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Review article

Multifunctional capacity and therapeutic potential of lactoferrin

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ABSTRACT

Lactoferrin (LF) is a glycoprotein with high functional versatility that is found in most body fluids. The objective of this study was to gather and update information on the properties attributed to LF.

According to this review, LF is a good immunomodulatory agent that acts on both innate and adaptive immune responses. It possesses antimicrobial activity against parasites, fungi, and viruses and also has regenerative properties at tissue level and anti-carcinogenic activity. All of these properties endow LF with major therapeutic potential of which little advantage has been taken to date.

1. Introduction

Lactoferrin (LF) is a glycosylated globular protein first known as the "red protein" of milk. It was subsequently defined as an iron-binding protein due to its sequestration of Fe^{2+} and Fe^{3+} free ions and is therefore included in the group of metalloproteins [1]. It is found in human secretions such as breast milk (especially in the colostrum), seminal fluid, uterine secretions, tears, and saliva. LF is synthetized by different cell populations, including neutrophils (polymorphonuclear lymphocytes), macrophages, and glandular epithelial cells, and it is mainly secreted in response to inflammatory processes [1–4]. This biomolecule has a multifunctional capacity, including: immunomodulatory properties in relation to innate and adaptive immune responses [1–4]; antimicrobial capacity against bacteria, parasites, fungi, and viruses [5]; antioxidant and anti-inflammatory activity, contributing to its tissue regeneration capacity [6]; and anti-carcinogenic activity, by direct effect on transformed cells or by indirect effect *via* the immune system [7].

The broad functional capacity attributed to LF suggests that it may have major therapeutic potential, and this review of the literature was designed to provide an update of scientific knowledge on this biomolecule and its properties.

2. Immunological Properties of Lactoferrin

LF is considered to be capable of modifying innate and adaptive immune responses by inducing or suppressing immune system components [3,4,8].

LF plays an important role during the first stages of life, and human colostrum contains high concentrations (7 g/L), while breast milk has a lower concentration (1 g/L). A key function of colostrum is to provide neonates with essential components for the development of their immune system, and it therefore exerts a protective function [9,10]. This is provided at systemic and local level in the neonate intestine by supporting postprandial pH and favoring the protection and development of the immature intestine. LF modulates the immune response of lymphoid tissue associated with intestinal tissue and also promotes the concentration-dependent proliferation and differentiation of small epithelial cells, thereby affecting the mass, length, and expression of small intestine digestive enzymes [1,8,11]. These effects explain why LF is given to children as a dietary supplement in various countries. No adverse effects of its use have been reported to date [12].

One of the main functions of LF at immune system level is to interact with antigen-presenting cells, including macrophages, dendritic cells, and B lymphocytes [13]. Macrophages are phagocytic cells *par excellence*, with an essential role in controlling infection by the

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intracellular destruction of microorganisms or by inhibition of their replication through the secretion of cytokines or mediators such as nitric oxide (NO). They are also involved in inflammation, secreting inflammation mediators and proinflammatory cytokines, which participate in tissue repair as a final stage of the inflammatory process [13,14]. Macrophages are activated by interaction of LF with their LF receptors, increasing their phagocytic capacity and their synthesis of IL-12, a molecule that attracts more macrophages to the inflamed area and activates T $CD4^+$ lymphocytes [2,13].

Dendritic cells are a heterogeneous cell population highly specialized in antigen recognition, and they are considered to play a key role in the immune system by controlling the induction of immunity and tolerance. The interaction of LF with dendritic cells *via* specific receptors on their surface induces their maturation and therefore functional activity. Dendritic cells maturation by Talactoferrin, a recombinant human LF, displayed an enhanced release of IL-8 and chemokine CXCL10, as well as a significantly reduced production of IL-6, IL-10, and chemokine CCL20 [15].

LF acts on B lymphocytes and other antigen-presenting cells by activating and accelerating antigen processing, enabling the interaction and activation of T cells. The presence of LF can also stimulate B lymphocyte differentiation and maturation, increasing their capacity to present T lymphocytes [2]. The oral administration of LF was reported to increase IgA and IgG secretion in mice [2,16] and was even found to produce humoral recovery in immunosuppressed mice, suggesting that it can stimulate the proliferation and differentiation of activated B lymphocytes [17].

