proteinews

Issue 5

What's INSIDE

Role of Proteins in Immune System

Immunity and Nutrition

A well-functioning immune system is important for the survival.[1] As, impaired immune function increases the susceptibility to infections or disease.[2]

Immune system recognizes foreign pathogens

↓

Series of Responses

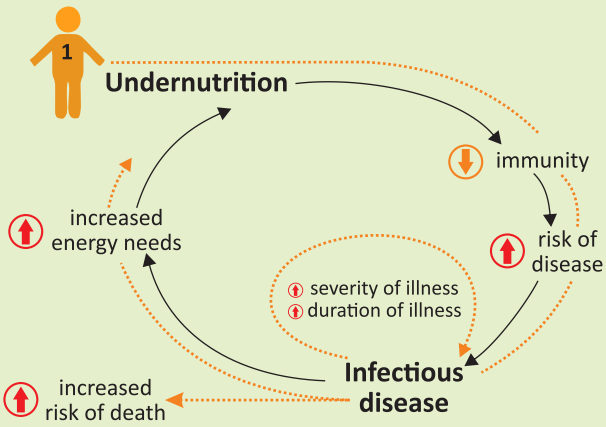
↓

Eliminate the infectious material

And an activated immune system increases the energy demand during infection periods. Thus, sufficient and proper nutrition is required for optimum functioning of the cells in the immune system to initiate effective responses against pathogens.[1]

Diet and nutrition are important for the development and maintenance of an effective immune system.[2] Whereas, poor nutritional status has an adverse effect on immune function and predisposes to increased mortality (figure 1).[3]

Figure 1: The vicious cycle of undernutrition and infectious disease[4]



Brought to you by:

Patients who are malnourished have deficits in immunologic response.[5] Protein-energy malnutrition can cause immunodeficiency which further increases the frequency and severity of infection.[6] It also alters the number of T-cells, phagocytic cells, and secretory immunoglobulin (Ig) A antibody response, as well as reduces levels of several complement components.[7]

Studies have reported "Better immune function in patients receiving nutritional supplementation prevents secondary infection.[5]

Most of the immune mechanisms depend on production of active protein compounds. Thus, adequate protein consumption is required to strengthen the immune system.[8]

Protein

Proteins are the frame work of cells, body defense systems, enzymes, and hormones. Adequate protein consumption is important to keep the immune system strong. The functioning of the immune system decreases in deficiency of protein and essential amino acid.[8]

Decrease in humoral and cell-mediated response and increase in oxidative stress was observed in severe protein and protein-energy deficiency. While, amino acid deficiency particularly arginine and glutamine decreases immune competence, i.e., impairment of T-cell development and growth, thymic integrity, and leukocytes energy source.[7]

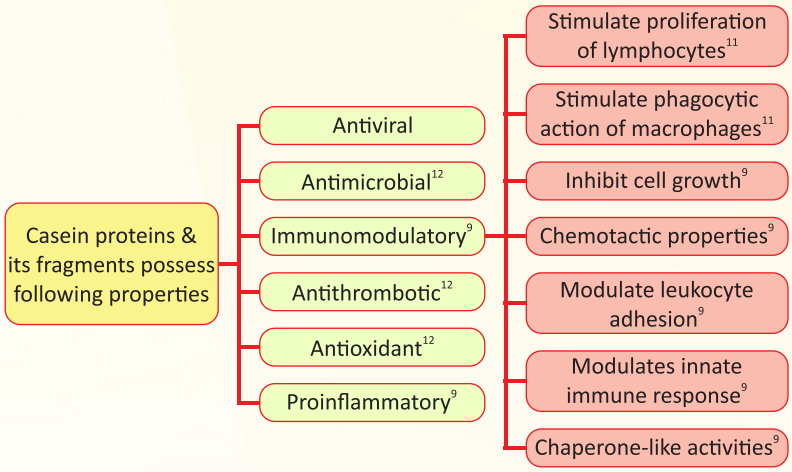
Casein is the major protein constituents of milk.

