Prion Propagation, Nucleic Acids & Neutrophils: Prion Protein Aggregation Triggered by Neutrophil Extracellular Traps (NETS)

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INTRODUCTION: Prion diseases are fatal neurodegenerative protein-misfolding diseases. The constitutive cellular isoform of prion protein (PrP^C) is expressed abundantly in the central nervous and lymphoreticular systems. PrP^C can be converted into its abnormal, β-sheet-rich isoform (PrP^{Sc}) that undergoes aggregation and triggers a neurodegeneration process. Following peripheral exposure, the replication burst of prions within secondary lymphoid organs is due to follicular dendritic cells that act as a reservoir providing PrP^C for conversion. This is critical for the spread of the disease to the brain .However, strong evidence suggest that adjuvant factors may play a role in lowering the free-energy barrier for the conversion. Our group reported that DNA can convert PrP^C into a β-sheet conformation, resulting in its aggregation. Thus, we asked what could be the source for DNA in a physiopathological context. Neutrophil extracellular traps (NETs) are DNA networks decorated with histones and granule proteins that trap and kill pathogens, being extruded by activated neutrophils in response to several stimuli. NETs were reported of being released in lymphoid tissues. Furthermore, NETs were recently found in association with amyloid fibrils in tissues of patients with other protein-misfolding diseases and these fibrils triggered the release of NETs. OBJECTIVES: Considering the large amount of DNA in NETs, this study aims to investigate whether NETs could induce PrP^C aggregation *in vitro*. **MATERIALS AND METHODS:** Murine recombinant PrP(23-231) was added into the supernatant from activated human neutrophils containing NETs. We used light scattering and electron microscopy to measure and characterize aggregation. **DISCUSSION AND RESULTS:** NETs dose-dependently triggered an instantaneous PrP^C aggregation which decreased over time due to protease activity in NETs. Amorphous aggregates and fibrils were observed. NETs previous treatment with DNase I inhibited PrP^C aggregation, pointing out the importance of the DNA**. CONCLUSION:** Our data suggest that NETs are an intriguing factor that must be appraised in studies concerning prion propagation mechanisms.

Palavra chave: neutrophil extracellular traps , prion protein, immunity
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