In summary, LF exerts an immunomodulatory function on antigen-presenting cells in general, producing their activation, maturation, and migration to inflamed areas [1,2,4,13].

In a murine study, Tomita M et al. [18] found that LF bound to receptors on enterocytes, dendritic cells, and lymphocytes, inducing the release of cytokines and increasing the number of NK, $CD4^+$, and $CD8^+$ cells. This response favors the systemic immune response, with an increase in immune cells, humoral factors, and cytokines in lymph nodes and spleen that then migrate to the whole organism. These effects are largely attributable to the immunomodulatory role of LF, with increases in cytokines of the TH1 response, maturation of dendritic cells, a greater activation of macrophages, and a higher cytotoxicity of peritoneal NK cells.

LF can also modulate the functional capacity of T lymphocytes by acting on the maturation process, inducing CD4 expression and therefore directing differentiation of immature T lymphocytes toward the $CD4^+$ T lymphocyte subpopulation [2,14]. It can also change the balance between TH1 and TH2 subpopulations of $CD4^+$ cells by promoting TH1 responses (IL-2 and IFN-γ synthesis) and inhibiting TH2 responses (IL-4, IL-5, and IL-13 synthesis), activating cell responses and reducing the release of inflammatory factors. Thus, LF controls allergic rhinitis by inhibiting the response of TH2 and TH17 lymphocyte subpopulations, which are directly involved in allergic responses [19].

However, LF may possess anti-inflammatory activity, and various clinical trials found that LF may prevent sepsis by controlling TNF-α, a cytokine directly implicated in septic shock [20].

3. Antimicrobial Activity of LF

The antibacterial activity of Lf has been documented in the past, both *in vitro* and *in vivo* for Gram-positive and Gram-negative bacteria and some acid-alcohol resistant bacteria. Differents studies shown that LF structure plays an essential role in this activity [2,4,21].

3.1. Antibacterial activity

Various highly diverse microorganisms (*Haemophillus influenzae*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Listeria monocytogenes*, *Legionella pneumophila*, *or Mycobacterium tuberculosis*) have proven susceptible to the action of LF, which can have bactericide and/or bacteriostatic effects [21].

One of the mechanisms underlying the bacteriostatic activity of LF is its capacity to bind to large amounts of iron, impeding its utilization by microorganisms for growth [22].

The bactericidal activity of LF mainly occurs by direct interaction with bacterial surfaces. Thus, the permeability of the bacterial membrane of Gram-negative bacteria can be damaged by interaction of the protein fraction of LF (its structure has cationic areas) with the A lipid of the lipopolysaccharide (LPS) (anionic character) and its subsequent neutralization [22]. LF can interfere with bacterial adhesion by binding with LPS, thereby inhibiting of one of the most important virulence factors of these microorganisms [4,21,23].

The interaction of LF with LPS or other bacterial membrane proteins is known to enhance the effect of natural bactericides such as lysozymes, which are secreted in high concentrations alongside LF in mucosa. LF acts against Gram-positive bacteria by binding to anionic molecules (*e.g.*, lipoteichoic acid) on the bacterial surface, reducing the negative load on the bacterial cellular wall. This favors contact between lysozyme and peptidoglycan, facilitating the enzymatic effect [1]. LF can also enhance the effect of certain bactericide drugs, such as Rifampicin [21,22].

Furthermore, the interaction of LF with fractions of microbial origin promotes the release of proinflammatory mediators, including cytokines (IL-1, IL-6, IL-8, IL-12 and TNF-α), lipid mediators, and reactive oxygen species. Its ability to bind to bacterial oligonucleotides means that it impacts on B cells, probably by interacting with Toll-like receptors (TLRs) such as TLR-9, mainly present in dendritic cells, macrophages, and B lymphocytes, which play a key role in the onset of the inflammatory response and pathogen detection [8,21].