Casein

Casein is the main source of amino acid.[9] Caseins proteins and its fragments are multifunctional and exert numerous immunomodulatory action such as it chemo-attract immune cells such as monocytes, act as chaperones, stimulate cellular immune functions such as macrophage phagocytosis (figure 2).[10] Casein proteins and its fragments regulates the innate immune response by both -

- Up-regulation to enhance killing of viruses
- Down-regulation to reduce detrimental conditions such as sepsis

Figure 2: Properties and Immunomodulatory actions of Casein and its fragments



Also, it link the innate immune system to the adaptive immune system by activating or enhancing the functions of B- and T-cell.[11]

Casein is a potent inflammatory mediator which leads to the chemotactic migration of neutrophils.[13] Casein affect B lymphocyte proliferation by suppressing lipopolysaccharide mediated tumor necrosis factor (TNF)-α release.[14] With the mitogenic and IgA enhancing effect, casein phosphopeptides has beneficial effects on the immune system.[11]

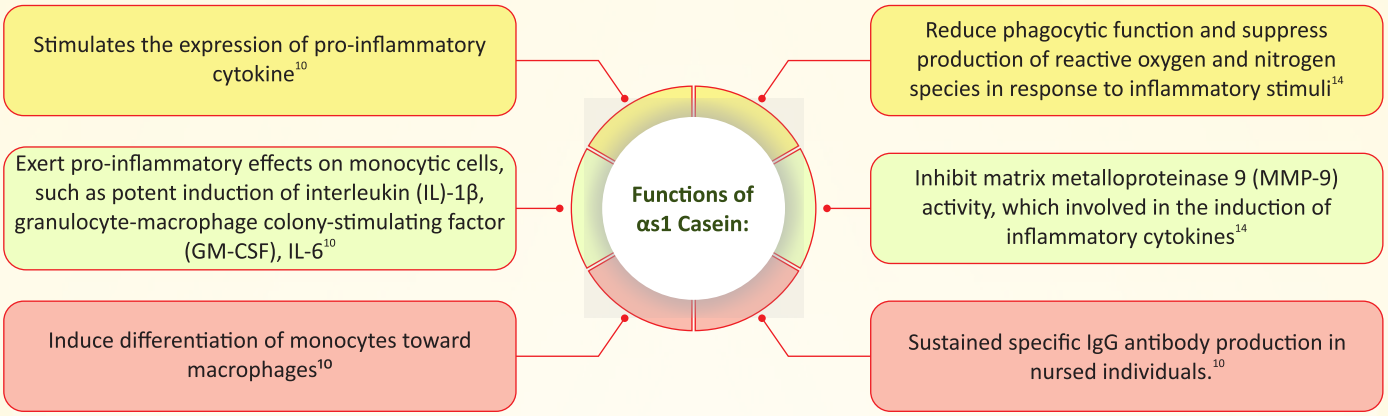
Thus, a casein-derived bioactive nutraceutical with immuno-modulatory properties which have prominent role in both

innate and adaptive immunity would be of great importance.[16] Casein proteins have several different subunits or types, including:[11]

- Alpha s1 (αs1) casein
- Alpha s2 (αs2) casein
- Beta (ß) casein
- Kappa (κ) casein

Alpha Casein

α-casein is an immunogenic protein.[15] Apart from the nutritional functional, αs1 casein may possess an immunomodulatory properties.[9] It also exerts pro-inflammatory properties through toll-like receptor (TLR-4) and inflammasome pathway in a phosphorylation-dependent manner.[10]



While, αs2-casein have activity against a range of Gram-positive and Gram-negative bacteria.[17] The peptides derived from αs2-casein are:

- **Casocidin:** Derived by hydrolysis of αs2-casein by chymosin. It have antibacterial properties against *Staphylococcus spp, Sarcina spp, Bacillus subtilis, Diplococcus pneumoniae,* and *Streptococcus pyogenes.*
- **Isracidin:** Released by of chymosin. It have antibiotic properties against *Staphylococcus aureus* and *Candida albicans.*[18]

Beta Casein

ß-casein is an important source of amino acids. It has two primary variants of ß-casein, termed A1 and A2, and several rare sub-variants.[19] Functions of ß-casein:

