Abstract:
Significant outbreaks of prion disease linked to oral exposure of the prion agent have occurred in animal and human populations. These disorders are associated with a conformational change of a normal protein, PrPC, to a toxic and infectious form, PrPSc. None of the prionoses currently have an effective treatment. Some forms of prion disease are thought to be spread by oral ingestion of PrPSc, such as chronic wasting disease and variant Creutzfeldt-Jakob disease. Attempts to obtain an active immunization in wild-type animals have been hampered by auto-tolerance to PrP and potential toxicity. We used an attenuated Salmonella vaccine strains that was made to express multiple repeats of the intact mouse PrP. Salmonella vaccine strains are a well characterized method to induce mucosal immunity. In addition to the oral immunization we boosted the immune response by adding ip immunizations with recombinant PrP. This proved to be a highly effective means of inducing high anti-PrP gut secretory IgA titers without apparent signs of toxicity. Our immunization procedure proved to be a highly effective means of inducing high anti-PrP gut secretory IgA titers without apparent signs of toxicity. 100% of mice with a high mucosal anti-PrP titer IgA and a high systemic IgG titer, prior to challenge, remained without symptoms of PrP infection at 400 days (long-rank test $p<0.0001$ versus sham controls). The brains from these surviving clinically asymptomatic mice were free of PrPSc infection by Western blot and histological examination. In addition we have developed tissue culture models of prion infection and used these for screening of antibodies which could be used for passive immunization. Using these models we have identified some anti-PrP antibodies that are highly effective at clearing prion infection in these experimental systems. These promising findings suggest that immunomodulation may be an effective means to prevent prion infection.

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