OLIGOMERIZATION INTERFACE OF RAGE RECEPTOR REVEALED BY MS-MONITORED HYDROGEN DEUTERIUM EXCHANGE

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Objectives: RAGE receptor - Abeta peptide interaction is thought to be involved in Alzheimer Disease. RAGE is responsible for active transport of Abeta across blood brain barrier, leading to increased accumulation of potentially neurotoxic species in the CNS. The RAGE-Abeta complex is an established field of potential AD therapy. Moreover, RAGE receptor plays an important role in diverse pathophysiological states such as neurological disorders, stroke, amyloidoses, diabetic complications and tumors. Formation of RAGE-Abeta complex leads to the activation of proinflammatory pathways. It has been concluded before that ligand binding domain is structurally uncoupled from cytoplasmic domain suggesting receptor oligomerization as a requirement for receptor activation.

Methods: Hydrogen/deuterium exchange mass spectrometry (HXMS) is a fast growing technique to study protein structure, dynamics and interaction in solution. In this work, we used hydrogen deuterium exchange and mass spectrometry to map structural differences between monomeric and oligomeric form of RAGE. To construct a dimeric form of the receptor, two RAGE molecules were covalently bound by a dityrosine, linking the two tyrosine residues engineered to the C-terminus of the protein construct.

Results: We have found that the oligomerization of the extracellular part of the receptor leads to structural changes, which focus in the vicinity of C1-C2 linker region.

Conclusions: To accommodate so obtained experimental constraints, we have constructed a new model of dimeric/tetrameric forms of extracellular RAGE. This model on the one hand explains the HDex results and on the other hand provides a mechanistic explanation of ligand-dependent signal transduction into the cell.