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Letter to the Editor

Role of the complement in *Leptospira* virulence and infection

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We read with great interest the recent article published by Sun et al. reviewing the literature concerning the virulence of pathogenic *Leptospira* species and pathogenesis of leptospirosis [1]. As noted by the authors, this virulence results from adherence factors, invasive enzymes, and endogenous toxins inherent to these spirochetes, which can facilitate the mechanism of diffusion and inflammatory response.

While this provides strong evidence for the virulence of *Leptospira*, it also suggests the susceptibility of the hosts' complement system to these factors. Here, we would like to expand this discussion on how the hosts' complement system is hijacked by *Leptospira* strains in human systems to better understand their mechanisms of infection and inflammation. Physiologically, the complement system plays integral roles through the classical, lectin, and alternate pathway, namely the production of opsonins that promote phagocytosis, recruitment of inflammatory mediators via C3a and C5a anaphylatoxins products generated by the basophil and mast cell immune response, mobilization of inflammatory mediated by C3a and C5a fragments, activation of B lymphocytes and production of antibodies, and organization of the C5b-9_n membrane attack complex to direct lysis of infected cells.

However, pathogenic *Leptospira* have the capacity to override complement activation, hijack host complement regulators, and target key complement proteins via self- and host-expressed proteases [2]. Serum-resistant leptospires have the capacity to regulate activation of the complement system at the C3/C4 level, which restricts the deposition of C5, C6, C7, C8, C9, and C5b-9_n seen in nonpathogenic strains [2]. Depositions of C3 alongside IgM, IgG, and IgA on the alveolar basement membrane in a guinea pig model of severe pulmonary leptospirosis [3], might suggest pathogenic strains directly or indirectly inactivate classical, lectin, and alternative pathways. These strains are also capable of secreting metallopeptidases, maintaining a high polarity for diffusion across the bloodstream into internal organs and containing proteases that easily cleave terminal complement proteins, such as C6, C7, C8, and C9 [2,4]. C3 and C3 fragments, factor B (alternative pathway), C4b (lectin pathway), and C2 (lectin pathway) are also inactivated by these proteases [2,4]. These strains are notably activators of regulators of complement activation proteins that inhibit the complement system.

Taken together, we can understand that *Leptospira* evade complement-mediated killing through: (i) direct effects of endogenous proteases and virulence factors described by Sun et al., (ii) action through hosts' complement response regulation pathway to trigger a nonselective autoimmune response, and a possible (iii) indirect inactivation of complement pathways by an unknown mechanism.

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Conflicts of interest

The authors declare no conflicts of interest.

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