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(REVIEW ARTICLE)

Review: Lactoferrin a natural glycoprotein as antiviral agent

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Abstract

Lactoferrin is a great multifunctional natural glycoprotein, it is distributed widely in various tissues especially in exocrine glands. It is abundant in exocrine fluids such as breast milk and colostrum, in mucosal secretions, and in secondary granules of neutrophils. Lactoferrin have many physiological functions, it enhances and strengths the immune system of the body by sequestering iron and prevent pathogenic bacteria and viruses from using iron for their growth and replication, also it competes bacteria and viruses on the binding receptor sites of host cells. The low death rate of infants and children during COVID-19 pandemic is revealed to the antiviral activity of lactoferrin and other bioactive components. Lactation of infants from breast milk for two years will increase immune response against bacteria and viruses.

Keywords: Lactoferrin; Glycoprotein; Breast Milk; Antiviral

1. Introduction

Lactoferrin was identified and isolated by Sorensen from bovine milk in 1939 and in 1960 was determined as an iron binding protein in human milk and bovine milk [1-4]. Lactoferrin is produced by the body from exocrine glands, such as maternal milk, tears and secondary granules of human neutrophils. Neutrophils after degranulation was found as the main source of lactoferrin in blood plasma [5-7]. It is also found in most mucosal secretions such as uterine fluid, vaginal secretion, seminal fluid, saliva, bile, pancreatic juice, small intestine secretions, and nasal secretion [8]. The higher levels of lactoferrin are present in milk and colostrums [7-10] and its plasma levels change during pregnancy, and with menstrual cycle. The concentration of lactoferrin in the blood increases during infection, inflammation, excessive intake of iron and in tumor growth [11].

2. Structure

Lactoferrin or lactotransferrin is a glycoprotein with a molecular weight of about 80 kDa, and a member of a transferrin family, where 60% of its amino acid sequence has identity with serum transferrin. Lactoferrin has high affinity to bind and transfer iron Fe (III) in the body. Its affinity to bind Fe (III) ion is two times more than transferrin, also it acts as a donor of Fe^{3+} ions [12]. Lactoferrin is reversibly chelate two Fe^{3+} ions and preventing the precipitation of iron as insoluble iron hydroxide. Three different isoforms of lactoferrin have been isolated. Lactoferrin-α is the iron binding form, but has no ribonuclease activity, lactoferrin-β and lactoferrin-γ demonstrate ribonuclease activity but they are not able to bind iron [13].

Lactoferrin is composed of a single polypeptide chain containing 703 amino acids folded into two globular lobes. These lobes are called C–(carboxy) and N–(amino) terminal regions, are connected with a α-helix. Each lobe consists of two domains known as C1, C2, N1, and N2. The domains create one iron binding site on each lobe (Figure. 1). Two ferric ions

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can be bound by one lactoferrin molecule. Four amino acid residues are most important for iron binding (histidine, twice tyrosine, and aspartic acid), while an arginine chain is responsible for binding the carbonate ion [7, 14].

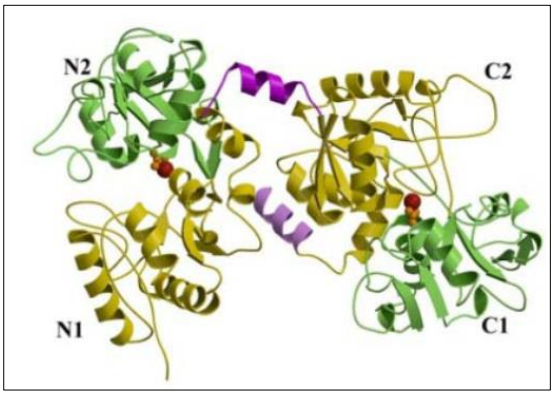

Figure 1 Structure of lactoferrin

There are three forms of lactoferrin according to its iron saturation: apolactoferrin (iron free), monoferric form (one ferric ion), and hololactoferrin (binds two Fe^{3+}ions) (figure 2). The tertiary structure in hololactoferrin and apolactoferrin is different [15].

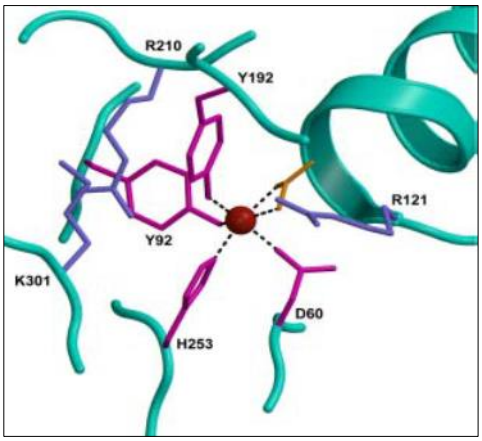

Figure 2 Iron binding site in the N-lobe of lactoferrin

Lactoferrin is a glycosylated protein, has a different sites of glycosylation sites, mostly on the surface of the molecule. The most common sacharide is mannose, hexoses and hexosamines. The degree of glycosylation varies and determines the rate of resistance to proteases or to very low pH [1,7]. Lactoferrin is also capable of binding other metal ions like Al^{3+}, Ga^{3+}, Mn^{3+}, Co^{3+}, Cu^{2+}, Zn^{2+}etc., but the affinity for these ions is much lower compared to iron. Apart from CO_3^{2-}, lactoferrin can bind a variety of other anions like oxalates and carboxylates. Lactoferrin can affect the metabolism and distribution of various substances [7].

