CBR

The Centre for Blood Research Seminar Series

Wednesday, March 12th, 2014
LSC 3 - Life Sciences Centre
2350 Health Sciences Mall
12-1pm

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"The Assembly of the Membrane Attack Complex (MAC) of Complement"

Complement is an innate immune system consisting of about 30 plasma proteins and 15 membrane receptors. The final outcome of complement activation on cells is the assembly of the Membrane Attack Complex (MAC), which is transmembrane pore assembly (Mr~900,000) consisting of C5b through C9 arranged as a circular polymer. Application of a variety of methods inclusive of molecular biology and X-ray crystallography has elucidated the molecular mechanism as to how these proteins assemble. The first step is the specific cleavage of C5 (Mr~190,000) by the complex protease, C5 convertase. A single peptide bond in the α-chain is cut releasing C5a (Mr~9,000), a proinflammatory peptide, while generating a larger unstable fragment C5b (Mr~181,000) that has a limited time to complex with C6. C5 activation is accompanied by an outward displacement of the globular C5d domain enabling a linker within C6 to fit into a newly formed hydrophobic groove. After the addition to C5b-6 of C7 a hydrophilic to amphipathic transition occurs enabling the new intermediate C5b-7 to anchor to an outer leaflet of a phospholipid membrane. Transmembrane pores are first formed when C8 adds to membrane bound C5b-7 generating C5b-8. This then initiates the circular polymerization of C9. As the complex continues to grow, the pore size increases ultimately terminating at the final circular structure that has an inner diameter of about 100 Å. The embedment into phospholipid bilayers of C6 through C9 is mediated by MACPF domains each consisting of about 350 amino acids. Although similar in fold to an analogous domain found in the microbial Cholesterol Dependent Cytolyins (CDC), the MACPFs in the assembled MAC, like perforin, is apparently inverted relative to that of the CDCs. The molecular architecture of the quaternary structure of the MAC is still under investigation.

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