutrition to obtain health benefits, such as enhancing body functions or reducing the risk for certain diseases:

- **Beta-lactoglobulin** – This protein is highly regarded as an excellent source of essential amino acids including cysteine, which is important for the synthesis of glutathione.[14] Beta-lactoglobulin is a natural carrier for retinol and other lipophylic structures in milk.
- **Alpha-lactalbumin** – This small molecular weight protein (14 kDa) with a high degree of branched amino acids is a component of lactose synthase, which catalyzes the final step in lactose biosynthesis in the lactating mammary gland. Alpha-lactalbumin is a calcium binding protein with ability to induce apoptosis in tumor cells.[15]
- **Immunoglobulins** – This diverse group of proteins, including IgA, IgG1, IgG2, IgM, and IgE, provides passive immunity to infants and may stimulate immune function in adults.
- **Bovine serum albumin** – This protein is a carrier for fatty acids and many small molecular weight molecules. It is also an important source of essential amino acids, including cysteine.[14]
- **Lactoferrin** –This glycoprotein is well recognized as a major anti-microbial constituent of milk. Lactoferrin has well-defined, direct antimicrobial activity, including an iron-dependent bacteriostatic property and bacteriocidal action on LPS-bearing gram negative bacteria.[16] The immunoregulatory functions of lactoferrin are explained in the following section.
- **Lacotoperoxidase** – This milk enzyme provides natural anti-microbial activity that can be utilized in a variety of applications.
- **Glycomacropeptide** – This relatively small peptide (8.0 kDa) is a casein-derived product, which becomes a whey component during the cheese-making process. It is a fragment of kappa-casein containing amino acid residues 106-169. The lack of phenylalanine in glycomacropeptide makes it highly desirable nitrogen source in the special diets formulated for phenylketonuria patients. Glycomacropeptide is also recognized for its contribution to colonization and growth of bifidobacteria in the gut of newborn infants.[17]
- **Lysozyme** – This highly anionic enzyme possesses antibacterial activity against a number of bacteria. It functions in association with lactoferrin or immunoglobulin A. In addition, lysozyme can limit the migration of neutrophils into damaged tissue and might function as an anti-inflammatory agent
- **Proline Rich Polypeptides (PRP)** – These whey-derived peptides are usually found at higher concentration in colostrum than in mature milk. Because of their high hydrophobic index they tend to aggregate. Interestingly, all these peptides are characterized by high content of proline, an amino acid suspected to be responsible for the neuroprotective effects of PRP in patients with Alzheimer's disease.[18]

The range of physiological responses that can be affected by milk-derived bioactive components is enormous, and includes functions related not only to digestion and absorption but also to the systemic functions of the immune system. The challenges to health care providers are to identify what ingredient constitutes specific activity, what is the optimal concentration, and possibly, whether any composition with other ingredients can increase the performance of such functional food. Indeed, over the last decade, an increasing body of evidence has accumulated showing that a combination of several bioactive ingredients may provide better health benefit. Many recently introduced products, such as Colostrinin, Neuroadvance, Biovien or Normalife, have emerged from research on proprietary blends of proteins, peptides and essential fatty acids.

While the health benefits, including improvement in cognitive functions, antimicrobial effects or immune stimulatory activities have been reported by patients taking these products, further research is needed, to fully appreciate the variety of physiological processes affected by such compositions. Nevertheless, the combination therapy or blending biologically active ingredients for single application seems to be superior over the individual applications in numerous studies.

