P-1.38

Srage, a Potential Therapeutic Approach to Hiapp Amyloid Fibrillation and Toxicity

Ramzi Chellali [1], Marie France Giraud [1], Ghislaine Guillemain [2], Lucie Khemtemourian [1]

[1] CBMN, Pessac, France

[2] CRSA, Paris, France

The receptor for advanced glycation end products (RAGE) binds various amyloid proteins, including human islet amyloid polypeptide (hIAPP), promoting fibril formation and toxicity. However, recent studies suggest that sRAGE, the extracellular domain of RAGE, inhibits hIAPP fibrillation and toxicity, presenting sRAGE as a potential model for developing peptide therapies to reduce amyloid proteins' toxicity.

During my PhD, we produced and purified sRAGE fragments (VC1, V, and truncated VC1) and confirmed their structural integrity via mass spectrometry and circular dichroism. While VC1 and truncated VC1 were well-structured, the V domain exhibited lower stability. Then, the aggregation kinetics of hIAPP in the presence of these fragments was assessed through Thioflavin T fluorescence assays and Transmission Electron Microscopy (TEM), the results revealed that VC1 and truncated VC1 equally inhibit hIAPP fibrillation, whereas the V domain is less effective. TEM images confirmed the absence of fibrils with VC1 and truncated VC1. Further analysis showed that VC1 binds hIAPP monomers and oligomers, preventing fibril formation. Moreover, both VC1 and truncated VC1 protected SH-SY5Y cells from hIAPP-induced toxicity. Further biophysical investigations are underway to identify the key binding residues of the sRAGE and to determine the thermodynamic parameters of the interaction.