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Popular Article

Lactopontin: A Bioactive milk protein and its health benefits

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Introduction

Milk is a natural source of nutrients and bioactive proteins necessary for the health and growth of infants. The milk proteins possess bio-functional activities with considerable physiology for health and protection against infection and disease. Milk contains different types of bioactive proteins like lactoferrin, lactoperoxidase, immunoglobulins, mucin-1, lysozyme, lactophorin and several other milk proteins derived bioactive components. Among the many different components likelipids, lactose, human milk oligosaccharides, proteins are crucial nutritional and bioactive molecular factors in human milk. In recent years, osteopontin (OPN) in milk are also known as lactopontin (LPN) (Shiraga *et al*., 1992: Senger *et al*., 1989), has concerned that much attention. Lactopontin is one of the important minor bioactive milk protein. Lactopontin is also known as early T cell activation gene-1, uropontin, nephropontin, urinary stone protein, osteopontin, bone sialoprotein, and secretory phosphoprotein but it is commonly named as osteopontin. OPN was first identified in bone tissue as a bone matrix protein (Brown *et al*., 1992; Schack , Schack *et al*.,2009) and has a various physiological fluids of human, rat, mouse, pig, cow, buffalo and rabbit but milk is the its richest source. LPN is classified as matricellular protein of interleukin family. Lactopontin is recognized as an early acting cytokine regulating the intensity and duration of immune response by exerting a variety of effects on lymphocytes and other immune cells.

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Lactopontin occurrence in milk

Lactopontin has been isolated from milk of various species by a combination of different techniques like anion exchange, size exclusion, hydrophobic interaction, negative affinity and reverse phase-high performance liquid chromatography (HPLC). The average value of Lactopontin in human milk is 138 mg/L, it is about 8 times higher than in bovine milk (18 mg/L) (Schack *et al.*, 2009). Microarray analyses of cells in human milk observed that the secreted phosphoprotein gene of LPN is highly expressed throughout the lactational stages (Nagatomo *et al.*, 2004). Lactopontin value was observed 3-22 mg/ l of milk, however, by the ELISA and immunological assays for lactopontin value has shown very high levels of 39.7 mg/ l in bovine milk. Lactopontin has been quantified from both milk and whey.

Biochemical function of Lactopontin

Lactopontin is a highly phosphorylated and sialic acid rich glycoprotein. Lactopontin is a glycosylated protein containing 1 N-linked and 5-6 0-linked oligosaccharides containing up to 33 carbohydrate residues. Its primary structure containing about 300 amino acid (AA) residues with variability depending on the species and total amino acid residues are serine, glutamate and aspartate residues. Lactopontin containing about 30 phosphorylated serine or threonine residues. Lactopontin has sulfated tyrosine in bone marrow but with non-sulfated tyrosine residues in bovine milk. Lactopontin mainly found in monomeric, dimeric and multimeric forms as revealed by dynamic light scattering and 180 kDa in western immune blotting. Its molecular mass is 32-34 kDa based on its amino acid residues but SDS-PAGE reveals a molecular mass of 50 to 60 kDa for its predominant form and molecular mass of 46, 30 and 20 kDa for minor components. Lactopontin contains iso-electric point (pI) is 3.8 and absorptivity at 280 is 0.72. It binds aluminum depending on its phosphyration and binding of Ca^{2+} is reduced in the presence of high Mg^{2+} concentration in the physiological pH range. LPN is capable to stabilize calcium by forming a soluble complex with calcium (Holt *et al.*, 2014), due to its integrins and receptors binding properties, LPN shows bioactivities in intestinal development, brain development, and immunological development (Jiang *et al.*, 2016). It has distinct functional domains; two integrin binding, two heparin binding and a typical arg-gly-asp (RGD) cell adhesion domain and a poly-aspartate sequence in the N-terminal part of the molecule contributes to its acidity, calcium and hydroxyapatite binding ability. Lactopontin also has a region with high sensitivity to multiple proteases, most notably to thrombin which cleaves it into two independent functional domains.

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Proteolysis derived bioactive components

Lactopontin is structurally and functionally modified by the proteolytic activity and its fragments can be produced by enzymatic or chemical changes. There is *in vitro* and *in vivo* evidence that thrombin cleavage modulates integrin binding protein functions with most of the biological activity residing in the N-terminal fragment and it is cleaved by certain matrix metalloproteinase. Lactopontin is stable to proteolysis by gastric proteases at the value of pH 4.0 and above while its fragments are slightly degraded. It has been reported that even at pH 2.0 the intact molecule is resistant to digestion by infant gastric proteases.

Health benefits of Lactopontin

Lactopontin functions are elusive in milk and it is yet to be established if lactopontin or peptides derived from it are absorbed from the gastrointestinal tract. The lactopontin retain their biological activity and are transported to possible sites for action within the body. It is strongly association with the physiological activity and clinical pathology. There are various health benefits of lactopontin like-

i. Lactopontin binds to the hydroxyapatite matrix of bone via a conserved unique stretch of aspartate residues. Its gene is associated with resistance to bacterial and viral infections including infection with *Mycobacterium*, *Bacillus Calmette-Guerin* and *Rikettsia tsutsugamushi*.

ii. Lactopontin has cell attachment capability and many cell types bind via multiple integrin receptors.

iii. It acts as a cell regulator factor by preventing the apoptotic cell death after a wide range of stresses and ameliorates damage after ischemia or reperfusion.

iv. It helps to the generation of immunoglobulins (Ig) and cell-mediated immune responses.

v. Lactopontin inhibits nitric oxide synthase exerting beneficial effects on surrounding tissues in case of injury.

vi. It is beneficial to pulmonary granuloma formation due to tuberculosis, sarcoidosis, formation and structure of wound healing.

vii. It has beneficial to heart coping with stress, cardiac hypertrophy and fibrosis, restenosis, repair of myocardial wounds, coronary artery diseases, atherosclerotic and calcified plaques.

viii. It has an important function of the urinary tract defense against the formation of renal stones and inhibits the nucleation, growth and aggregation of calcium oxalate crystals.

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ix. Lactopontin prevents ectopic calcification occuring with renal failure, cardiovascular disease (CDs), diabetes, muscle cell calcification and aging process.

x. It is associated with allergic conjuctivitis, calcium phosphate deposition in the middle ear, periodontal disease, multiple sclerosis, arthritis and intestinal pneumonia.

xi. Lactopontin has been identified as a novel target for the treatment of inflammatory liver diseases in patients suffering from massive liver necrosis in hepatitis.

xii. Lactopontin has related to a leading biomarker candidate for tumor progression and disseminated cancer.

Conclusion

Lactopontin (LPN) is a highly phosphorylated, *O*-glycosylated acidic protein. It is a unique type of OPN. It presents at the highest concentration and a higher degree of posttranslational modifications (PTMs) in human milk. Lactopontin is present in milk and the intestinal tracts of infants after consumption as a mixture of intact protein and peptides, which can bind with diverse integrin and receptors in the target cell and drive downstream signaling pathways. Lactopontin is found to play important roles in developing the immune activity, intestinal and nervous systems in early life. Lactopontin has also shown to support preterm for infants health. Lactopontin can form protein complex with another milk bioactive protein, lactoferrin (LF), to withstand proteolysis and perform more efficient biological activity. Therefore, Lactopontin showed great potential for early life and health benefits.

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