Universität Basel

Research Project

Specificity, selectivity and pharmacokinetics of compstatin: a comprehensive multidisciplinary analysis

Third-party funded project

Project title Specificity, selectivity and pharmacokinetics of compstatin: a comprehensive multidisciplinary analysis
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The complement system plays a major role in innate immunity as it confers immune surveillance and first-line defense against non- or altered-self entities such as microbes or apoptotic cells. Yet, misguided complement activation may trigger or contribute to severe clinical conditions or complications, including autoimmune, hemolytic, inflammatory and age-related disorders and transplant rejection (PMID) [1]. Owing to its cascade organization, involving 50 plasma proteins, receptors and enzymes, complement provides multiple points for novel pharmacological intervention [2]. However, few complement-targeted drugs have reached the clinic, and the available options primarily target peripheral steps in cascade initiation or effector generation. For many acute-phase or multifactorial complement disorders, blocking the activation of the central complement component C3 is considered important [3]. Derivatives of compstatin, a peptidic inhibitor of C3 activation [4], are the most advanced compounds in this class, with two candidate drugs being evaluated in clinical trials. However, its narrow species-specificity for primate C3 currently restricts a broader exploration of potential benefits of C3 inhibition in various established animal models of complement disorders. Furthermore, despite considerable progress in structure optimization, some pharmacokinetic and physicochemical properties of the compstatin class remain to be improved to fully unleash its unique therapeutic potential.

The main objective of this project is to understand target binding and complement inhibition by compstatin in the human system at the atomic level and identify key determinants of its narrow species specificity. We will utilize this knowledge for designing compstatin analogs that recognize non-primate C3 and, for example, inhibit mouse, rat or pig complement. Simultaneously, we will assess compstatin's target selectivity for C3 over the orthologous C4 and C5 proteins and explore options for achieving C4-, C5- or pan-specific inhibitors for research or clinical applications. Finally, we will analyze and optimize the pharmacokinetic properties of compstatin with special emphasis on solubility and bioavailability.

The proposed rationalization and optimization efforts will be driven by well-established in silico simulation techniques such as molecular dynamics simulations, free energy methods, homology modeling, and post-MD analyses, supported by novel approaches based on deep learning (Prof. Markus Lill, Computational Pharmacy). Thanks to project collaborations with strong experimental groups, in silico findings will be experimentally verified by employing peptide synthesis and characterization, chemical modification

and labeling, and target binding and functional assays in vitro (Prof. Daniel Ricklin, Molecular Pharmacy) as well as pre-clinical assessments of cellular permeability in vitro and in vivo (Prof. Henriette Meyer zu Schwabedissen, Biopharmacy; all at University of Basel).
Our studies are expected to extend preclinical evaluation options of compstatin-based drugs in animal models and enhance their pharmacokinetic profile, thereby facilitating clinical development of this important inhibitor class. Selectivity studies with C4/C5 may provide insight into complement activation and potentially reveal novel inhibitors. Finally, atomic level insight into the structure-activity/property relationships of cyclic peptides may be used for the design of this compound type in general.

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