Immune Supporting Properties of Milk

Part 2: Lactoferrin – a multifunctional protein that packs an immunity punch!

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Introduction

In Part 1 of this series of articles on the immune supportive and enhancing properties of milk and milk components, we provided readers with (i) an introduction to the architecture of the human immune system, a complex array of innate and adaptive elements (**see** Part 1, Figure 1) that are designed to provide us with protection from 'foreign invaders' (e.g., bacteria, viruses); and (ii) components in milk that provide support to the health of our immune system and in some cases enhance its effectiveness (**see** Part 1, Table 1).

In this Part 2 article, we home in on one of these immune supporting protein components found in milk – lactoferrin (LF) – that appears to play a critical role in the development, maturation, health and ongoing effectiveness of our immune system. With the COVID-19 pandemic still front of mind for most of us, we also put a spotlight on the potential of LF as a prophylactic and even therapeutic adjunct in the treatment of COVID-19.

Multifunctional properties of lactoferrin

LF, an iron binding glycoprotein found in milk (**Figure 1**), is arguably the 'hottest' dairy ingredient right now and for good reason. The more we discover about the molecular properties of LF, the more apparent the multiple roles and many areas of useful application of this remarkable protein become. The multifunctional properties of LF are illustrated in **Figure 2**. Several of these properties are relevant to immune health and enhancement, including immunomodulation, anti-inflammatory, antiparasitic, antifungal, antibacterial and antiviral.

Figure 1: Powdered lactoferrin isolated from bovine milk. The pinkish color comes from the iron bound to the protein.

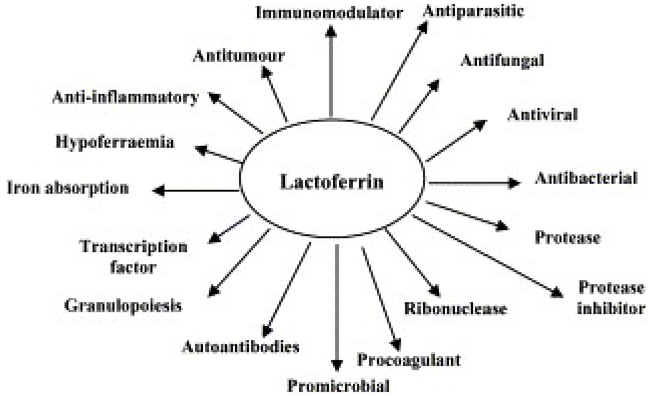

Figure 2: The properties of and potential roles for lactoferrin based on growing scientific evidence and the molecular characteristics of the protein (adapted from Brock, 2002).

The past several decades have witnessed a huge amount of scientific research devoted towards a better understanding of the molecular basis and the mechanisms for many of the observed properties of LF. Indeed, until relatively recently LF was thought to be primarily a bacteriostat, i.e. a molecule that prevented the multiplication of bacteria. This activity was manifested though the ability of LF to bind iron and thus starve the bacterial cells of this essential micronutrient. Through this mechanism, LF complemented the immature immune system of the newborn and thus provided partial protection against bacterial infections. While the binding of iron by LF is an important aspect of the antimicrobial role of the protein, our modern-day knowledge of the molecular structure-function of LF demonstrates that the mechanism of its antimicrobial action is far more sophisticated. The mechanism also involves direct binding to the microbial cell, in essence fulfilling the role of a decoy as well as interactions with receptors on the human cell membrane, thus blocking the microbe from invading the host cell (Kell *et al.*, 2020).

For more detailed information on the structure, function and applications of LF we recommend the following review articles to the reader – González-Chávez *et al.* (2009), García-Montoya *et al.* (2012), and Iglesias-Figueroa *et al.* (2019).

Immune-enhancing properties of lactoferrin with particular reference to antiviral activity and COVID-19

The more we learn about the structure-function relationship of LF, the more aware we become about the importance of this protein to our overall immune health and the role that LF can play as an adjunct in enhancing the effectiveness of our immune system.