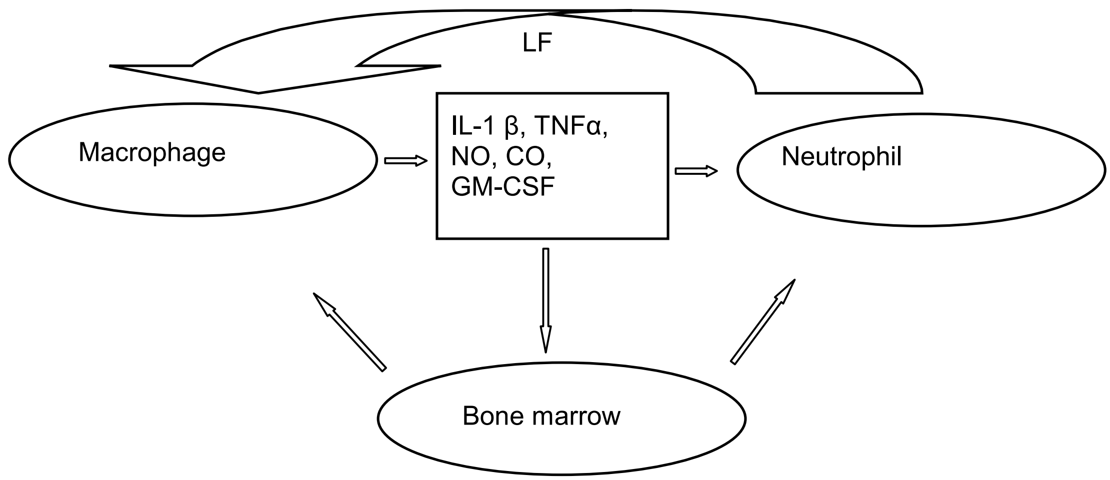

Figure 1. Modulatory effects of lactoferrin on outcomes of acute inflammation.
Insult defined by infection, toxic mediators (LPS) or trauma leads to activation of the monocyte/macrophage system and stimulates the production of IL-1ß, TNF-a, GM-CSF, CO and NO, which in turn activates circulating neutrophils and stimulates the production of fresh neutrophils and monocytes/macrophages from the bone marrow. Activated neutrophils degranulate at the site of injury and release massive amounts of the secondary mediators, including lactoferrin. By binding to the specific receptors on monocytes, lactoferrin attenuates the production of cytokines, which reduces the production and activation of fresh monocytes and neutrophils.

IMMUNOREGULATORY FUNCTIONS OF LACTOFERRIN

Lactoferrin is an iron binding protein thought to be an important component of the human host defense system and is particularly active at mucosal surfaces. A variety of biological functions have been ascribed to lactoferrin.[19-23] Of significance in this article are lactoferrin's bacteriostatic,[24] bactericidal,[25] and immunoregulatory properties.[26-30] Consideration of the physiological circumstances in which lactoferrin exerts its action may provide a guide through the maze of reactions and interplays. For example, during the development of an initial response to a Gram negative bacteria infection, vascular inflammation occurs within minutes and coincides with the burst of pro-inflammatory cytokines, such as tumor necrosis factor (TNFα), interleukin-1β (IL-1β), and colony stimulating factor (CSF) – all of which are derived from activated monocytes/macrophages. Subsequent to the release of cytokines, neutrophils acutely increase in the blood. Within an hour after the initial response to an insult, the bone marrow may speed up the production of fresh neutrophils by up to five times that of normal. Large numbers of neutrophils begin to invade the tissues that attract these cells. The feedback control of inflammation begins with degranulation of neutrophils and a massive release of lactoferrin (Figure 1). This in turn may affect the monocyte/macrophage system in two ways: (1) by suppressing the production of cytokines when lactoferrin binds to the specific receptor, or (2) by reducing the number of primed neutrophils for superoxide formation when lactoferrin binds to CD14 receptor as a complex with LPS.[31-35] In either way, the initial direct effect of lactoferrin (binding to LPS and/or receptor) will be translated into a cascade of immune responses with a variety of activities that often are not attributed to lactoferrin. Although the signals by which lactoferrin is released from neutrophils are different depending on the type and severity of insult, as well as the insults duration and location, lactoferrin seems to respond to those signals by sensing the physico-chemical, cellular, and humoral circumstances. Furthermore, when released from neutrophils, lactoferrin can modify the immune status of cells to develop adequate responses to pathogens or clinical insults.[36,37]

