The germinal center reaction

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

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List of Design Committee Members: Dominique Gatto, PhD, and Robert Brink, PhD

Activity Objectives

1. To understand the formation and structure of the germinal center (GC) reaction.
2. To identify the role of GC regulation in pathological disease states.

Recognition of Commercial Support: This CME activity has not received external commercial support.

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: D. Gatto has received research support from the Alliance for Lupus Research and the National Health and Medical Research Council of Australia. R. Brink has received research support from the National Health and Medical Research Council of Australia.

The germinal center (GC) reaction is the basis of T-dependent humoral immunity against foreign pathogens and the ultimate expression of the adaptive immune response. GCs represent a unique collaboration between proliferating antigen-specific B cells, T follicular helper cells, and the specialized follicular dendritic cells that constitutively occupy the central follicular zones of secondary lymphoid organs. The primary function of GCs is to produce the high-affinity antibody-secreting plasma cells and memory B cells that ensure sustained immune protection and rapid recall responses against previously encountered foreign antigens. However, the process of somatic mutation of antibody variable region genes that underpins GC function also carries significant risks in the form of unintended oncogenic mutations and generation of potentially pathogenic autoantibody specificities. Here we review the current knowledge on the recruitment, selection, and differentiation of B cells during GC responses and the implication of defects in GC physiology for autoimmune, inflammatory, and malignant diseases. Recent advances in documenting cellular movement within GCs and some of the key migratory signals responsible for GC formation are also discussed. (J Allergy Clin Immunol 2010;126:898-907.)

Key words: *Germinal center, antibody response, B-cell differentiation, somatic hypermutation, affinity maturation, B-cell migration*

The presence of areas with high mitotic activity in lymph nodes and other lymphoid tissues was first described in 1884 by Walther Flemming.[1-3] He named these structures with strong cell division ***germinal centers*** (GCs) under the assumption that they were the main origin of lymphocytes. Although this notion was subsequently disproved, GCs remain a key source of effector B-cell populations and are crucial for the generation of humoral immunity. In particular, GCs function to generate the high-affinity antibodies that form a key defense against infectious pathogens and are crucial to the efficacy of virtually all vaccines. However, although GC reactions provide a cellular milieu for the affinity maturation of antibody responses, they also bear the risk of generating autoreactive B-cell clones and B-cell lymphomas. This article presents an overview of the current understanding of the GC reaction based on the study of human tonsils and murine lymphoid tissues and discusses the association of GCs with disease.

INITIAL STAGES OF B-CELL ACTIVATION AND DIFFERENTIATION

GCs develop in B-cell follicles of secondary lymphoid organs in response to antigen challenge. Mature B cells continuously recirculate through secondary lymphoid organs in search of signs of infection and, on reaching the follicles, move rapidly within

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Received for publication June 14, 2010; revised September 14, 2010; accepted for publication September 14, 2010.

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0091-6749/$36.00

doi:10.1016/j.jaci.2010.09.007

Terms in boldface and italics are defined in the glossary on page 899.

Abbreviations used
AID: Activation-induced cytidine deaminase
BCL-6: B-cell lymphoma 6
CD40L: CD40 ligand
CSR: Class-switch recombination
EBI2: Epstein-Barr virus-induced gene 2
FDC: Follicular dendritic cell
GC: Germinal center
ICOS: Inducible costimulator
IgV: Immunoglobulin variable region
SHM: Somatic hypermutation
STAT: Signal transducer and activator of transcription
T-B: T zone–B zone
T_{FH}: Follicular T helper
UNG: Uracil DNA glycosylase

them to survey these areas for antigen. On antigen encounter, B cells initially congregate at the boundary between B-cell follicles and T-cell areas in search of T-cell help.[4] This movement is directed by the rapid upregulation of the ***chemokine*** receptor CCR7 consequent on antigen activation.[5] Cognate encounters with T cells at the T zone–B zone (T-B) boundary drive initial B-cell proliferation and are required for the induction of GC responses. Notably, the interaction of the TNF receptor family member CD40, which is constitutively expressed by B cells, and its ligand, CD40L (CD154), which is expressed by activated T_H cells, is crucial for formation of GCs.[6,7] Thus GCs are believed to be heavily dependent on T_H cells, although transient GC formation has been observed in the absence of T-cell help under some experimental conditions.[8]