- Mitogenic effect on human T, B, and monocyte cells[20]
- Enhance production of oxidant species and pro-inflammatory cytokines[14]
- IgA-enhancing effect on B cells[20]
- Enhanced CD19+ proliferation and IL-6 production of cells mediated by TLR4[21]

The active peptides production from the ß-casein are opiate-like ß-casomorphins, morphiceptin and immunostimulating peptides. They stimulate phagocytic activity of macrophages and can have a role in the proliferation and maturation of T cells and natural killer cells for the defense of the neonate against a large range of bacteria.[22]

Hence, food products containing ß- casein can be beneficial for the human body's immune response.[20] Histidine residue at 67th position of A1 ß-casein allows cleavage of the preceding 7 amino acid residues which leads to the formation of the peptide ß-casomorphin-7 (BCM-7).[19]

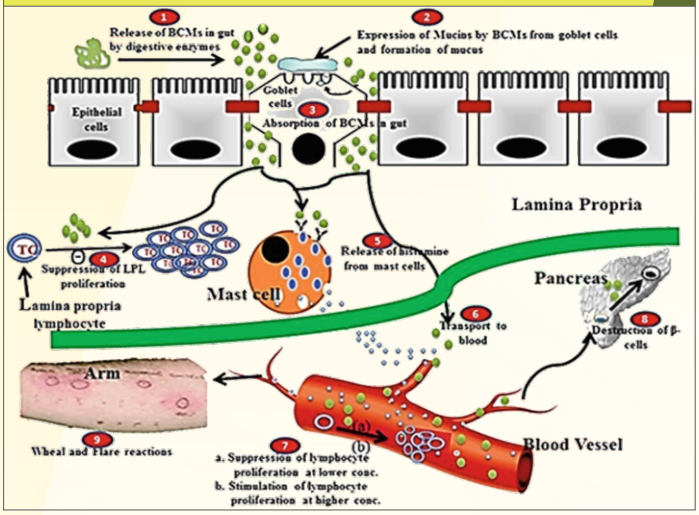
ß-casomorphin

BCM-7 is a peptide sequence present in the milk protein ß-casein. It exerts many immunological activities like chronic inflammatory responses, such as allergy, mucin production, lymphocyte proliferation, skin reactions (figure 3).[23]

BCM-7 contributes to innate immunity.[23] It trigger histamine release from peripheral leukocytes and stimulate secretion by peritoneal mast cells. BCM-7 also alters lymphocyte proliferation through a pathway mediated by opiate receptors.[19] It increased the prolactin level which act as a regulator of the immune system.

Thus, dairy products containing BCM-7 can improve intestinal protection and support innate immunity.[23]

Figure 3: Immunological roles of BCMs on different cells[23]



Kappa Casein

The κ-casein is an immunogenic protein.[15] Some of the fragments of κ-casein are:

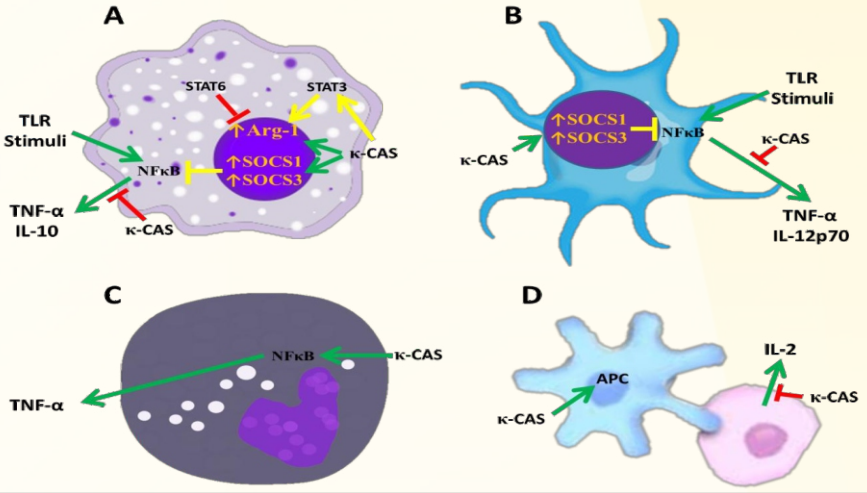
- **Caseinoglycopeptide (CGP):** Affect lymphocyte function and can modulate specific antibody responses.[13]
- **Glycomacropeptide (GMP):** Exhibit protective effects, increases IL-1Rα antagonist and reduces the upregulation of iNOS and IL-1.[14]
- **Caseinomacropeptide (CMP):** Possess growth-inhibitory activity against pathogens *Streptococcus mutans, Porphyromonas gingivalis* and *Escherichia coli.* It also depresses platelet aggregation, inhibit *influenza virus* hemagglutination and cholera toxin binding, and immunomodulating activities.[17]
- **Kappacin:** Novel antimicrobial peptide which limit gastrointestinal tract infection in the developing neonate and have antibacterial activity.[17]