As we note above, the antibacterial properties of LF have been recognized for some time but we now know that LF is an effective antiviral agent, efficacious against a wide range of both DNA and RNA viruses (Kell *et al.*, 2020). Examples include rotavirus, hepatitis C, norovirus, polio, herpes simplex, and even HIV. LF appears to act primarily in a preventative manner but may also have therapeutic potential. The mechanism behind the antiviral action of LF involves a 3-pronged defence of the host cell from invasion, including direct binding to virus particles, and complemented by binding to specific and non-specific virus receptors on the host cell membrane (**Figure 3**). These actions prevent the virus from entering the host cell and thus prevent the virus from reproducing.

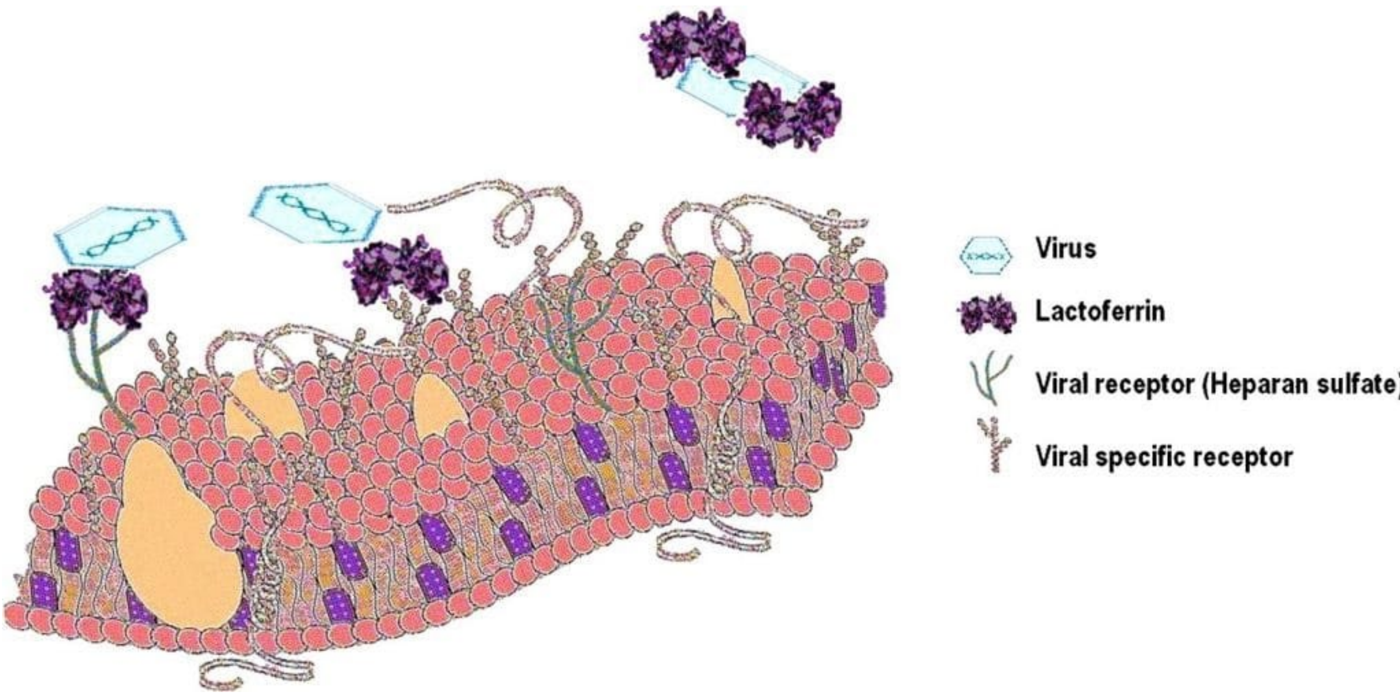

Figure 3: Schematic illustration of the antiviral activity of LF that includes (i) binding to the virus particle itself and preventing adhesion to cell surface receptors; (ii) binding to non-specific virus receptors (e.g., heparin sulfate); and (iii) binding to specific virus receptors on the cell membrane. The latter two actions prevent the virus particle from being transported into the cell and thus prevent the virus from reproducing (illustration from González-Chávez *et al.*, 2009).

It is important for the reader to note that demonstration of the antiviral action of LF is not limited to laboratory experiments. In some elegant work from Japan, Wakabayashi *et al.* (2014) demonstrated in clinical trials that daily consumption of LF (≈100 mg) in a drinkable yogurt or other dairy beverage significantly protected subjects from norovirus infection compared to a control group not consuming LF.

