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Research Article

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Anti-Inflammatory and Immune-Modulatory Properties of Milk Lactoferrin

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Abstract

Lactoferrin, a pleiotropic and multivalent natural protein, derived from bovine and camel milk has become the center of attention in current scientific arena due to its divers immune-modulation and inflammation related properties. Lactoferrin has immense role in host immune defenses as several important immune cells have surface receptors specific for lactoferrin. It has been studied at a great depth for its contribution to immune system as covered in this chapter at the interface between innate and adaptive defenses. The medicinal and biological benefits of lactoferrin are due to its diverse chemical structure. Furthermore, the anti and pro inflammation characteristics of the molecule makes it of utmost interest in medical and therapeutic field. Lactoferrin has the potential to serve as a clinical marker in a number to inflammation related maladies and can be used as a treatment option in oxidative stress mediated inflammation related disorders and for harmful immune allergies. Future research on lactoferrin can not only present it as a prognostic or diagnostic biomarker but also as a remedial solution to cure inflammation related disorders.

Keywords: Immune-Modulation, Lactoferrin, Milk

1. Introduction

The immunological reactions are intended to interrelate with the surroundings in order to safeguard the host from foreign drivers, providing a health status through efficient riddance of infectious invaders like viruses, bacteria, fungi, or parasites and through regulation of systemic responses from host immunological supervision [1]. Inflammation is one of the most complex pathophysiological immune responses to both microbial and non-microbial damage and acts through activation of thousands of immunological mediators and diverse cellular species. Though inflammation has an essential role in repair of tissues and/or elimination of pathogens, if it is not contained in an effective time dependent manner, it can be destructive to the host and lead to acute and frequent persistent inflammation mediated ailments. It is established that the generation of principal immunological such as chemokines and cytokines is reliant on the inflammation mediated cellular response, in particular that of innate immune cells (macrophages, dendritic cells, and neutrophils) and hence further results in release of resultant immune species and consequent activation of adaptive defense mechanisms [2]. Immunomodulators are natural or man-made substances that can change the immunological response through augmentation or reduction of mediators of immune cascade including the innate and adaptive components of immunological reactions [3]. Recent research has discovered lactoferrin (LF), a pleiotropic protein, as an important component in modulation of immunological reactions to lead directed interactions amongst innate and adaptive arms and related responses of immune system. Hence, lactoferrin acts as a bridge between innate and adaptive defense functions through regulation of target cellular response. It is also known for its modulation of presentation of antigen and production of T helper cellular response [1]. Lactoferrin is a significant modulator of adaptive immune functions through stimulation of T cell maturation into helper cells and the conversion of immature B cells into effective antigen presention immune cells [4-7]. Lactoferrin has a crucial role in first line defensive mechanism of host and provides protection from a range of microbial invaders and, prevents inflammation mediated maladies [8-13].

This chapter focuses on the role of lactoferrin as a natural me-

diator in immunomodulation and showcases its inflammation related properties in different pathological states. Though lactoferrin can be obtained from a number of sources such as human, camelid, buffalo, bovine, porcine and caprine but this chapter has discussed around bovine and camel derived lactoferrin.

2. Receptors for Lactoferrin on Immune System Cells

It was a challenging effort to identify receptors for lactoferrin which are involved in immune modulatory events. Recent discoveries have contributed to the identification of lactoferrin receptor (LfR) which are accountable for its influence on leukocytes. Human lactoferrin was discovered for the first time as a vital defense component of mature milk and colostrum. This discovery lead to promote the hypothesis which states its role in protection of neonatal gastrointestinal barriers. In accordance to this hypothesis, LfR was identified in duodenal mucosa of small intestine during inception of iron delivery [14].

In a recent study conducted on mouse small intestine it was proposed that lactoferrin act as a major iron source during early life stages [15]. Successive binding affinity studies have identified lactoferrin receptors on T-cells, B-cells, monocytes intestinal cells and platelets [16,17]. The lipoprotein receptor-related protein 1 (LRP1) and 2 (LRP2) are primary lactoferrin receptors and they are multi-ligand receptor proteins of low density. The LRP family members are known as endocytic receptors and LRP-1 also has a signaling receptor function [18].

