# Proteotoxic insults and synaptic dysfunction in the aging brain

## ABSTRACT:

This project sought to investigate the hypothesis that age-related altered metallostasis and neuroinflammation-related proteotoxic seeds induce changes in synaptic protein networks that are critical to neuronal function. For this we studied mechanisms through which pro-inflammatory S100 proteins modulate synaptic processes, related to metal ion homeostasis and proteotoxic insults.
We demonstrated that inflammatory S100 proteins influence metal ion homeostasis at the synapse. We showed that extracellular levels of S100B are not toxic and are taken up by neurons. We proved that S100B, either expressed in cells or added extracellular, scavenges zinc ions through specific binding resulting in a redistribution of the intracellular zinc pool. Then we gather evidence that increased neuronal S100B only significantly affects calcium levels upon zinc scavenging in vitro. This led to the proposal of a new role of S100B as a neuro-protective mediator acting on excitotoxicity via its effects on calcium and zinc homeostasis. Indeed, we established that zinc binding to S100B mediates anti-excitotoxic activity effects.
We also characterized protein interactions between S100B and neuronal aggregation-prone proteins. We demonstrated that monomeric Aβ42 interacts preferentially with calcium-bound S100B and pinpointed the interaction at promiscuous peptide-binding region within the interfacial cleft of the protein. We showed that this results in a delay of aggregation and in a decrease in the toxicity to neuroblastoma derived cell cultures. This resulted in a clear demonstration of a relationship between protein aggregation and inflammatory processes that take place in the synaptic milieu and are critical to neuronal function.

**Keywords**

Synaptic Biochemistry, Brain Proteostasis, Neurometals, Neurodegeneration, Neuroinflammation

## Published Work:

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