C3aR as Putative Target for Inflammation

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Technology description

Novel C3aR agonists and antagonists for inhibiting pro-inflammatory activities of the human complement system

Novel agonists to C3aR have been designed using a de novo design framework. The best predicted peptides were experimentally validated using a rat basophilic leukemia cell degranulation assay and a monocytic cell calcium flux assay.

Of the peptides tested using a degranulation assay in C3aR-transfected rat basophilic leukemia cells, two were prominent agonists (EC50 values in the nanomolar range) and two others were partial agonists (IC50 values in the nanomolar range). Further testing of these lead compounds in a calcium flux assay in U937 cells yielded similar results, although with reduced potencies compared to transfected cells. The partial agonists also displayed full antagonist activity when tested in a C3aR inhibition assay. In addition, the electrostatic potential profile was shown to potentially discriminate between full agonists and partial agonists.

The peptides will be tested in human primary cells (human neutrophils), and mouse cells (peritoneal macrophages) before testing in inflammation animal models as published findings confirm C3aR as a putative therapeutic target for inflammation.

Publication:

Bellows-Peterson, ML, Fung HK, Floudas CA, et al. ¿De Novo Design with C3a Receptor Agonist and Antagonist Activities: Theoretical Predictions and Experimental Validation, Journal of Medicinal Chemistry, 2012, 55(9) 4159-4168.

Background

A de novo design framework with a ranking metric based on fold specificities was applied to the design of C3a receptor (C3aR) agonists and antagonists. The design is based upon the structure of C3a, which activates C3aR. C3a is a 77-residue peptide that mediates the pro-inflammatory activities in the human complement system and possibly has opposing immunological roles in some cellular systems. Improper activation of the complement system can cause tissue injury in various pathological conditions and contributes to several immune diseases, including stroke, heart attack, reperfusion injuries, and rheumatoid arthritis. The crystal structure of C3a, as well as flexible template structures generated by MD simulations with explicit solvation via water molecules, was employed as the design template.

The framework utilizes two stages: a sequences selection stage and a binding affinity calculation stage. The sequence selection stage produces a rank-ordered list of amino acid sequences with the lowest energies based upon the template structure. The second stage re-ranks the sequences from stage one using either a fold specificity or an approximate binding affinity. Since structural information of the C3a:C3aR complex was unknown, only fold specificity calculations could be employed. Fold specificity measures how likely a given sequence will fold into the design template structure. Thus the design was driven by the hypothesis that structure implies function, and novel sequences of C3a that adopt the C3a fold are potential candidates for C3aR agonists or antagonists.

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