3. Breast milk, a protector against COVID-19

A phenomenon has been found in all over the world, that infants and young children are rarely develop serious Coronavirus Disease 2019 (COVID-19) infections and almost never die of it compared to adults [16]. The U. S. Centers for Disease Control reports, that there is no deaths in children of less than 18 years of age [17]. Even in china no deaths in children 0–9 years of age among 72314 laboratory confirmed COVID-19 cases, while in Italy no death has been recorded under the age of 30 in a study of 1625 COVID-19 deaths [16]. These facts supports the hypothesis that the innate immunity of children could have molecules with antiviral activity against COVID-19 compared to adults. Also, mothers are recommended to feed their babies even if they have coronavirus (Covid-19). A preliminary evidences suggested that the breast milk isolated from positive COVID-19 mothers does not contain SARS-CoV-2 particles [18-20].

Breast milk is recommended as an important source of infant nutrition during the first 6months of life to protect the young children against infectious diseases. Numerous bioactive proteins in human milk are also responsible for the protection, and strength of body immunity including immunological factors such as IgA, IgG, live cells, cytokines, and active proteins and enzymes such as lysozyme and lactoferrin. Breast milk lactoferrin protect the body against infections, improves neurocognitive, also it supports the proliferation, differentiation, and activation of immune system cells and strengthen the immune response of the child [21, 22].

The concentration of lactoferrin is varies among the animal species. The highest concentrations has been showing in human´s milk compared with cow´s milk [23]. The concentration of lactoferrin varies, from 5.0–6.7mg/mL in the colostrum and 0.1–2.6mg/mL in the human mature milk [24, 25]. Cow´s milk shows lower concentrations of lactoferrin, with 0.83mg/mL in the colostrum and 0.09mg/mL in the mature milk [26].Results of Matylda and coworkers showed that the lactoferrin concentration during prolonged lactation ranges from 4.9 to 5.02 g/L. The highest lactoferrin content was recorded between 12 and 24 months of lactation. Above 24 months, concentration decreases, although not significantly. These data have shown that lactoferrin content above12 months of lactation is close to the lactoferrin concentration in colostrums [27]. The concentration of lactoferrin increases during inflammatory reactions and some viral infections, so if infants are exposed to Covid-19, lactoferrin can attenuate the virus cell, where the defense system (macrophages, others) of the host can kill the virus cell before the infants becomes sick. Also, symptomatic women make antibodies which are passed in milk and protect babies [28].

4. Antimicrobial activity

Lactoferrin possesses antibacterial and antiviral activities, and exert its activity in many ways.

- Chelation of two ferric ions per molecule: lactoferrin capable to chelate two ferric ions per molecule and prevent pathogenic bacteria and viruses to utilize host iron for replication and growth. Also chelation of lactoferrin to circulating iron ions is to prevent the formation of toxic hydroxyl radicals and precipitation of iron as hydroxide [18,29,30] The disorders of iron homeostasis, induced by inflammation and viral infection increase intracellular iron concentration which favors viral replication [31]. Lactoferrin restore iron homeostasis by its ability to chelate iron, decrease iron overload, diminish interleukin-6 (IL-6) levels, and modulate iron proteins. Iron homeostasis is guaranteed by the expression of some iron proteins such as transferrin, ferroportin, hepcidin, and ferritin [18].
- Bacteria and viruses enter into the host cell by binding to Heparan Sulfate Proteoglycans (HSPGs) on the cell surfaces. Lactoferrin has a binding affinity to HSPGs receptors and competing such molecules from binding to receptor sites. Lactoferrin play an important role in defense mechanism of host cell by occupying the entry sites of viruses and bacteria [30, 32, 33].
- Interaction with anionic compounds: Lactoferrin has a cationic features that can bind to anions such as oxalate and carboxylate and others. This property is important for host immunity, where lactoferrin can bind the anionic surfaces and protect the host cell from bacterial and viral adhesion and entry sites [29].

5. Conclusion

Lactoferrin is a vital glycoprotein in human body, it protects body from bacterial and viral infections. Lactation of infants for 2 years will support their immune system and protect them from pathogenic bacteria and viruses. Lactoferrin supplements (infant formulas, tablets, milk-products) are important in coronaviruse and respiratory tract infections to enhance the immune system of the body.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

We declare that we have no conflict of interest.

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