The demonstrated efficacy of LF against a range of viruses together with the long-established safety profile of the protein has prompted a number of researchers to explore the potential of LF in combating the SARS CoV-2 virus, the causative agent of the COVID-19 disease and current pandemic. These studies have examined the effectiveness of LF against a range of related viruses, including SARS-CoV, a very closely relative of SARS CoV-2. Through extrapolation several authors concluded it was likely that LF is an effective and natural adjunct for the prevention and treatment of COVID-19 (Wang *et al.*, 2020; Chang *et al.*, 2020). A further strong hint about the potential of LF as a therapeutic in the recovery from COVID-19 is the observation that infection by coronavirus triggers increased synthesis of the host's own LF. Indeed, the human LF gene of patients infected with the SARS-CoV during the short-lived SARS pandemic of 2002-2003 was upregulated approximately 150-fold from 'normal' levels (Reghunathan *et al.*, 2005). This result is strongly suggestive that patients infected by viruses of the SARS-CoV family have an increased requirement for LF at least during the infection. SARS is characterized by symptoms including fever, cough and shortness of breath and can progress to Acute Respiratory Distress Syndrome, in a manner that resembles morbidity associated with COVID-19.

An important but sometimes overlooked aspect of any disease caused by an invading microorganism is an inflammatory response by the body that can sometimes be extreme. The body responds to the invader by generating cytokines, small proteins that signal the immune system to start doing its job. While this priming of the immune system is a necessary response by the body, many of these cytokines are inflammatory. Indeed, in many patients suffering from COVID-19, the inflammation becomes extreme and is termed a “cytokine storm” leading to cell and organ scarring and damage, and sometimes death. The established anti-inflammatory properties of LF may be useful in limiting this “cytokine storm” because LF is known to down regulate pro-inflammatory cytokines and up regulate anti-inflammatory cytokines (Legrand, 2016). Indeed, LF has recently been proposed as a natural adjunct in preventing extreme inflammatory reactions in COVID-19 patients (Zimecki *et al*., 2021).

Much of the effort to date in combating the COVID-19 pandemic has been directed at the development of effective vaccines as a preventative measure to prime the body to fight off invasion by the SARS CoV-2 virus when exposed. With this effort now largely successful as evidenced by the widespread availability of a number of efficacious vaccines, attention has now turned to other preventative measures and to therapeutics in order to treat the disease once it takes hold. In an exquisite study recently reported in the prestigious journal, *The Proceedings of the National Academy of Sciences*, Mirabelli *et al*. (2021) explored a number of approved drugs and other natural agents using a cell profiling technique with an objective of potentially repurposing these drugs/agents as treatments for COVID-19. In this article, the authors noted the following . . .

“*. . . we discovered that lactoferrin, a glycoprotein found in secretory fluids including mammalian milk, inhibits SARS-CoV-2 infection in the nanomolar range in all cell models with multiple modes of action, including blockage of virus attachment to cellular heparan sulfate and enhancement of interferon responses. Given its safety profile, lactoferrin is a readily translatable therapeutic option for the management of COVID-19.”*

This ringing endorsement of LF in the fight against COVID-19 is testimony to the remarkable bioactive properties of this milk protein, notably in enhancing immune health and effectiveness. Of course, the ‘proof of the pudding’ relies on positive outcomes from large, randomly controlled trials (RCT) that compare human subjects receiving an LF-containing treatment with those receiving a placebo. So far, trial data is limited to small scale observational studies. For example, Serrano *et* *al*. (2020) reported that oral dosage of liposomal LF resulted in camplete and fast recovery within 4-5 days in a study involving 75 subjects with COVID-19 and prevention of infection in healthy persons, who had exposure to the infected subjects. The results of RCTs are eagerly anticipated and needed to establish effective delivery, dosage and treatment regimens. According to the publically accessible database clinicaltrials.gov, there are 7 RCTs in progress investigating the treatment of COVID-19 via LF supplementation, so hopefully the wait will not be too long!

Stay tuned for the next installment in this series of articles on the immune supporting properties of milk and milk components.

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** Several of these articles are 'open access' and can be downloaded from the internet free of charge.*