THE SCIENCE WORLD
A Monthly e Magazine
ISSN:2583-2212
Popular Article
June, 2023; 3(06), 1041-1044

Immunomodulatory effects of lactoferrin

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https://doi.org/10.5281/zenodo.8055012

Introduction

Lasctoferrin (LF) is an 80 kDa iron-binding protein of the transferrin family that is abundantly expressed in most biological fluids. It is now recognized that this glycoprotein is a key element in the mammalian immune system, playing an important role in host defence against infection and excessive inflammation. Lf can bind and sequester lipopolysaccharides (LPS), thus preventing proinflammatory pathway activation, sepsis and tissue damage. Lf is considered to be a cell-secreted mediator that bridges the innate and adaptive immune response. It is released from neutrophils (PMNs) in the blood and inflamed tissues. Lf has a direct antimicrobial role, as it limits the proliferation and adhesion of microbes (e.g., bacteria, viruses and parasites) and/or kills them. This effect of Lf is the result of its ability to sequester iron in biological fluids and destabilize the membranes of microorganisms. The metals that it binds are the $Fe2+$ or $Fe3+$ ions, also can exist free of $Fe3+$ (apo-Lf). It is a simple polypeptide chain folded into two symmetrical lobes (N and C lobes), which are highly. These two lobes are -helix between in human LFαconnected by a hinge region containing parts of an (hLF). Lf also acts as a first-line of defences by significantly impacting the development of adaptive immune responses. Iron sequestration by Lf reduces oxidative stress, thus altering the extension and specific production of cytokines. Lactoferrin has a strong modulatory effect on the adaptive immune system by accelerating the maturation of T-cell precursors into competent helper cells and by the differentiation of immature B-cells into antigen-presenting cells.

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Published 19.06.2023

Lf can also modulate both innate and adaptive immunities by acting as a Toll-like receptor (TLR4) or by interacting with lymphocytes and antigen-presenting cells (APCs).

Antimicrobial activities of lactoferrin

Several functions have been attributed to Lf. It is considered to be a key component of the innate host defence system because it can respond to a variety of physiological and environmental changes. The structural features of Lf provide additional functionalities beyond the Fe+3 homeostasis function common to all transferrins. Specifically, Lf exhibits strong antimicrobial activity against a broad spectrum of bacteria (Gram+ and Gram−), fungi, yeasts, viruses and parasites, although it seems to promote the growth of beneficial bacteria like Lactobacillus and Bifidobacterium. It also exhibits anti-inflammatory and anticarcinogenic activities and has several enzymatic functions. Lf plays a key role in maintaining cellular iron levels in the body. One of the first antimicrobial properties discovered for Lf was its role in sequestering iron from bacterial pathogens. This was believed to be the sole antimicrobial action of lactoferrin because apo-lactoferrin possessed antibacterial activity. It was later demonstrated that lactoferrin can also kill microorganisms through an iron-independent mechanism in which lactoferrin directly interacts with the bacterial cell surface.

Immunomodulatory and anti-inflammatory activity

Lf displays immunological properties that influence both innate and acquired immunities. Its relationship with the immune system is evident from the fact that people with congenital or acquired Lf deficiency have recurring infections. Oral administration of bLf seems to influence mucosal and systemic immune responses in mice. Lf can modulate both specific and non-specific expression of antimicrobial proteins, pattern recognition receptors and lymphocyte movement related proteins. The role that Lf plays in regulating innate immune responses confirms its importance as a first line host defence mechanism against invading pathogens, modulating both acute and chronic inflammation. Most intriguing is the ability of Lf to induce mediators from innate immune cells that subsequently impact adaptive immune cell function. Lf's positive charge allows it to bind to negatively charged molecules on the surface of various cells of the immune system, and it has been suggested that this association can trigger signalling pathways that lead to cellular responses such as activation, differentiation and proliferation. Lf can be transported into the nucleus, where it can bind DNA and activate different signalling pathways. In addition to inducing systemic immunity, Lf can promote skin immunity and inhibit allergic responses. It activates the immune system against skin allergens, causing dose-dependent inhibition of Langerhans cell migration and the accumulation of dendritic

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Published 19.06.2023

cells in lymph nodes. Leukocytes exposed to Lf modulate their cytokine production; proinflammatory cytokines, TNF-α, IL-6, and IL-1β can be modulated by Lf to increase or decrease .. It is well documented that IL-12 plays an important role in driving development of helper T-cell type 1 immunity. Therefore, the role of Lf in the regulation of proinflammatory cytokines and IL-12 clearly demonstrates communication between innate and adaptative immune responses.

Lactoferrin from other species

The different benefits of Lf have led us to be interested in using molecular strategies to develop recombinant Lf from different species to increase its availability. Because of its broad antimicrobial capacity, Lf could be used as a nutraceutical protein or adjuvant drug. Although colostrum contains high Lf levels, industrial companies will require the production or purification of Lf without affecting the alimentary industry uses of milk. Currently, highly purified bovine lactoferrin (bLf) and human lactoferrin (hLf) can be produced. In addition, lactoferrin from other species (*eg*, mouse, rat, chimpanzee, boar, sheep, goat, buffalo, camel and dog) was sequenced and found to vary by 2112 to 2530 bp. It has been possible to produce recombinant Lf specific to human, bovine, equine, porcine, caprine, yak and Kunming by using various expression systems (*eg*, bacteria, fungi, yeast, cell lines, insects, mammals and plants). While Lf is produced in quantities ranging from 0.756 mg/L to 10.6 g/L, human Lf remains the most expressed among all of the different expression systems.

Future applications of Lactoferrin

Lf has multiple activities, it can bind a significant number of compounds and substances, such as lipopolysaccharides, heparin, glycosaminoglycans, DNA and metal ions (*eg*, Fe, Al, Mn, Co, Cu, Zn) is involved in iron homeostasis; has a wide range of antimicrobial activity against bacteria, virus, fungi and parasites; and has anti-inflammatory, immunomodulatory, anticarcinogenic and enzymatic activities. Antibiotic-resistant microorganisms are extremely dangerous to humans, and extensive scientific research has resulted in the development of new antibiotics with different effects in an effort to solve the issue. The scientific community has targeted Lf as a promising candidate to help break the vicious cycle of antibiotic resistances. Oral Lf supplementation in human newborns can prevent infection or decrease the severity of an existing infection.

Conclusions

Lf is a versatile molecule that was moulded by natural selection to be a first-line defence in mammals. Its ability to exert multiple regulatory effects due to its cationic nature allows it to bind a

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Published **19.06.2023**

large number of surface molecules or metal ions during the development of microorganisms and induce host immune-modulatory activation, which influences the adaptive and innate immunities. The development of Lf expression systems for food and pharmaceutical applications are required, due to its plethora of abilities as a multifunctional, nutraceutical protein.

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Published **19.06.2023**