

patients who are more likely to have ongoing disease activity or subsequent flares.

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INFLAMMATION CRITICALLY REGULATES ANTIBODY PRODUCTION

Nicole Baumgarth. *Johns Hopkins University, Baltimore, MD, USA*

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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 supported 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- κ B 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, indicating that control of inflammation may curb pathogenic antibody responses.

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B Cell Biology

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ABC AND EXTRAFOLLICULAR RESPONSES: MECHANISTIC INSIGHTS FROM MURINE MODELS OF LUPUS AND INFECTION

Rebecca Elsner, Nikita Trivedi, Kevin Nickerson, Mark J Shlomchik. *Department of Immunology, University of Pittsburgh*

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Background Animal models and more recently studies in humans have implicated the “extrafollicular” (EF) B cell response—rather than the germinal center (GC) response—as being prominent and possibly pathogenic in lupus. This response can also generate so-called “age-associated B cells” (ABC, known also as “DN2” in humans) under some conditions, a type of inflammatory B cell the frequency of which is elevated in some lupus patients and animal models of lupus. However, the basic biology that underlies why some immune responses are directed toward the EF mode and others to the GC mode is not well-understood. Nor are the identities and functions of ABC well-defined, particularly in lupus. ABC have been termed memory B cells, implying a quiescent or

resting state, which seems incompatible with an ongoing inflammatory disease like lupus and raising the question of how these cells could contribute to pathogenesis

To understand the programming of B cell responses, we studied the response to Salmonella infection, which suppressed GCs while promoting strong EF responses. We discovered a particular cytokine network that suppressed the differentiation of GC B cells and T follicular helper cells, while at the same time enhancing the generation of EF plasmablasts and inflammatory T cells. I will present data on how this network functions as a molecular switch. 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.

Lay abstract I will present data showing how certain types of immune responses that promote lupus are controlled by the immune system. This in turn gives basic insight into lupus pathogenesis and may eventually help in categorizing types of lupus patients and designing and selecting appropriate therapies.

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

Cynthia Aranow*, Susan Malkiel, Ali Dalgish-Choi, Yemil Atisha-Fregoso, Betty Diamond. *Feinstein Institutes for Medical Research, New York, NY, United States*

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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.¹ 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).

LRI

$$\frac{\text{IgG } \alpha\text{DNA}}{\text{IgM } \alpha\text{DNA} \times \text{C1q}}$$

Objective To assess 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,