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View Abstract

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TITLE: USING ELISPOT TO STUDY IMMUNE CELL FUNCTION IN PRECLINICAL SEPSIS MODELS

PRESENTATION TYPE: Poster Only

PREFERRED TOPIC: Sepsis

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ABSTRACT BODY:

Introduction: Life threatening organ dysfunction due to a dysregulated host immune response to infection serves as the current definition of sepsis. Following the initial hyperinflammatory response, septic hosts often progress to a prolonged phase of immune suppression. Acknowledging immune suppression as a key pathophysiologic abnormality in sepsis has served as the premise for the identification and testing of novel therapies designed to boost the host immune response. Testing of such agents in mouse models of sepsis has proven their ability to reverse immune suppression and improve survival. This study was designed to test the feasibility of using an ELISpot bioassay to functionally monitor innate and adaptive immune cell fitness in preclinical sepsis models to assess the therapeutic benefit of potential immunomodulatory agents quickly and longitudinally (SPIES Study; GM139046).

Methods: Sub-lethal sepsis was induced in specific pathogen free (SPF) mice by cecal ligation and puncture (CLP) or systemic LPS administration. Serum cytokines were measured to demonstrate the magnitude and duration of the cytokine storm induced. ELISpot assays using diluted whole blood or splenocytes collected at defined timepoints after sepsis induction were done to measure immune cell function. Cells were stimulated *ex vivo* with anti-CD3/CD28 mAb or LPS to induce IFNg production from T cells or TNFa production from innate myeloid cells, respectively. Different immune modulators were given to the mice to determine their capacity to augment immune cell function.

Results: Both CLP and LPS induced the canonical cytokine storm in the periphery, as measured by increase serum cytokines. ELISpot testing of peripheral blood revealed significant reductions in number of cells capable of producing IFNg for at least 7 days after sepsis induction by CLP in SPF mice. The number of TNFa spot-forming units (SFU), however, was decreased only through the first 48 h after CLP. Interestingly, reduction in the number of immune cells in the blood making IFNg or TNFa was only seen through the first 6 h of LPS endotoxemia. Systemic administration of immune agonists, such as IL-7 or agonistic anti-OX40 mAb, increased both T cell responses in septic hosts, as measured by the number of IFNg spot forming units.

Conclusions: Interrogating the impact of sepsis on the functional capacity of the immune system is key to better defining the extent of immune suppression in the septic host. Moreover, there is a clear benefit in testing immune adjuvants in hypothesis-driven preclinical sepsis models, as these studies serve as valuable precursors to clinical testing. ELISpot provides the researcher the opportunity to test an array of immunostimulants, as well as monitor changes in immune cell function from different locations longitudinally from the initiation of the septic event.

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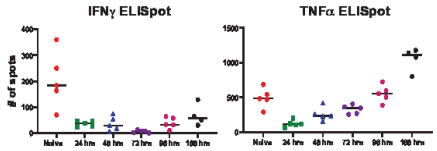
TABLE TITLE: (No Tables)



Serial blood samples were collected at the indicated timepoints after CLP surgery. Data show prolonged suppression of adaptive (T cell) immune response, but rapid recovery of innate responses.

AWARDS:

Disclosure: NO, there are no relationships to disclose.

Submission Rules Confirmation: I confirm that I have read and complied with the submission guidelines.

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