Functions of κ-casein

- Has immuno-suppressive properties, such as reduces phagocytic function & suppresses production of reactive oxygen & nitrogen species.[16]
- Induces M2-like phenotype in macrophages, which are hypo-responsive to TLR induced cytokine production through abrogation of NFB pathway.[16]
- Significantly suppressed cytokine production.[14]
- Has the potential to affect T or B lymphocytes[13]
- Impair macrophages ability to release key inflammatory cytokine mediators; TNF-α and IL-10 in response to LPS.[14]

proteinews

Figure 4: Immunomodulatory effects exerted by κ-CAS.[14]



(A). κ-CAS abrogated TLR dependent induction of cytokines in macrophages (A) and DCs (B) by attenuating NFκB signaling. In contrast, κ-CAS induced secretion of TNF-α from human monocytes in NFκB dependent manner (C) κ-CAS reduced capacity of all 3 cell types to induce T-cell response, significantly attenuating their ability to induce IL-2 from CD4+ T-cells (D).

Benefits of using bioactive proteins in immunomodulation

They do not exhibit unwanted side effects which are commonly observed with traditional chemical pharmacologic drugs. Due to the powerful immune-modulatory effects showed by fragment of κ-casein and since, most of the human diseases are immune-related. There is a potential and demand for the development of κ-casein fragment as an immunomodulatory nutraceutical and possible use as a novel immune therapeutic to treat inflammatory diseases like inflammatory bowel disease (IBD) in humans.[14]

Sufficient and proper nutrition is required for optimum functioning of the immune cells. Improvement in nutritional status is associated with improved immunity which prevents infection. Adequate protein consumption is important to keep the immune system strong. Casein protein-derived bioactive nutraceutical with immuno-modulatory properties which have prominent role in immunity would be of great importance. Food products containing ß- casein can be beneficial for the human body's immune response. κ-casein is a viable alternative to the drugs, as it have low toxicity, easily degraded and does not accumulate in body tissues.