Depending on their potential immune functions, the lactoferrin receptors are further divided into subclasses. The LfR is a surface protein of ~105kDa which shows its expression on activated human lymphocytes [19]. Human lactoferrin is released and internalized by human Jurkat T-cells, also 30–40% lactoferrin, during each cycle, is degraded [1]. The LfR are specific in nature across species barriers. Lactoferrin binds to human monocytes, in a similar manner observed in B-cells [20,21]. Similarly human lactoferrin is taken up by murine peritoneal macrophages [22]. Other cell types such as rat hepatocytes, placental cytotrophoblast cell line of human, bovine and murine brain endothelial cells also possess and internalize lactoferrin receptors [23,24]. The LfR endocytosis mechanism is clathrin mediated [24-26].

Various findings on binding affinities of lactoferrin to target cells suggest low binding affinity sites, which are facilitated by sulfated proteoglycans chains [26]. Bovine and human lactoferrin has binding affinity for monocytic cell line of human, THP-1. The binding affinity can be decreased by inhibition of sulfation on cell surface [27].

3. Lactoferrin Mediated Crosstalk in Immune Responses

Lactoferrin has been identified to have a profound role to act as a bridge between two innune responses i.e innate and adaptive host defense. Furthermore, the identification of LF receptors on a notable number of immune cells, and their established potential to bind LF, proves that this molecule can function as a modulator and affect both innate and adaptive immune function [28-33].

Lactoferrin alters the innate defense leukocytes through (1) increasing the action of natural killer (NK) cells (2) stimulation of neutrophils function via augmentation of phagocytes activity and changing generation of reactive oxygen species (ROS), and (3) induction of macrophages via upregulating cytokine and nitric oxide (NO) generation as well as blocking intracellular proliferation of pathogens [34-44]. Furthermore, lactoferrin has also been observed for its role in modulation of cytokine production from leukocyte populations. Lactoferrin can modulate the expression of pro-inflammation mediated cytokines, either to increase or decrease production as reliant upon the requirement of immune defenses in concert with the local environment [1,13,41,45,46-48]. Last not least, lactoferrin is capable of upregulating in vivo and in vitro expression of IL-12 in response to invading pathogens [49-53]. IL-12 has a prime role in the development of T-cell helper type 1 (TH1) immune defense [53,54]. Such modulation roles of lactoferrin pinpoint its role between the innate and adaptive immune defenses as an intermediate.

4. Mediation of Antigen Presenting Cell Function by Lactoferrin

Lactoferrin are able to affect the action of T cells related to specific antigenic presentation through modulation of APCs [55]. Macrophages, DCs and B cells present antigenic species to CD4+ T-cells through major histocompatibility complex II (MHC II). Macrophages and DCs have a chief role of maintenance, augmentation and generation of antigen specific functions of T cells, whereas the principal role of B cells is to capture foreign species through specific antibodies and present these foreign entities to T cells for subsequent maturation of antibodies and isotype switching [1]. Lactoferrin has diverse effects such immunological cells as evident from experimental data discussed.

5. Macrophages

Macrophages have prominent role in innate immune mechanisms including induction of phagocytosis of foreign entities and consequent release of pro-inflammation related mediators. These cells also allow cross talk between defense systems to promote antigen-specific T cells. Macrophages have specific receptor sites for lactoferrin as revealed in both human and bovine models [28,56]. Lactoferrin modulates the expression of pro-inflammatory cytokines and induction of type I interferon (IFN α/β), and affects the potential of macrophages to present foreign particles for antigen-specific CD4+ T-cells in the adaptive defense system [28,57]. This process leads to induction of several events that enable host to control intracellular invaders, that involves migration of macrophages at the site infection and/or inflammation. Lactoferrin administered into mice (sensitized to sleep red blood cells) enhanced the migration of macrophage migration via migration inhibition factor [58].

Lactoferrin can enhance the phagocytosis of both infected and inactivated macrophages [53,59]. IL-12, produced by macrophages, is a main modulator of IFNα and has a major role in the recruitment of macrophages at the site of infection [52,60]. IL-12 also enhances the release of IFNα from differentiated Th1 cells and memory T-cells as a co stimulator [61]. Enhanced IL-12 production has been observed in murine peritoneal macrophages following intraperitoneal administration of lactoferrin [44].

