

MS06-2-6 Different roles of protease binding sites of ecotin in inhibition of complement proteases MASP-1, 2 and 3

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Abstract

Ecotin is a serine protease inhibitor with broad specificity, amongst its targets there are pancreatic proteases trypsin and chymotrypsin and elastase, as well as various enzymes of the blood coagulation, contact and complement cascade systems, making it a main virulence factor of various microbes. It is a homodimeric protein with two protease binding sites in both of its monomers: the canonical primary binding loop and a secondary binding region, which is able to ensure that strong binding is established even if the S1/P1 interaction of the primary binding loop is not optimal. Focusing on the interactions of ecotin and mannan binding proteases (MASP-1, 2 and 3), essential enzymes in activating the lectin and alternative pathways of the complement system, we solved the crystal structures of MASP-2/ecotin and MASP-1/ M84R ecotin complexes [1] and compared them with the previously published MASP-3/ecotin complex structure [2]. Using these data, together with our functional studies, we could explain independent roles of the primary and secondary binding sites of ecotin in inhibiting these three related enzymes [1].

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References

- [1] Z. A. Nagy et al., Synergy of protease binding sites within the ecotin homodimer is crucial for inhibition of MASP enzymes and for blocking lectin pathway activation. , J. Biol. Chem. 2022, in press, <https://doi.org/10.1016/j.jbc.2022.101985>
- [2] C. Gaboriaud et al., The Serine Protease Domain of MASP-3: Enzymatic Properties and Crystal Structure in Complex with Ecotin. PLOS ONE. 2013 8e67962