MS07-P05 | STUDYING THE STRUCTURAL BASIS FOR SELECTIVITY IN COMPLEXES OF PEPTIDE INHIBITORS AND SERINE-PROTEASES OF THE COMPLEMENT SYSTEM

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Mannan-binding lectin-associated serine proteases (MASPs) are trypsin-type serineproteases that play a key role in the activation of the complement system via the lectin pathway. Selective peptide inhibitors of MASP-1 and MASP-2 were developed using the phage display technique based on the sunflower trypsin inhibitor (SFTI). SFTI is a member of the Bowman-Birk inhibitor family and forms a stable β-hairpin structure in solution, which is stabilized by a disulfide bond. This structure remains essentially unchanged upon complex formation with trypsin. The metabolic stability of the evolved inhibitors were increased by replacing the disulfide bond with a thioether containing linker. The efficiency of the peptides proved to be highly dependent on the linker length.

To find the structural basis of the selectivity and the significantly different efficiancy of the peptides, we studied the inhibitors and their complexes with MASPs using X-ray crystallography, ECD spectroscopy and MD simulations. We solved the crystal structure of the MASP-1 specific inhibitor, SFMI-1 in complex with MASP-1 and refined the structure to 2.7Å resolution. It was found that directed evolution of SFTI, a peptide with a stable β-hairpin structure, resulted in highly flexible peptides. Despite the high flexibility of the selected inhibitors, the binding mode of the most efficient peptides is highly similar to that of found in the SFTI / trypsin complex.

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