

BIO_02 - Effect of lactoferrin as an immunomodulator and gene regulation of ferritin in different tissues of K18-hACE2 mice infected with SARS-CoV-2

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Introduction: Bovine lactoferrin (bLf) is a multifunctional glycoprotein with high affinity for Fe⁺³ and has been highlighted as a molecule with an antiviral effect. Also playing an immunomodulatory role by stimulating innate and acquired immunity cells. Studies showed that bLf can maintain iron balance in patients with COVID-19, regulating proteins as ferritin, reducing disease severity. So, it is important to understand the immunomodulatory mechanisms of bLf in SARS-CoV-2 infection.

Objectives: Investigate the immunomodulatory role of bLf during a SARS-CoV-2 infection in K18-hACE2 mice through inflammatory cytokines expression and the role of bLf in iron homeostasis.

Methodology: Animals were treated with bLf (10mg/10µL) by intranasal route for 72 hours (at 12 hours intervals) before (BC), after (AC), and before-after (BAC) challenge with SARS-CoV-2 (Wuhan). Mice challenged with SARS-CoV-2 were used as positive control, while mock group was inoculated with saline. After RNA extraction of the tissues and cDNA synthesis, was analyzed the expression of genes that regulate the immune response by RT-qPCR. Moreover, serum levels of cytokines were quantified using liquid microarray assay. Work approved by Ethics Committee on Animal (LW-08/20).

Results: An assessment of the genic expression identified that the ferritin gene (*FTH1*) had its expression reduced after the infection with SARS-CoV-2, after the treatment with bLf, *FTH1* levels were restored to baseline (AC; p=0.003 and BAC; p=0.013) in brain tissue. However, bLf altered the expression of some pro-inflammatory cytokines only in the lung tissue. We observed an increase in *IL6* and *IL1B* in animals treated in BC p=0.007; and AC; p=0.041 group, respectively, in relation to positive control. The *IL18* presented a decrease with bLf treatment (BAC; p=0.037). In addition, serum levels of the IL-6, IL-1B were also increased (AC; p=0.004 and BAC; p=0.044), and GM-CSF (AC; p=0.014) induced for treatment with bLf. In contrast, a decrease was observed in IFN γ (AC, and BAC).

Conclusion: bLf showed an important role in restoring *FTH1* levels in the brain on SARS-CoV-2 infection. In addition, induced the production of pro-inflammatory cytokines in the lung and serum of treated mice, indicating an immunomodulatory role in the viral infection.

Keywords: Bovine Lactoferrin, SARS-CoV-2, immunomodulatory, ferritin