3.2. Antiviral activity

The antiviral activity of LF against DNA and RNA viruses with or without viral envelope has been known since 1994 [24]. LF can protect the host from viral infections by inhibiting the binding of the virus to target cells, thereby hindering its subsequent intracellular replication, and by improving systemic immune functions [25].

Various action mechanisms have been proposed to underlie antiviral effects of LF, and one of the most widely accepted is based on its ability to bind to and block viral receptors such as glycosaminoglycans, especially heparan sulfate (HS). Thus, the binding of LF to HS avoids the first contact between host cell and virus, preventing viral infection [26]. Immune system modulation is another proposed mechanism, and LF was found to increase the phagocytic activity of macrophages in infections by vesicular stomatitis virus infections [2]. LF administration also enhances Natural Killer (NK) cell activity and the response of TH1 lymphocytes, which secrete cytokines that protect against viral infection [25].

In an *in vitro* study on the HepG2 cell line of hepatocytes infected with hepatitis B virus (HBV), Li et al. [27] found that replication of the virus was significantly inhibited by treatment with LF or iron- and zinc-saturated LF, suggesting that LF may be a potential resource in anti-hepatitis B therapy.

In vitro studies and clinical trials have demonstrated that treatment with complete LF or previously purified fractions can inhibit hepatitis C virus (HCV) replication at intracellular level, but contradictory data have been published on their capacity to prevent entry of the virus into the target cell [24].

LF has demonstrated a powerful inhibitory activity against human immunodeficiency virus (HIV), while some LF fragments, such as lactoferricin, were found to exert a mild inhibitory action on HIV-1 reverse transcriptase and HIV-1 integrase [26]. According to Carthagena et al. [28], LF can interfere with HIV-1 transmission at mucosal level, blocking its binding to epithelial cells, and with its transmission from dendritic cells to T $CD4^+$ cells, two crucial steps in HIV diffusion from

mucosa to lymphoid tissue.

In other viral processes, *e.g.*, skin infection by herpes simplex virus (HSV-1), LF increases the TH1 lymphocyte production of cytokines, including IFN- γ, IL- 12, and IL- 18, which act to protect the host against infection [25].

3.3. Antifungal activity

The wide-spectrum antifungal activity of LF or its fractions against yeasts and molds is well documented [29,30], and a synergic effect has been reported in combination with other antifungal drugs [31]. The action of *Candida* genus yeasts is the most widely recognized mechanism in mycosis [32], and LF at concentrations of 10 and 100 μg/mL were found to inhibit the growth of two strains of *C. albicans* and *C. glabrata* isolated from the saliva of elderly people. These findings suggest that LF may be useful to reduce the risk of aspiration pneumonia in people of advanced age [33].

3.4. Anti-parasitic activity

The anti-parasitic activity of LF is complex and differs among species. The main action mechanism in most parasites is the sequestration of iron, which plays a major role in the host-parasite interaction. However, some studies have also proposed an increase in the T cell response as an action mechanism, and Mossallam [34] observed an increase in T $CD4^+$ lymphocytes after administering LF to both immunosuppressed and immunocompetent mice before infecting them with *Toxoplasma Gondii*. In contrast, some parasites such as *Trichomonas foetus* and *Trichomonas* vaginalis utilize LF for their growth [22].

4. Anticarcinogenic Activity

LF exerts antineoplastic activity by different action mechanisms according to the cancer type, including: cell membrane alteration, apoptosis induction, cell cycle arrest, cell immunomodulation, anti-angiogenic action, metastasis inhibition, and even cell necrosis. However, the molecular bases of most of these mechanisms are poorly understood and require further in-depth research [35].

LF has even been proposed as a possible chemopreventive agent; although, it is not completely degraded or absorbed by the intestine when administered orally and is therefore retained in the digestive system; however, this can induce changes in the gastrointestinal immune system that may lead to a systemic immune response against carcinogenesis [36]. In the same line, other food supplements have shown beneficial effects in the treatment of different neoplastic processes [37].

