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Sommario	Lactoferrin (Lf) is a cationic glycoprotein able to chelate two ferric ions per molecule. Human Lf (hLf), a key element of host defenses, is secreted by exocrine glands and by neutrophils. HLf and bovine Lf (bLf), possessing high sequence homology, exert identical functions, such as antimicrobial and antiviral activities. In the last decades, other important Lf activities have been discovered, including the anti-inflammatory one. This Lfs function is strictly dependent by the binding with specific host cell receptors, leading to Lf cell internalization and translocation into the nucleus, thus directly down-regulating pro-inflammatory genes’ expression. In this regard, our group has recently demonstrated the bLf ability in counteracting the tight interplay between inflammatory and iron homeostasis disorders in inflamed macrophages, by down-regulating interleukin (IL)-6 synthesis and rebalancing the expression of main iron-handling proteins, namely ferroportin (Fpn), transferrin receptor 1 (TfR1) and ferritin (Ftn). Here, the role of bLf in different infection models is presented, highlighting its ability to exert a potent action against infection as well as iron and inflammatory disorders. The first model regards a cystic fibrosis (CF) mice suffering from Pseudomonas aeruginosa chronic lung infection. Treatments with aerosolized bLf for 7 days were effective in significantly reducing

	pulmonary bacterial load. Furthermore, for the first time, we showed that bLf treatment was effective in rebalancing the expression of both iron exporter Fpn and iron storage Ftn, thus reducing pulmonary iron overload. The second model concerns the role of bLf against Chlamydia trachomatis infection in vitro and in vivo. C. trachomatis, an obligate intracellular pathogen causing infections associated to inflammation, requires iron for its replication. In in vitro study bLf interferes with C. trachomatis entry into human epithelial cell line when cell monolayers were pre-treated or treated with the protein at the moment of the infection. Lf exerts a potent anti-inflammatory activity down-regulating IL-6 and IL-8 synthesis as well as rebalancing the expression of Fpn and TfR1 in infected cells. In addition, pregnant women asymptomatically infected by C. trachomatis, after 30 days of bLf intravaginal administration, were negative for C. trachomatis with a decrease of cervical IL-6 levels. The third and last model regards the in vitro study of bLf antiviral activity against the new coronavirus infection (SARS-CoV-2). The coronavirus infection causes severe acute respiratory syndrome characterized by massive systemic levels of pro-inflammatory cytokines. In in vitro preliminary results, bLf, through its competitive binding with viral component(s) and its interaction with host surface receptors, blocks SARS-CoV-2 entry in different cell models. Interestingly, the in silico results strongly support the hypothesis of a direct recognition between the lactoferrin and the spike S glycoprotein, thus hindering the viral entry into the cells. Moreover, we performed a randomized, prospective, interventional study assessing for 30 days the effect and tolerability of an oral (1 gr/day) and intranasal (about 16 mg/nostril) liposomal lactoferrin on 10 asymptomatic and 22 mild-to-moderate COVID-19 patients. After 15 days of treatment, rRT-PCR revealed a negative conversion of SARS-COV-2 RNA of the naso-oropharingeal swab in 28 patients (87.5%) and in 4 after 30 days. A significant reduction of D-Dimer, IL-6 and ferritin blood levels was observed together with a fast clinical symptoms recovery. No adverse effects were observed.
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