BIO_05 - bLf-PrP interaction: the antiprion effect of bovine lactoferrin

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Introduction: The cellular prion protein (PrP^C) is found in various tissues, but abundantly in the central nervous system. PrP^C can undergo a structural conversion on its endogenous rich α-helix form to a pathogenic isoform, PrP scrapie (PrP^{Sc} or PrP^{res}), turning into a β-sheet rich structure. This conversion triggers protein aggregation, which accumulates in the nervous tissue and progressively causes synaptic dysfunction and loss of neuronal cells. Prion disease is fatal and progresses rapidly. Lactoferrin (Lf) is an iron binding protein widely known by its multiple functions, such as antiviral, antimicrobial and antitumor activity. Lf has already been found in brain cells damaged by several neurodegenerative diseases and has been studied for its anti-inflammatory and antioxidant function, coordinating the iron ion imbalance that can generate oxidative stress. It is important to investigate the possible antiprion activity of bovine lactoferrin (bLf) because little is known about the role of this protein in prion disease.

Objective: Our goal was to evaluate the interaction between recombinant PrP and bLf, characterizing the molecular details involved in this interaction.

Methodology: Techniques such as polarization, dynamic and static light scattering, SAXS and isothermal titration calorimetry monitored the interaction of the complex PrP:bLf. The RT-QuIC assay was performed to induce the *in vitro* formation of fibrillar aggregates. The dot-blot assay was used to assess whether apo (iron-unsaturated) and holo-bLf (iron-saturated) were able to decrease the presence of PrP^{res} in ScN2a cells.

Results: Through spectroscopic and calorimetry data, it was possible to identify the interaction between bLf:PrP^C. The ScN2a cell assay showed that the highest concentrations of apo and holo-bLf were able to decrease the presence of PrP^{res}. The RT- QuIC data showed that both apo and holo-bLf were able to totally inhibit *in vitro* fiber formation even at very low concentrations. This effect was observed using infected brain homogenates and liquor from sCJD and gFFI patients. While in the fibrilization kinetics assay with fibers produced *in vitro*, only the highest concentration of apo-bLf was able to decrease the formation of fibers, on the other hand, all holo-bLf concentrations were able to totally inhibit the formation of amyloid fibers. Possibly, the direct interaction of bLf with PrP^C inhibits the structural conversion of the prion protein.

Conclusion: The results shows that lactoferrin is a potent inhibitor of the conversion of the prion protein. These studies are important to understand the possible application of bLf as an antiprion agent.

Keywords: Bovine lactoferrin; Prion protein; Interaction