Design and evaluation of glycomimetics as ficolin antagonists

Oliver SCHWARDT [1], Said RABBANI [1], Daniel RICKLIN [1]

[1] Molecular Pharmacy Group, Department of Pharmaceutical Sciences, University of Basel, SWITZERLAND

oliver.schwardt@unibas.ch

As integral part of the host's antimicrobial defense, the complement system can mount a quick and effective response by causing inflammation and cell lysis and by inducing downstream immune processes [1]. The recognition of microbial carbohydrate signatures by pattern recognition receptors (PRRs) of the complement system's lectin pathway, including mannose-binding lectin, collectins, and ficolins plays a critical role in this process [2]. Moreover, as observed during severe cases of COVID-19, a fulminant activation of complement can do more harm than good by causing adverse thromboinflammatory states [3]. Therefore, there is an unmet need to elucidate this interaction network on a molecular level and to develop glycomimetic entities to inhibit (or enhance) such recognition events.

The three members of the human ficolin protein family (ficolin 1-3) are oligomeric lectins that bind mainly *N*-acetylated glycans such as Glc*N*Ac, Gal*N*Ac and Neu*N*Ac, although with different binding specificity [4]. Ficolins have been identified as PRRs for a wide range of disease-triggering pathogens, including eukaryotic protozoa [5], bacteria [6], and viruses [7]. In addition, ficolins play a major role in the pathogenesis of several autoimmune diseases [8].

We assess the binding of natural glycans to the protein's recombinantly expressed CRDs and use screening and rational design to generate glycomimetic ligands, which are subsequently characterized, optimized, and evaluated in relevant assays. These results will further improve our understanding of the ficolin's role in complement activation.

Bibliographic references:

[1] D. Ricklin et al. (2010), Nat. Immunol. (11) 785-797.
[2] T. Fujita (2002), Nat. Rev. Immunol. (2) 346-353.
[3] A. Polycarpou et al. (2020), EMBO Mol. Med. (12) e12642.
[4] Y. Endo et al. (2015), Int. Rev. Cell. Mol. Biol. (316) 49-110.
[5] A. R. Ambrosio et al. (2021), Life Sci. (282) 119793.
[6] S. J. Catarino et al. (2021), Immunol. Lett. (229) 27-31.
[7] V. Murugaiah et al. (2021), Viruses (13) 824.
[8] P. Wang, Q. Wu, Z. W. Shuai (2021), Pharmacol. Res. (163) 105266.