However, these systemic responses by endogenous lactoferrin are different from those obtained upon oral administration of an exogenous molecule. Exogenous lactoferrin must activate different signaling pathways to induce specific biological effects. As mentioned before, by virtue of iron sequestration, lactoferrin can control the physiological balance between reactive oxygen species (ROS) production and the rate of their elimination, which naturally protects against oxidative cell injury. Oxidative stress has been implicated in a variety of pathological and chronic degenerative processes including the development of cancer, atherosclerosis, inflammation, aging, neurodegenerative disorders, and defense against infection.[38-39] Although it is known that oxidant species are produced during metabolic reactions, it is largely unknown which factor(s), of physiological or pathophysiological significance, modulate their production in vivo. Under normal physiological conditions, the rate and magnitude of reactive oxidant formation is dependent on the availability of the transition metals. In particular, traces of iron can be detrimental to the physiological processes under reactive oxygen conditions. The formation of hydroxyl radical via the iron-dependent Haber-Weiss reaction has been implicated in phagocyte microbicidal activity and lipid peroxidation. Reactive oxygen species, in particular the hydroxyl radical, can react with all biological macromolecules (lipids, proteins, nucleic acids and carbohydrates). Among the more susceptible targets are polyunsaturated fatty acids. Abstraction of a hydrogen atom from a polyunsaturated fatty acid initiates the process of lipid peroxidation, and the intermediates, such as hydroxyalkenals (HNE), become new radicals that have the ability to induce functional changes in many biologically important macromolecules (Figure 2).

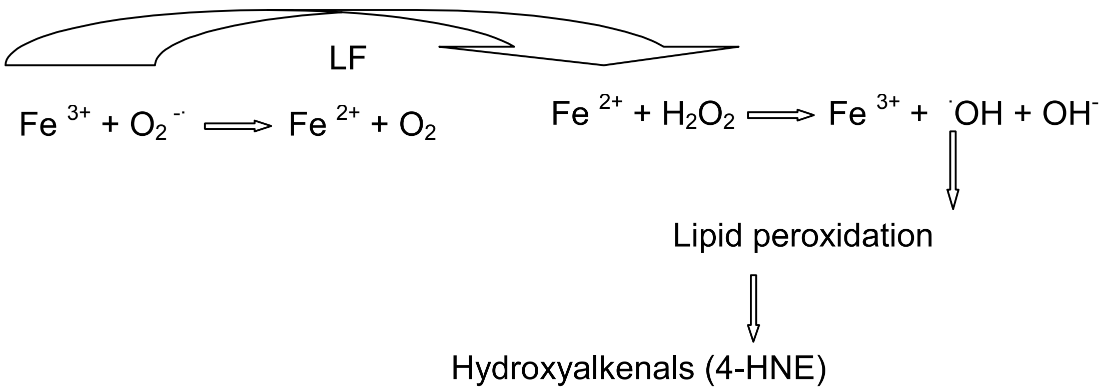

Figure 2. Reactive oxygen species (ROS) in iron-dependent oxidative stress.
At normal physiologic conditions, superoxide will spontaneously dismute and produce hydrogen peroxide. In the presence of free iron, hydrogen peroxide can be reduced to highly reactive hydroxyl radical. These reactions are regulated not only by metal chelators, such as lactoferrin, but also by the oxidative stress-controlling enzymes such as superoxide dismutase, glutathione peroxidase and catalase. A fine balance between ROS and antioxidants is required to maximize often-beneficial effects of ROS production (e.g. microbicidal effect of neutrophils).

Human Study

The effects of oral administration of lactoferrin on the proliferative response of peripheral blood mononuclear cells (PBMC) to mitogens, and the ability of PBMC cultures to produce IL-6 and TNFα, both spontaneously and upon LPS activation, were evaluated in healthy human individuals.[40]The responsiveness of the immune cells before and after lactoferrin treatment, consisting of 40 mg lactoferrin per patient for 10 days, was evaluated by measuring the level of IL-6 and TNFα. Two categories of individuals were selected based on the initial immune responsiveness of PBMC, relative to IL-6, high and low responders (Table 2). The additional moderate group was selected relative to TNFα (not shown). The *in vivo* effects of lactoferrin appeared to be regulatory and depended on the immune status of a given individual prior to the treatment. The down regulatory action of lactoferrin could be revealed already one day after treatment in the high-responding group. In the low responding group, on the other hand, the up-regulatory effect of lactoferrin became more evident two weeks after cessation of treatment. Lactoferrin affected to a much greater degree the ability of PBMC to produce TNFα and IL-6 spontaneously.

