

Prion diseases impact several mammalian species, and the apparent unabated spread of chronic wasting disease (CWD) raises ecological and potential zoonotic concerns. To date, mechanism(s) behind prion spreading and invariable death remain largely unknown. Further, the function of the host cellular prion protein remains unaddressed.

Previous findings suggest the Complement system facilitates peripheral prion accumulation. We asked whether the central player in the Complement system, C3, also contributes to neuropathology seen in CWD mouse models. Indeed, C3 contributes to neuropathology because mice C3-deficient survive significantly longer than C3-sufficient mice upon intracerebral challenge.

Complement regulatory protein Factor H (fH) limits autoimmunity by binding host proteins and inhibiting Complement deposition. We show fH directly binds CWD prion amyloid and aids in disease transmission because fH-deficient mice propagate fewer prions in the lymphoreticular system and resist disease longer than their fH-sufficient cohorts. These data suggest preventing the Factor H:prion interaction may limit disease progression.

Likewise, we show Complement protein C1q and receptors CD21/35 directly bind prion amyloid. While genetic ablation of both CD21 and CD35 protect mice from chronic wasting disease, the relative importance of each splice variant remained unknown. We provide evidence CD21 promotes prion disease more-so than CD35, and these findings highlight specific cell-type roles in prion pathogenesis. Further, we show soluble CD21 may provide a therapeutic avenue to combat prion disease *in vivo*.

Lastly, we assessed the role of the cellular prion protein, PrP^C, in eliciting adaptive immunity. We report B cell activation, from early events such as SRC phosphorylation and calcium mobilization, to antibody production, partially rely on PrP^C expression. Collectively, data generated from these bodies of work not only highlight C3, Factor H, C1q, and CD21 as potential therapeutic target to combat prion disease, but also identified a function of the cellular prion protein.