6. Dendritic Cells

DCs can alter the differentiation of naïve T-cell, and redirect the function of memory T-cell [62-64]. In case of DCs as well, both

human and bovine models have shown lactoferrin specific receptors and both bovine and human lactoferrin can interact with the surface receptors of peripheral blood derived DCs [33,65]. The potential of DCs to capture foreign antigenic entities or migrate upon stimulated is vital in the promotion of immune reactions specific to antigenic particles as well as its adeptness to mature, described by downregulating the uptake of antigens and upregulation of MHC II, CD86, CD40 expressions and promotion of T cells. It has been shown that recombinant lactoferrin leads to enhancement of CD86 expression in DCs stimulated via nickel sulphate [66]. Lactoferrin has been considered to acts as a novel factor for the maturation of human DCs [67].

7. Lactoferrin Regulates Adaptive Immune Responses

Lactoferrin, a polyvalent molecule, has notable role in modulation of antigen specific adaptive immune defenses as discussed below.

8. T lymphocytes

Lactoferrin specific receptor sites are observed on all subsets of T cells, even on δγ T-cells [29]. Human and bovine models have revealed surface receptor sites for lactoferrin on the T-cell line (Jurkat), and lactoferrin interacts to these sites via receptor facilitated endocytosis [68-70]. T lymphocytes are influenced in various manners by lactoferrin, most often reliant on the state of T cell differentiation, maturation, as well as activation. Lactoferrin derived from human milk can stimulate maturation of murine CD4−CD8− T cells and favor CD4 expression, via induction of intracellular MAP kinase pathways through Erk2 and in the presence of p56lck [7,71]. Human lactoferrin has also been observed to enhance T-cell receptor (TCR) complex component called human T-cell ζ-chain [72]. Lactoferrin has a dual effect of T cell response. It reduces the overall production of cytokine upon being added to mitogen activated T cells [73]. Human or bovine milk derived lactoferrin in cultured in murine splenocytes has shown reduced IL-2 and IFN-γ production [74].

Recombinant lactoferrin, in a T cell activation model induced via nickel, reduced proliferation of T cell, production of IL-5 and expression of CCR4 chemokine [75]. On the other hand, in vivo experimentation demonstrated that lactoferrin increased T cell mediated DTH response through measurement of swelling in footpad upon introduction of antigenic proteins such as BCG, sheep red blood cells and ovalbumin [44,76,77]. In fact, the administration of lactoferrin reveals a mechanism for promotion of adaptive cell reconstitution via proliferative cascades because lactoferrin can contribute towards the reconstitution of humoral defense reaction in immune-compromised people [78,79].

Lactoferrin effect on T cells can further be defined in terms of the specific targeted cellular subsets. Lactoferrin holds the ability to direct alteration and modulations towards the steadiness of TH1 and TH2 immune functions through T cell secreted cytokines, IL-4, IFN-γ, and IL-5. Camel milk lactoferrin has been described to improve the balance between Th1/Th2 mediated cytokine production during hepatocyte injury [80,81]. It is of quite interest that oral administration of lactoferrin leads to enhanced TH2 mediated T cell cytokines in murine that mitogen stimulated splenocytes and intramuscular administration of lactoferrin enhanced TH1 related T-cell cytokine [82].

9. B lymphocytes

Lactoferrin has an essential role in improvement of depleted immunoreactivity. This role of lactoferrin is evident from its ability to affect B cells. Lactoferrin can stimulate maturation of immature mice B cells as described via enhanced production of complement 3 receptor and promotion of IgD acquisition present of B cell surface. In the presence of lactoferrin, cultured immature B cells had enhanced capacity to stimulate T cell proliferation specific to antigenic species, denoting indirectly increased B-cell antigen presentation [6]. T cells are stimulated through B cell presented antigens to lead induction of cytokines needed for isotype switching events. Lactoferrin oral administration enhanced release of overall IgG and IgA from murine Peyer's patches, having specific titers of antibodies observed to be increased in both intestinal secretions and serum [82,83]. To summarize, it is demonstrated that B cells, an established antigen presenter, can be acted upon by lactoferrin in order to enable consequent T cell interactions that favor enhanced response of antibodies.

10. Significance of Lactoferrin Sugar Residues for Immune Activation

The grasp of the molecular foundation of different properties of lactoferrin resides in its patterns of glycosylation [84]. In bovine lactoferrins five glycosylation sites are present one at Asn-233, second at Asn-2281, third at Asn-368, fourth at Asn-476 and fifth one at Asn-545. The glycans present on first Asn-233 and last Asn-545 sites are of rich mannose type [85]. While the rest are complex type glycans which possess mannose moieties (Table 1).