REFERENCES: 1. Childs CE, Calder PC, Miles EA, Diet and Immune Function, Nutrients. 2019 Aug 16;11(8):1933.; **2.** Rytter MJH, Kolte L, Briend A, Friis H, Christensen VB, The Immune System in Children with Malnutrition—A Systematic Review. PLoS ONE. 2014; 9(8): e105017.; **3.** Woo J, Ho SC, Mak YT, Law LK, Cheung A, Nutritional Status of Elderly Patients during Recovery from Chest Infection and the Role of Nutritional Supplementation Assessed by a Prospective Randomized Single-blind Trial, Age and Ageing 1994:23:40-48.; **4.** The vicious cycle of undernutrition and infectious disease: How does it work and what role do vaccines play?, https://immunizationevidence.org/featured_issues/undernutrition-and-infectious-disease/, last accessed on 5th February 2021.; **5.** Nayel H, El-Ghoneimy E, El-Haddad S, Impact of Nutritional Supplementation on Treatment Delay and Morbidity in Patients with Head and Neck Tumors Treated with Irradiation, Nutrition. Jan-Feb 1992;8(1):13-8.; **6.** Marcos A, Nova E, Montero A, Changes in the immune system are conditioned by nutrition, Eur J Clin Nutr. 2003 Sep;57 Suppl 1:S66-9.; **7.** Gershwin ME, Nestel P, Keen CL, Handbook of Nutrition and Immunity, © 2004 Humana Press Inc.; **8.** Karacabey K, Ozdemir N, The Effect of Nutritional Elements on the Immune System, J Obes Wt Loss Ther 2012, 2:9.; **9.** Vordenbäumen S, Braukmann A, Petermann K, Scharf A, Bleck E, von Mikecz A, et al., Casein α s1 is expressed by human monocytes and upregulates the production of GM-CSF via p38 MAPK, J Immunol. 2011 Jan 1;186(1):592-601.; **10.** Vordenbäumen S, Saenger T, Braukmann A, Tahan T, Bleck E, Jose J, et al., Human casein alpha s1 induces proinflammatory cytokine expression in monocytic cells by TLR4 signaling, Mol Nutr Food Res. 2016 May;60(5):1079-89.; **11.** Sun H, Jenssen H, (September 12th 2012). Milk Derived Peptides with Immune Stimulating Antiviral Properties. Hurley WL, Milk Protein: © 2012 Sun and Jenssen; licensee InTech.; **12.** Ul Haq MR, Kapila R, Sharma R, Saliganti V, Kapila S, Comparative evaluation of cow β-casein variants (A1/A2) consumption on Th2-mediated inflammatory response in mouse gut, Eur J Nutr. 2014 Jun; 53(4):1039-49.; **13.** Cross ML, Gill HS, Immunomodulatory properties of milk, Br J Nutr. 2000 Nov;84 Suppl 1:S81-9.; **14.** Lalor R, Immunomodulatory properties of bovine caseins on innate immune cells, August 2019, http://doras.dcu.ie/23614/1/Immunomodulatory%20properties%20of%20bovine%20caseins%20on%20innate%20immune%20cells.pdf, last accessed on 5th February 2021.; **15.** Fuc E, Złotkowska D, Stachurska E, Wróblewska B, Immunoreactive properties of α-casein and κ-casein: Ex vivo and in vivo studies, J Dairy Sci. 2018 Dec;101(12):10703-10713.; **16.** Lalor R, O'Neill S, Bovine κ-Casein Fragment Induces Hypo-Responsive M2-Like Macrophage Phenotype, Nutrients. 2019 Jul 23;11(7):1688.; **17.** Malkoski M, Dashper SG, O'Brien-Simpson NM, Talbo GH, Macris M, Cross KJ, et al., Kappacin, a novel antibacterial peptide from bovine milk, Antimicrob Agents Chemother. 2001 Aug;45(8):2309-15.; **18.** Szwajkowska M, Wolanciuk A, Barłowska J, Król J, Litwińczuk Z, Bovine milk proteins as the source of bioactive peptides influencing the consumers' immune system – a review, Animal Science Papers and Reports.2011;29(4):269-280.; **19.** Sadler MJ, Smith M, Beta-casein proteins and infant growth and development, Infant. 2013; 9(5): 173-76.; **20.** Kawahara T, Katayama D, Otani H, Effect of beta-casein (1-28) on proliferative responses and secretory functions of human immunocompetent cell lines, Biosci Biotechnol Biochem. 2004 Oct;68(10):2091-5.; **21.** Tobita K, Kawahara T, Otani H, Bovine beta-casein (1-28), a casein phosphopeptide, enhances proliferation and IL-6 expression of mouse CD19+ cells via Toll-like receptor 4, J Agric Food Chem. 2006 Oct 18;54(21):8013-7.; **22.** Migliore-Samour D, Jollès P, Casein, a prohormone with an immunomodulating role for the newborn? Experientia. 1988 Mar 15;44(3):188-93.; **23.** Raies ul Haq M, Kapila R, Shandilya UK, Kapila S, Impact of Milk Derived β-Casomorphins on Physiological Functions and Trends in Research: A Review, International Journal of Food Properties.2014; 17(8):1726-1741.