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Activation of the classical complement pathway and auto-immune diseases

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The classical pathway of complement activation triggers lysis and opsonization of invading pathogens and stimulates inflammatory and adaptive immune responses resulting in auto-immune diseases and graft-rejection in organ transplantation. It is initiated via large multicomponent assembly, known as C1 (790kDa), that binds to immune complexes, protein modulators (e.g., C-reactive protein), and polyanionic structures on pathogens and apoptotic cells. It is composed of a large recognition subcomponent, C1q (460kDa), with a bouquet-like architecture consisting of six collagenous stems, each linked to a globular head, and four serine protease subcomponents, two C1r polypeptides (90kDa) and two C1s polypeptides (80kDa) that in the absence of C1q form a Ca^{2+}-dependent heterotetramer. Binding to pathogens induces auto-activation in a stepwise fashion: C1r auto- activates and then activates C1s. C1s subsequently cleaves substrates C4 and C4b-bound C2 to form the C3 convertase (C4b2a), the next enzyme in the pathway. Here we describe the structure of the C1r–C1s interaction in the form of a complex between the CUB1-EGF-CUB2 fragments of each protease highlighting the conformational changes during activation. The fragments form Ca^{2+}-dependent heterodimers both in solution and in the crystals. The interface is extensive and spans all three domains of each protease. Supporting the traditional arrangement in which C1r-C1s heterodimers are linked via interactions between the catalytic domains of C1r. In association with C1q, the C1r-C1r contacts would prevent auto-activation of C1r as the proteases fold up with the C1r-C1s dimers at the center. Disruption of the C1r contacts when C1 binds to an activating surface very likely triggers auto-activation of C1r and subsequent activation of C1s. Activation is likely facilitated through hyper flexibility at the C1s EGFCUB2 junction, enabling considerable movement of the catalytic domains.

Biography

Jamal Almitairi is a 3rd year PhD student at the University of Leicester working in structural biology and complement related diseases. Part of his work was published in the following journal: PNAS

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