In addition to expressing CD40L, activated T_H cells also secrete cytokines that deliver signals through specific cell-surface receptors that serve to drive B-cell proliferation and differentiation. Cytokine signals play a central role in triggering the molecular events that lead to the onset of immunoglobulin class-switch recombination (CSR) and thus the production of IgG-, IgE- and IgA-expressing B cells. Typically, signals delivered through cytokine receptors lead to the preferential targeting of the intracellular enzyme activation-induced cytidine deaminase (AID) to one of the switch recombination sequences located at the 5′ end of each of the γ, ϵ, and α immunoglobulin heavy chain constant region genes. Demethylation by AID of deoxycytidine residues in the targeted switch recombination sequences and the proximal μ heavy chain switch recombination sequence is followed by excision of the resulting deoxyuracil bases by uracil DNA glycosylase (UNG). This ultimately triggers recombination between the switch recombination sequences such that the downstream heavy chain gene assumes the original location of the μ heavy chain gene immediately 3′ of the rearranged immunoglobulin heavy chain variable region gene and is expressed as IgG, IgE, or IgA.[9] The process of immunoglobulin ***isotype switching*** can be

GLOSSARY

AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME: Autoimmune lymphoproliferative syndrome is a disorder of lymphocyte apoptosis characterized by an increased incidence of autoimmunity, nonmalignant lymphoproliferation, and susceptibility to malignancy. Patients might have increased numbers $CD3^+\alpha\beta^+CD4^-CD8^-$ (double-negative) T cells. Most cases are due to mutations in Fas.

CHEMOKINE: Chemokines are the largest family of cytokines. They act by binding to G protein–coupled receptors. Their function in the immune system is to coordinate leukocyte trafficking and activation.

DENDRITIC CELLS: Dendritic cells are hematopoietic cells that function as antigen-presenting cells for naive lymphocytes. Their name is derived from their multiple, thin membranous projections.

GERMINAL CENTER: The germinal center is a specialized structure within secondary lymphoid organs in which responding B cells undergo somatic hypermutation and selection for increased antigen affinity (affinity maturation).

GERMLINE: The germline is the cellular lineage from which eggs and sperm are derived. Germline mutations can be passed to the next generation.

INDUCIBLE COSTIMULATOR (ICOS): ICOS is a member of the CD28 family of costimulatory receptors on T cells. ICOS binds to ICOS ligand on antigen-presenting cells. Function-loss mutations in the *ICOS* gene have been reported in patients with common variable immunodeficiency.

INTEGRIN: Integrins are cell-surface proteins that mediate adhesion. Leukocyte adhesion deficiency I is caused by mutations in a subfamily of integrins containing the conserved β_2 chain (CD18).

ISOTYPE SWITCHING: Isotype switching is the process of changing the class (isotype) of antibody production. There are 5 different antibody isotypes (IgM, IgD, IgG, IgA, and IgE), which are determined by the type of heavy chain present. Isotype switching allows an antibody-producing cell to alter the biological effects of its secreted product without affecting its specificity.

OPSONINS: Opsonins are various proteins (eg, complement or antibodies) that bind to foreign particles and microorganisms, making them more susceptible to the action of phagocytes. Mannose-binding lectin is an example of an opsonin that initiates complement activation.

PLASMABLAST: A plasmablast is an immature plasma cell still capable of proliferating and presenting antigens to T cells. A plasmablast can differentiate into a plasma cell, which is a terminally differentiated antibody-secreting B lymphocyte. Development of plasma cells is dependent on the induction of the transcription factor BLIMP-1.

SILENT MUTATION: A silent mutation is a mutation having no detectable effect, such as DNA base changes that do not alter the amino acid sequence of the encoded protein.

SOMATIC MUTATION: A somatic mutation is a mutation relating to nonreproductive parts of the body that is therefore not inherited. In the immune response antibody variable regions undergo intense somatic mutation (hypermutation) within germinal centers.

SPLENIC MARGINAL ZONE: The splenic marginal zone is the interface between the red pulp and the white pulp in the spleen. Antigen from blood first encounters B cells in the marginal zone.

SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION 3 (STAT3): STAT3 is necessary for the development of T_H17 cells, and mutations in the *STAT3* gene are associated with hyper-IgE syndrome.

TINGIBLE BODY MACROPHAGES: Tingible body macrophages take on a distinct "starry-sky" appearance after phagocytosing cellular debris.

TWO-PHOTON MICROSCOPY: Two-photon microscopy is a form of laser scanning fluorescence microscopy that allows images of living cells and other microscopic objects.

ZINC FINGER: Zing fingers are small protein domains that use zinc ion binding to help stabilize the protein's folds. Zinc fingers are present in a variety of proteins, including those that participate in replication, repair, transcription, signaling, proliferation, and apoptosis.

The Editors wish to thank Daniel A. Searing, MD, for preparing this glossary.