Camel milk has the highest concentration of lactoferrin, almost 30 to 100 times greater than bovine milk and holds 74.9% similar homological affinity with bovine lactoferrin. It has been shown that camel derived lactoferrin is rich with methionine whereas bovine lactoferrin is rick with valine [86].

Glycosylation is important for adjuvant activities of lactoferrin; that is elevated delayed type hypersensitive response generation for ovalbumin can be stopped via methyl-α-D-mannopyranoside addition [76]. The results of comparison research between human and bovine lactoferrin have shown that bovine lactoferrin has stronger adjuvant effect than human lactoferrin.

Monosaccharide	Percentage of total MW (%)	
	Bovine lactoferrin	Human lactoferrin
Mannose	4.84	1.35
N-acetylglucosamine	4.25	2.48
N-acetylgalactosamine	0.85	-
Acetylneuraminic acid	0.6	1.0
Galactose	0.45	1.08
Fucose	0.21	-
Total	11.2	5.9

Table 1: The percentage sugar content of lactoferrin

Form these studies, it is suggested that primary receptor of lactoferrin for its immunotropic activities is mannose receptor (MR). However, no studies are reported that show its direct binding to mannose receptor. So, it is still an ongoing research to identify lactoferrin sugar residues that stimulate interactions with its receptors and participate in different immune regulatory responses.

Although many receptors have been discovered, and most of them function as adhesion molecules or in the endocytic process but have few intracellular cross talks.

11. Role of Lactoferrin in Inflammation- An Immune Response to Injury

Lactoferrin has demonstrated immunomodulatory properties that effect both innate and acquired defenses [26]. Its connection to host immune defenses is evident from the fact that acquired or inherited lactoferrin deficient patients suffer from recurrent infections [87]. Oral intake of bovine milk derived lactoferrin has been observed to effect murine mucosal and systemic immune defense responses [82]. Lactoferrin can regulate nonspecific and specific production of pattern recognition receptors, antimicrobial proteins and proteins related to lymphocyte movement upon oral intake in mice [50]. The function that lactoferrin has in modulation of innate immune defenses authenticates its significance as a first line host defense mechanism in opposition to foreign antigenic particles, controlling both acute and chronic inflammation [13,88-90].

12. Anti-Inflammatory Properties of Lactoferrin

The anti-inflammation function of lactoferrin has been researched at great lengths for the last decade. Lactoferrin effects the anti-inflammation mechanisms by blocking the secretion of cytokines that stimulate recruitment and activation of defensive cells directed at the site of inflammation. Bovine lactoferrin has been reported to modulate production of cytokines via splenocytes of obstructive jaundiced rats [91]. Furthermore, lactoferrin also increases the release of inflammatory cytokines IL-4 and IL-10, and decrease colitis in rats [92]. Camel lactoferrin has been reported to attenuate rheumatoid arthritis through suppression of mitogen activated protein kinase (MAPK) signaling cascade as experimented in arthritic rats [93]. It also reduced the levels of TNF-α and IL-10 and protein expression of NF-κBp65, COX-2 and iNOS. The interaction of lactoferrin with lipopolysaccharide (LPS) is linked to its role in downregulation of pro-inflammatory cytokines expression through its Lfc domain [94-96]. Of quite interest, it has been shown that Lfc on its own can also neutralize the action of LPS [97,98]. Lactoferrin competes for LPS binding against serum LPS-binding protein (LBP) and hence blocks the transfer of endotoxin to mCD14 that are presented on macrophage surface [99]. Lactoferrin has also been reported to reduces the generation of hydrogen peroxide that is mediated via interaction of LPS to L-selectin of neutrophils [100]. Besides binding to CD14 and LPS, other methods of the inhibition of pro-inflammation mediated mediators have also been demonstrated. Lactoferrin internalization in monocytic cells could lead to reduction in IL-6 production stimulated via TNF-α as an outcome of blockade of NF-kB binding to the TNF-a promoter [97,101]. Furthermore, the anti-inflammation potential of Lactoferrin on B-cells is due to its binding capability with CpG-containing oligonucleotides [102,103]. In adjuvant stimulated rat model of arthritis, bovine lactoferrin has been reported to hinder TNF-a and enhance IL-10 production [104]. Recombinant human and bovine milk derived lactoferrin has also been described to hinder LPS mediated murine preterm delivery through blockade of IL-6 expression [105].

