Computational Modeling of the Complement System Under Homeostasis, Renal Disease, Meningococcal Infection, and Therapeutic Interventions

Abstract:

The complement system plays a major role in the immune system to recognize and clear invading pathogens. Although activation of the complement system is tightly controlled, dysregulation leads to a cascade of events that is implicated in autoimmune disorders and infectious diseases. Here, to gain a systems-level understanding of the complement system, we developed two comprehensive quantitative models that describe the biochemical reactions of the complement system under a renal disorder known as C3 glomerulopathy (C3G) and bacterial infection by Neisseria meningitidis. Our C3G model is composed of (ODEs) 290 ordinary differential equations with 142 kinetic parameters that describe the state of complement system under homeostasis and disease (C3G). Furthermore, we introduced therapy states by modeling known inhibitors of the complement system, a compstatin variant (C3 inhibitor) and eculizumab (C5 inhibitor). We then evaluate our system by generating concentration-time profiles of biomarkers such as C3, C3a-desArg, C5, and fC5b-9. Our model shows compstatin treatment to have strong restorative effects on early-stage biomarkers such as C3 and C3a-desArg, whereas eculizumab has strong restorative effects on late-stage biomarkers C5 and fC5b-9. These results also implicate the need for patient-tailored therapies that target early stage complement activation under C3G and that treatment may depend on the specific manifestations of a patient’s genetic profile in complement regulatory function. After our modeling efforts in C3G, we continued complement modeling for Neisseria meningitidis. This pathogen can cause meningococcal disease and studies have shown individuals with deficiencies in the complement system, notably the membrane attack complex (MAC), have a 7,000- to 10,000-fold higher risk of developing meningococcal disease. We subsequently developed a quantitative biochemical model to assess dynamics of MAC production. Bacterial infection by composed of 670 ODEs with 328 kinetic parameters Our model shows highest MAC deposition on Neisseria meningitidis is mainly dependent on a concentration barrier where immune activators are at least three orders of magnitude higher than regulators. This makes rising levels of immune regulators as early intervention markers for the sporadic meningococcal disease. Altogether, our models serve as frameworks to simulate disease-specific scenarios. Subsequently, this can lead to early diagnosis, patient-specific treatments, and aid in drug discovery to identify novel inhibitory sites.
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