INFLAMMATION CRITICALLY REGULATES ANTIBODY PRODUCTION

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Antibodies are generated through two distinct pathways following B cell activation: the rapid generation of short-lived antibody-secreting plasma blasts and plasma cells (so called extrafollicular responses, EFRs) and the slower development of germinal center reactions (GCs). During the latter, B cells undergo clonal expansion, diversification and affinity maturation, and the generation of long-lived plasma cells as well as memory B cells that often respond to a repeat challenge with EFRs. The mechanisms regulating the differentiation of B cells along one or the other response type are incompletely understood, but critical for understanding how to intervene in ineffective or harmful humoral responses. Using a mouse model of influenza infection, we demonstrate that the development of EFRs is dependent on B cell intrinsic and extrinsic, inflammatory, Toll-like receptor (TLR) signals. B cell-intrinsic TLR signals support antigen-stimulated B cell survival, clonal expansion, and the differentiation of B cells via induction of IRF4, the master regulator of B cell differentiation, through activation of NF-kB c-Rel. Provision of sustained TLR4 stimulation after immunization altered the fate of virus-specific B cells towards EFRs instead of GCs. Thus, acute inflammatory signals enhance antibody production as a means to provide rapidly protective antibodies in infections. During chronic inflammation, the same signals may drive a continued and potentially harmful autoantibody response. The mechanisms regulating the differentiation of B cells towards EFRs instead of GCs are dependent on B cell intrinsic and extrinsic, inflammatory factors. To understand the role of ABC, we studied them in both the immune response to Ehrlichia muris and in the MRL/lpr murine model of lupus, with contrasting results. I will present these data emphasizing that ABC in lupus are a dynamic and heterogeneous population that undergoes clonal expansion and contributes directly to pathogenesis.

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THE LUPUS RISK INDEX (LRI) AS A BIOMARKER IN PATIENTS WITH LUPUS NEPHRITIS

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Background Identification of prognostic and predictive biomarkers in lupus nephritis (LN) is an area of intense study and interest. Non-invasive laboratory markers that associate with the likelihood of responding to therapy and/or assess clinical response in patients with active LN remains an unmet need. The Lupus Risk Index is a score that associates with the risk of developing SLE. It is lowest in Caucasian females and increases in populations with increased risk of developing SLE (African American, Sister's of patients with SLE), and is highest in SLE. Its components (IgM and IgG anti-DNA antibodies and C1q) are each associated with renal disease (or protection from renal disease).

AIMS To test the LRI as a LN biomarker that predicts a clinical response to induction therapy, or whose early changes may precede a clinical response, or that associates with a clinical therapeutic response.

Methods The LRI was determined on retrospective specimens collected from two LN clinical trials sponsored by the Immune Tolerance Network (ITN): CALIBRATE (n=43) and ACCESS (n=134) as well as healthy controls (n=70). Both trials enrolled subjects with active proliferative LN (Class III, IV A or V). We tested the association between the LRI levels and clinical response and/or renal disease in these groups. We then compared the performance of the LRI with disease-specific biomarkers (IgM and IgG anti-DNA antibodies and C1q) to determine the potential role of the LRI as a LN biomarker.

Results LRI levels were significantly increased in patients with active proliferative LN compared to controls. The LRI levels were also significantly associated with clinical response and renal disease. The LRI was better at distinguishing between patients with and without clinical response and renal disease compared to the disease-specific biomarkers.

Conclusion The LRI is a promising biomarker for predicting clinical response to induction therapy and renal disease in patients with LN.