13. Pro-Inflammatory Properties of Lactoferrin

In some events, lactoferrin and LPS complex can act as inducer of inflammation mediated species in macrophages via TLR-4, although it is evident from a number of studies that lactoferrin itself, can lead to macrophage activation and release of IL-8, TNF-α, and nitric oxide (NO) [41,42]. It has been discovered that taking pretreatment of lactoferrin and LPS complex, cells become tolerant to LPS [42]. Lactoferrin has been shown to restore the humoral defense reaction and enhance IL-6 production in cyclophosphamide (CP) mediated immunocompromised mice via alveolar and peritoneal cells [78,106]. Indirectly, there is no role of TLR-4 in bovine lactoferrin mediated production of IL-6 from murine peritoneal cells, still the expression of TLR-4 is essential for optimal lactoferrin mediated CD40 expression [107]. In another study is was found that TLR-4 is essential for the activation of anti-viral state within host cells to combat vesicular stomatitis virus, while on the other hand TLR-4 is not mandatory in lactoferrin stimulation for the production of TNF-α [43]. It has been demonstrated in murine CP immunocompromised model, that lactoferrin can reconstitute an immune reaction mediated via T cells by renewal of pool of T cell and hence, improved the CD3+ T cells and CD4+ T cell pool [79]. Recent report showed that lactoferrin oral intake in herpes simplex virus type 1 murine infection model, can enhance cytokine response and prevent loss of body weight [49]. Pepsin hydrolysate from bovine lactoferrin can promote IL-18 in murine epithelial cells of small intestine, that leads to expression of a number of genes involved in immune-stimulation such as IFN-g and other

pro-inflammation mediators [108]. From this effect bovine lactoferrin can contribute towards the inhibition of metastasis and carcinogenesis. Bovine lactoferrin also functions as an inhibitor of angiogenesis via induction of serum IL-18 and hinderance of endothelial functions [109]. Consistent injection of bovine milk derived lactoferrin can lead to a Th1-cytokine dominant environment in the peripheral blood of chronic hepatitis C (HCV) patients that contributes to the elimination of chronic HCV via IFN treatment [110]. Enhanced production of TNF-α and IFN-g has been demonstrated in lactoferrin treated murine model as compared to non-treated group upon stimulation via by heat-killed Candida albicans from cervical lymph node cells [111].

14. Lactoferrin as Inflammatory Marker

Elevated levels of lactoferrin in blood and other biological fluids as observed in septicemia lead to the consideration that lactoferrin can be used as a marker for inflammation related maladies [112]. Elevated levels of lactoferrin have been quantified in synovial fluid but not in serum from rheumatoid arthritis patients, hence lactoferrin has been put forward as a consistent marker of activation of peripheral blood mononuclear cells at inflammation sites in rheumatoid synovitis [11]. Likewise, elevated levels of lactoferrin have been noticed in the severe acute respiratory syndrome (SARS) to be secreted from peripheral blood mononuclear cells [113]. Furthermore, fecal lactoferrin offers a non-invasive diagnostic marker to measure the intestinal inflammation in patients that suffer from diarrhea and abdominal pain [114,115]. Lactoferrin has proved to be a specific and reliable biomarker for chronic inflammation mediated bowel ailments [116]. Enhanced concentration of camel lactoferrin has been observed in mastitis as an indicator of inflammation and can be used as a marker of bacterial udder inflection in cattle [117]. The evidence not only confirms the critical role of lactoferrin in inflammation related conditions but also showcases its application as a clinical biomarker in such conditions.

15. Role of Lactoferrin in Oxidative Stress

Lactoferrin due to its iron sequestration property, is involved in the regulation of biological balance of reactive oxygen species (ROS) generation and their elimination rate, which naturally protects against oxidation related cellular injury. Lactoferrin modifies innate immune responses which in turn alters the generation of immune regulatory mediators, responsible for adaptive immune system development. It is identified that lactoferrin is involved in the maintenance of cellular redox balance by up-regulating antioxidant enzymes [118].

Oxidative stress contribute to several chronic degenerative processes such as neurodegenerative disorders, inflammation, aging, atherosclerosis and development of cancer [119,120]. The research is still ongoing to identify the exact oxidative species produced during metabolic processes. The factors of pathophysiological and physiological significance responsible for an imbalance ROS production that result in oxidative stress in vivo remain unidentified.

