

Does Lactoferrin Protect against Coronavirus?

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Abstract

Lactoferrin (Lf) is a protein with several functions of the transferrin family that is present in milk, saliva, tear and nasal secretions.

Lactoferrin is present in nature, purified from milk (human colostrum so called "first milk", human milk and then cow milk) or produced in laboratory.

Lactoferrin is a components of the immune system and as such has many multiple physiological functions (anti-microbial, anti-inflammatory, and immunomodulatory): in particular it seems to block the entry of the virus into the cells: the union between the SARS-CoV-2 spike protein with its receptor (ACE-II receptors) would be prevented by Lf.

Thus, the treatment with Lf could be useful in this disease.

Keywords: *Lactoferrin; Covid-19; SARS-CoV2*

In December 2019, a novel coronavirus (at the time officially named SARS-CoV-2) emerged in the city of Wuhan. The new Coronavirus spreads rapidly throughout the world.

As of November 5, 2020, a total of 48,539,872 infected cases and 1,232,791 confirmed deaths due COVID-19 have been reported in 215 countries and territories around the worldwide [1,2].

The first symptoms are commonly recognized as fever, dry cough, tachypnea, and shortness of breath, diarrhea, confusion, chest pain, vomiting, nausea, sore throat, sneezing, nasal congestion, sputum production, anosmia and dyspepsia, rash on the skin, or discoloration of fingers or toes, and viral conjunctivitis [3-5].

COVID-19 is characterized by systemic inflammation and oxidative stress-induced cell injury, it is able to remove and transport unbound iron from body fluids and areas of inflammation, thus avoiding the damage caused by toxic oxygen radicals and decreasing the presence of ferric ions.

"Cytokines storm" induces several complications such as acute respiratory distress syndrome (ARDS) anemia, acute cardiac injury, and secondary infections [5-7].

Lactoferrin (Lf), a 70-80 kDa iron-binding glycoprotein, transports iron in the blood and serum [8,9].

Lf is present in milk, saliva, tear and nasal secretions; it is produced by mucosal epithelial cells in many mammalian and fish species and secondary neutrophil granules [10-12].

Lf performs several protective and physiological functions: direct antimicrobial activities against a wide range of microorganisms, including bacteria, viruses, fungi and parasites, anti-inflammatory and anticancer responses, regulations of iron absorption in the bowel [13-15].

It was first isolated in 1939 from cow's milk [14] and in 1960 it was shown that Lf is the principal protein that binds iron in human milk [15]. The concentration of Lf, present in the milk and in the colostrum is of 7 g/L.

Bovine lactoferrin (bLf) has been studied extensively since the 1960s, when technological advances allowed it to be extracted from milk and characterized [16,17].

Lf predicts the risk of acquiring upper respiratory tract infections with its established *in vitro* antiviral efficacy against a wide range of viruses (especially respiratory ones) *in vitro* including SARS-CoV2 and some bacteria, in synergy with vitamin C.

Lf has unique immunomodulatory and anti-inflammatory, specially it is able to "down-regulate" the expression of pro-inflammatory cytokines (e.g. IL-6) and to enhance the adaptive immune response.

These effects might be especially relevant to the pathophysiology of severe COVID-19 cases [18].

Lf binds free iron and inhibits the replication of the novel coronavirus; unlike ovotransferrin, which retains iron up to a pH around 5.5, Lf retains it up to a pH of around 3, favoring the sequestration of iron even where pH is commonly acid due to the ongoing inflammatory process and thus limiting the availability of iron essential for the survival and development of microbes.

Notably, oral ingestion of Lf, ovotransferrin, lysozyme in human and animal studies is protective, thus the consumption these products could prevent or treat severe COVID-19 disease [7].

Lf is able to stimulate growth natural killer cells and stimulates neutrophil aggregation and adhesion in immune defense; its action takes place in the anchoring phase of the virus to the target cell and by interfering with this mechanism, it inhibits its colonization [19,20]. Thus it may contribute to the prevention and treatment of Coronavirus infection, thanks to its immunomodulatory and anti-inflammatory properties [20]. Lf is available as an oral supplement, and studies suggest that supplemental Lf can be used to treat or prevent several diseases [21].

Conclusion

Systemic inflammation, oxidative stress, dysregulation of iron metabolism and coagulation are physio pathological mechanisms of COVID-19.

Lt binds iron and is transferred through a variety of receptors, that are used by coronaviruses to enter cells, thereby blocking their entry. Thus, Lt might contribute to the prevention and therapy of COVID-19. Further clinical trials are needed to explain the role of Lt in SARS-CoV2 infection.

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