The most widely studied action mechanism of LF against tumor formation is its chelating activity. The presence of iron in tissues is considered to increase oxidative stress on genetic material, giving rise to carcinogenesis, and LF therefore acts at tissue level by capturing these ions [36]. Nevertheless, Luzi et al. [38] recently reported that iron-free bovine LF (apo-bLf) has apoptotic capacity in human epithelial cancer cells (HeLa).

5. Regenerative Properties

Various studies have demonstrated the regenerative properties of LF in different tissues.

In bone, LF was found to activate osteoblast proliferation and bone matrix secretion and to inhibit osteoblast apoptosis and osteoclastogenesis [39]. Studies in mice and healthy postmenopausal women showed that dietary LF supplementation improved bone density and resistance, suggesting that LF may be a promising candidate for osteoporosis prevention [40].

In soft tissues, LF was found to support numerous wound-healing processes by participating in the inflammation stage and by directly promoting skin granulation and epithelialization. These actions are based on its ability to stimulate fibroblast and keratinocyte proliferation and migration and to increase the synthesis of extracellular matrix components, including collagen and hyaluronic acid [6,41], explaining the high therapeutic potential of LF in wound healing.

LF exerts its action on fibroblasts through their lipoprotein receptor. Interaction between them produces the phosphorylation of extracellular regulating kinases 1 and 2 (ERK1/2), which participate in mitosis regulation and post-mitotic functions in differentiated cells and are essential for cell division, therefore contributing to tissue regeneration. Interaction with the lipoprotein receptor is also related to kinase activation, which phosphorylates the myosin light chain. It has also been demonstrated that LF can stimulate the expression of IL-18, which plays a major role in early wound healing stages by increasing the concentration of granulocyte-macrophage colony stimulating factor (GM-CSF), which is related to early stages of skin regeneration, allowing macrophages to secrete growth factors and keratinocytes to synthesize collagen for the formation of extracellular matrix [42].

A systematic review by Hassoun and Sivamani [43] concluded that LF can be beneficial for acne, psoriasis, and diabetic ulcerations. However, they reported that only a few studies had addressed this question and called for further research to establish LF as complementary therapy in the clinical setting (Table 1).

In conclusion, LF can be considered a product of therapeutic and/or nutraceutical interest due to its well-documented functional versatility. Additional advantages include its inexpensive production (bovine milk) and good tolerance. Further research in humans is warranted to develop the major therapeutic potential of this biomolecule.

Table 1
Previous studies on LF and their objectives.

Reference	Objective	Methodology	Main results
Wang et al., 2013. [19].	To investigate the potential use of LF in the treatment of allergic responses and immune-mediated inflammation in AR using a murine model.	*In vivo* study.	Intranasal administration recombinant human LF (rhLF) inhibits the allergic inflammation of allergic rhinitis. Following that, rhLF treatment may be a novel therapeutic approach for prevention and treatment.
Reyes Cortes et al., 2017. [23].	To identify the exact mechanism of action of LF peptides, which have antibacterial activity against several pathogenic bacteria.	*In vitro* study.	LF peptides reduced bacterial growth by their interaction with and penetration into the bacteria.
Wong et al., 2014. [28].	To test LF, lactoferricin and lactoferrampin inhibitory effect toward the activities of HIV-1 reverse transcriptase, HIV-1 protease and HIV-1 integrase.	*In vitro* study.	Some LF fragments (Human lactoferricin, Human lactoferrampin and bovine lactoferrampin) exert an inhibitory action on HIV-1 reverse transcriptase and HIV-1 integrase.
van der Does et al., 2012. [30].	To study the antifungical benefits and the mechanism of action of peptides derived from LF.	*In vitro* study.	The antifungal effect of LF is secondary to the modulation of the immune system of the host leading to the resolution of infections by (multidrug)-resistant pathogens.
Luzi et al., 2017. [38].	To examinate the effects of bovine apo-LF on ROS production, glutathione content, and energy homeostasis on Human epithelial cancer cell.	*In vitro* study.	The study showed that bovine apo-LF treatment inhibited the growth of HeLa cells through apoptosis.

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Conflict of interest statement

The authors declare that they have no conflict of interest and/or competing financial interest. This article does not contain any studies with human participants or animals performed by any of the authors.

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