PEPTIDE SELF ASSEMBLY CONFERENCE 2026
MAINZ. GERMANY
FROM DYNAMIC STRUCTURES TO FUNCTIONAL MATERIALS

Molecular Determinants of Self-Assembly in the Immunodominant 33-mer Gliadin Peptide

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Gluten-related disorders (GRDs), which are multiorgan diseases affecting around 5% of the general population, include the autoimmune disease celiac disease (CeD) (1), wheat allergy (WA), and other less well-understood conditions such as non-celiac gluten sensitivity (NCGS) and gluten ataxia (2). In wheat gluten, gliadins are the most investigated as a CeD trigger. The main problem with these proteins is that they are resistant to proteolytic digestion by human proteases, and large undigested gliadin peptides reach the small intestinal epithelium, where, in predisposed people, they trigger gluten-related disorders (3).

Importantly, these proteolysis-resistant gliadin peptides (PRGP) can self-assemble into various nanostructures, including oligomers, thin plates, and amyloid-like fibrils (4). In the last decade, we have been working to understand the self-assembly process of the immunodominant 33-mer peptide, 57LQLQPF (PQPQLPY)3 PQPQPF89, which has a PPII secondary structure, a low critical aggregation concentration of 75 nM, and forms oligomers above 50 μM. Above this concentration, there is a shift in the secondary structure towards higher β-structure, forming large thin plates that activate inflammatory pathways such as NFkB in macrophages (5). Due to 33-mer repetitive sequences, the molecular understanding of the self-assembly process remains unclear.

Here, we present our latest efforts to elucidate the 33-mer self-assembly process by synthesizing a library of hexapeptides comprising different 33-mer domains and investigating their folding and self-assembly propensities using NMR, Circular dichroism, and advanced microscopy in combination with cellular models.

References:

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