Under normal physiological cellular condition, the magnitude and rate of ROS production and their elimination highly depends upon the efficiency of antioxidant enzymes, glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD). SOD is involved in the conversion of superoxide radical (•O−2) into less damaging hydrogen peroxide (H2O2), while GPx and CAT converts hydrogen peroxide into water or molecular oxygen (O2) and water respectively. Nevertheless, the superoxide radical undergoes enzymatic degradation in further two steps when free ferric ions (Fe3+) are present. The superoxide molecule in converted into ferrous salt (Fe2+) by reacting with ferric ion in the first step. The second step also called Fenton reaction, the ferrous ion is converted into hydroxyl radical ferric salt (Fe3+), which is an alcohol. The hydroxyl radical formation in an iron dependent process has its implication in microbicidal activity within the lipid peroxidation events and phagocytes. The lipid peroxidation is initiated when hydroxyl radical reacts with polyunsaturated fatty acids resulting in a hydrogen atom abstraction. It also results in the production of hydroxyalkenals intermediates which induce physiological changes in different macromolecules. These macromolecules involve lipids, proteins and DNA [121]. This ferric sequestration ability of lactoferrin protects against oxidative damage to cells.

Lactoferrin participate in general homeostasis by modulating the generation of metabolically active molecules, and it is demonstrated in tissue trauma models. Okazaki et al [118]. examined the antioxidant potential of bovine lactoferrin against renal tubular oxidative injury in ferric nitrilotriacetate-induced rat model [122]. This study showed that lactoferrin elevated the level of serum creatinine and reduced the level of urea nitrogen in blood. The results showed restoration of antioxidant enzymes functions in bovine lactoferrin treated group and protection against oxidative renal tubular damage. So, it is suggested from this study that lactoferrin uptake prevents against iron-mediated renal damage.

Other studies conducted on endotoxemic mice showed that lactoferrin reduced the LPS mediated oxidative stress by decreasing mitochondrial dysfunction [123]. It was shown that lactoferrin attenuated the mitochondrial damage in the LPS treated animal liver. It was demonstrated by significantly decreased mitochondrial DNA damage and release of hydrogen peroxide from mitochondria.

Furthermore, in another report it has been described that camel lactoferrin reduces lipid peroxidation due to hepatic iron overload in chronic hepatitis C virus patients and hence has a role in reduction of ROS [124]. Camel lactoferrin has also exhibited anti-oxidant potential through inhibition of oxidative harm stimulated via cadmium chloride and aluminum chloride via upregulation of antioxidant enzymes in albino rats [125].

So, it is concluded that lactoferrin is involved in the modulation of cellular death and damage induced by inflammation. Necrotic and apoptotic cell death are crucial to the sepsis-related pathology and SIRS development. These are highly linked to the mitochondrial dysfunction which is characterized by enhanced membrane permeability, altered cellular ATP levels and ROS production. Bioenergetics and mitochondrial defects are becoming highly recognized role players in several acute and chronic disorders, and lactoferrin has demonstrated potent role in amelioration of these problems [123].

16. Role of Lactoferrin in Immune Allergies

In vivo studies have demonstrated that lactoferrin shows protective role against lung and skin allergies [126,127]. Lactoferrin is excessively present in allergy patients. Allergy is a process in which the activation of basophils, mast cells, TNF-a and IL-1β results in the stimulation of antigen presenting cells [128]. In the proposed mechanism of skin allergies, lactoferrin binds to the keratinocytes and prevents TNF-a release from these cells [129]. In another explanation it is found that lactoferrin has the ability to destabilize tryptase which is a pro-inflammatory protease and released from mast cells [130]. Lactoferrin dislodges tryptase from heparin, that maintains its enzymatic activity. Recently, it is discovered that inhibition occurs due to lactoferrin absorption by mast cells and it shows interaction with cathepsin G and chymase in addition to tryptase [131].

17. Conclusion

The chapter establishes the role of lactoferrin, a polyvalent and pleiotropic molecule, in immune-modulation and inflammation evident from the data reported. The presence of receptors of lactoferrin on various immune cells emphasizes the role of this natural protein in modulation of immunological responses. The understanding of interaction of lactoferrin with immune cells is of critical importance to provide future solution to inflammation related ailments. The anti and pro inflammation mediated responses of lactoferrin pinpoint that it can be used either as a prognostic or diagnostic based biomarker or as a viable remedial agent.

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