Generally, the spontaneous cytokine production was progressively decreasing. Since spontaneous cytokine production is dependent on cell-to-cell interaction via receptors,[41] including accessory adhesion molecules, such as LFA-1. The regulatory effects of lactoferrin on cytokine production could be also associated with the modulation of LFA-1 receptor expression.[42] A third parameter reflecting the effects of oral treatment of volunteers with lactoferrin, was a twofold increase in the content of neutrophil precursors in the circulating blood. This phenomenon resembles a similar event in the circulation elicited by infection or elective surgery, due to the release of endogenous lactoferrin from neutrophils. Therefore, it is concluded that immunomodulation by lactoferrin can lead to normalization of immunological imbalance or immunodeficiency.

Table2. Effect of orally administered lactoferrin on the spontaneous production of IL-6 by human PMBC

Initial Response	IL-6 Concentration (pg/ml)		
	Day 0	Day 1	Day 14
Low Responders	12.6±2.3	58.3±12.6	83.4±31.5
High Responders	280.1±19.5	121.5±24.1	78.6±18.6

Initial response: Low responders 0-49 pg/ml; High responders >199pg/ml.

CONCLUSIONS

Nutritional immunomodulation in disease and health promotion is a relatively new issue that confronts today's healthcare providers. The interrelationships among functional foods, immunity, disease, and health are complex, consisting of issues such as oral tolerance and the effects of specific nutrients on immune function or immune profiles in different physiologic conditions. It is the gastrointestinal tract, which possesses immunoregulatory properties, and maintains immunological function to protect the body during insult-induced metabolic imbalance from invading pathogens. It involves not only the gut wall barrier but also macrophages, other phagocytic cells and mast cells.

Over the past decade, pharmacologists have been diligently working on the development of immunomodulatory agents that promise to be effective in the treatment of many forms of chronic disorders, including bacterial and viral infections, various immunodeficiencies, and natural aging discomforts. Although many clinical protocols have been successfully developed for the pharmaceutical formulas, the functional food protocols are still to be developed. We must have a better understanding of how the presence of an insult is communicated through the various effector cells within the mucosal layer of the gastrointestinal tract to design more effective therapies. It is not just the severity of an environmental insult that determines the extent of the resultant injury but, rather, how the injury occurs within the context of the immune response to insult. In addition, we need to take into consideration the benefits of combining different bioactive ingredients, to complement many of the immune responses that are compromised during the development of chronic disorders, including naturally progressing aging processes.

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A4M
AMERICAN ACADEMY OF ANTI·AGING MEDICINE

Anti-Aging Wisdom

from the A4M

SUBJECT: Healthful Eating Trends

Mediterranean Diet: A notably low incidence of chronic diseases and high life-expectancy rates is present in populations living along the Mediterranean Sea (particularly Greeks and southern Italians):

- diet features grains, fruits, vegetables, legumes, nuts,
- diet features good fats -- olive oil and omega-3 fatty acids (fish)
- diet includes red meat only sparingly

Okinawan Diet: Elderly Okinawans have among the lowest mortality rates in the world from a multitude of chronic diseases of aging and as a result enjoy not only what may be the world's longest life expectancy and the world's longest health expectancy:

- low caloric intake
- high vegetables/fruits consumption
- higher intake of good fats -- omega-3s,
- monounsaturated fat
- high fiber in diet
- high flavonoid intake

Antioxidants (Vitamin A, C, E, and selenium) protect cells by neutralizing free radicals and beneficially altering the risk of disease:

- A study at UCLA School of Public Health found that men who took 300 mg of vitamin C daily had a 45% lower risk of heart attack compared with men who took less than the U.S. government Recommended Daily Allowance (RDA)
- In a Harvard study, vitamin E lowered heart attack risk by 41%
- Selenium decreases infection rates in the elderly, while vitamin E improves their immune response