Sepsis and the Humoral Immune Response

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Background

Sepsis is a systemic inflammatory response to infection characterized by early signs such as fever, tachycardia, and leukocytosis followed by late signs such as hypotension as the patient’s condition progresses to septic shock and organ failure1. The condition is highly prevalent, as 750,000 people in the United States are admitted to the hospital for sepsis each year, making up 10% of all ICU admissions. Despite improvements in diagnosis and treatment, acute mortality remains around 30%. Patients that survive the initial septic event often have impaired functioning, low quality of life, and prolonged immunosuppression resulting in increased risk of death for years to come.

Mouse models of sepsis including cecal ligation and puncture (CLP) along with human studies have further characterized sepsis on a cellular level. Global transient lymphopenia leads to asymmetric recovery of naive antigen-specific CD4 and CD8 T cell precursors2. Immunization studies show deficits in primary CD4 T cell dependent B cell responses. While CLP mice produce significantly reduced antigen specific antibodies following immunization, they actually have higher total IgM and IgG antibody production than sham mice. These antibodies are auto-reactive and attack nuclear antigens3.

Due to the dysregulation of primary CD4 T cell dependent B cell responses, questions of the value of vaccines in sepsis survivors arise. In the best case scenario, patients will require a schedule of booster doses in order to improve lackluster response. In the worst case scenario, vaccines induce large scale autoantibody production and inflammatory autoimmune syndromes.

Research is needed to both characterize the B cell compartment following sepsis and to determine safety and efficacy of vaccines for post-septic patients. To begin to explore this topic, we investigated antibody production following live infection with influenza A.

We hypothesized that influenza specific antibody production would be significantly lower in CLP than in sham mice.

CLP Validation

I. Survival

Figure 2. Kaplan-Meier survival curves. Curves demonstrate 77% survival for inbred C57BL/6 mice (A) and 84% survival for outbred Swiss Webster mice (B) that underwent CLP surgery. In contrast, 100% of either breed that received sham surgery survived.

II. Weight

Figure 3. average weight change following surgery. As mice experienced transient weight loss, but CLP mice took longer to regain weight lost during sepsis. Similar results seen for C57BL/6 (A) and Swiss Webster (B) mice.

III. Transient lymphopenia

Figure 4. B220+/CD19+ cell populations in various mice. Data in Swiss Webster mice (A) show transient lymphopenia as cell numbers begin to recover by day 7. Similar lymphopenia is seen in pet store mice (B). While B6 mice co-housed in a BSL3 facility (C) and specific pathogen free mice (D) showed numerical growth by day 30, no difference was observed in sham and CLP mice on day 2, possibly due to the lack of a digest to free B cells from the spleen.

Conclusions and Future Directions

I. Summary

- CLP mimics clinical sepsis presentation
- CLP limits influenza specific antibody production
  - Predominantly loss of class switching and IgG expansion

II. Future Directions

- Protection study utilizing serum from influenza infected mice
- Develop optimized method of imaging germinal centers in septic animals
- Further characterize antibody production following vaccination

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References