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Review article

Emerging roles of granulocytes in B cell responses☆

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ABSTRACT

Protective antibody responses require cognate interaction between B cells and T helper cells in the germinal center of lymphoid follicles. This interaction leads to the formation of plasma cells that secrete high-affinity antibodies of different classes with distinct effector functions. Growing evidence shows that B cells receive additional helper signals from a variety of cells of the innate immune system, including dendritic cells, macrophages, follicular dendritic cells and epithelial cells. Granulocytes are a fundamental component of the innate immune system, as they are the first leukocytes that infiltrate infection and inflammation sites in order to clear invading microbes and necrotic cells. Granulocytes utilize opsonizing antibodies to enhance their phagocytic and killer functions, but recent studies indicate that granulocytes also optimize antibody diversification and production. In this article, the mechanisms by which different subsets of granulocytes deliver helper signals to B cells and plasma cells are discussed.

Papel de los granulocitos en las respuestas de las células B

Palabras clave:
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RESUMEN

Las respuestas de anticuerpos requieren la interacción de linfocitos B y T helper en los centros germinales de folículos linfoides. Esta interacción induce la formación de células plasmáticas que secretan anticuerpos de alta afinidad y con distintas funciones efectoras. Recientes avances demuestran que los linfocitos B reciben señales adicionales de una variedad de células del sistema inmune innato, incluyendo células dendríticas, macrófagos, células dendríticas foliculares y células epiteliales. Los granulocitos representan un componente fundamental del sistema inmune innato, ya que son los primeros leucocitos que se infiltran en los sitios de infección e inflamación para eliminar microbios invasores y células necróticas. Los granulocitos utilizan anticuerpos opsonizantes para mejorar sus funciones fagocíticas y líticas, pero estudios recientes indican que también pueden optimizar la

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diversificación y producción de anticuerpos. En esta revisión discutiremos los mecanismos por los cuales los granulocitos proporcionan señales de ayuda a las células B y células plasmáticas.

Introduction

Granulocytes are innate immune cells characterized by the presence of a multilobulated nucleus and a variety of cytoplasmic granules that permit the identification of three morphologically and functionally distinct granulocyte populations known as neutrophils, eosinophils and basophils.[1] Similar to other innate immune cells, granulocytes sense the presence of microbes by detecting highly conserved microbial molecular signatures through a broad array of pattern recognition receptors (PRRs), including Toll-like receptors (TLRs). These nonspecific microbial sensors deliver activation signals that stimulate the phagocytic and cytotoxic functions of granulocytes, thereby promoting the initial containment and clearance of invading microbes.[2] In addition to containing cytotoxic and inflammatory compounds, neutrophils, eosinophils and basophils release cytokines, chemokines and other immune mediators that promote the recruitment and activation of monocytes and dendritic cells (DCs).[3–5] These innate immune cells internalize microbial antigens and process them in the context of major histocompatibility class-II (MHC-II) complexes that are presented to $CD4^+$ T cells to initiate highly specific adaptive immune responses, including antibody production by B cells. Granulocytes can further modulate adaptive immune responses by acquiring DC-like MHC-II-dependent antigen-presenting function and by releasing cytokines that modulate the activation and differentiation of T cells.[3,5] The role of granulocytes in B cell responses is less understood. Here we discuss recent evidence that indicates the existence of unexpected functional interactions between granulocytes and B cells in lymphoid organs such as the bone marrow, lymph nodes and the marginal zone of the spleen.

B cell responses

Mature B cells located in the follicles of lymph nodes and spleen generate specific antibody-mediated immune protection and memory upon activation by antigen. Mature B cells originate from bone marrow B cell precursors that generate a primary antibody repertoire following V(D)J recombination, an antigen-independent process mediated by recombination-activating gene (RAG) endonucleases that assemble antigen-binding immunoglobulin (Ig) variable regions from individual V (variable), D (diversity) and J (joining) gene segments.[6] Transitional and mature B cells emerging from the bone marrow co-express IgM and IgD receptors capable of recognizing virtually any antigen present in the environment. These B cells enter the circulation and colonize secondary lymphoid organs to initiate immune responses against intruding antigens.[7]

Protein antigens initiate T-cell-dependent (TD) Ig responses in lymphoid follicles, a microenvironment that favors the cognate interaction of follicular B cells (also known as B-2 cells) with $CD4^+$ T helper (Th) cells expressing the tumor necrosis factor (TNF) family member CD40 ligand (CD40L, or CD154).[8] This initial Th cell-B cell interaction is followed by a germinal center (GC) reaction that further involves interaction of B cells with T follicular helper (Tfh) cells expressing CD40L and the cytokine interleukin-21 (IL-21).[9] TD responses usually generate long-lived memory B cells and plasma cells that secrete high-affinity antibodies, but can also activate an alternative extrafollicular pathway that elicits short-lived plasma cells secreting low-affinity antibodies.[10]

Importantly, the GC reaction involves the up-regulation of activation-induced cytidine deaminase (AID), a DNA-editing enzyme that is essential for the induction of Ig somatic hypermutation (SHM) and class switch recombination (CSR).[11] SHM introduces point mutations at high-rates in recombined V(D)J genes encoding the antigen-binding variable regions of Ig molecules, thereby providing the structural correlate for selection of high-affinity antibody mutants by antigen.[12] CSR involves the replacement of constant μ ($C\mu$) and $C\delta$ genes encoding IgM and IgD with $C\gamma$, $C\alpha$ or $C\varepsilon$ genes encoding IgG, IgA or IgG, providing novel effector functions without changing antigen specificity.[13] A non-canonical form of CSR from $C\mu$ to $C\delta$ has also been described in humans' lymphoid structures associated with the upper respiratory tract for the generation of specialized IgD producing B cells.[14,15]

Memory B cells enter the circulation and patrol lymphoid organs to react against recall antigens, whereas plasma cells home to the bone marrow and populate survival niches that promote the continuous release of high-affinity antibodies into the circulation.[16] While follicular B-2 cells mediate slow-appearing but high-affinity antibody responses against TD protein antigens, extrafollicular B cells such as B-1 cells and splenic marginal zone (MZ) B cells induce fast-appearing but low-affinity antibody responses against T-cell-independent (TI) carbohydrate and glycolipid antigens.[17]

Neutrophils

Neutrophil biology

Neutrophils are the most abundant leukocytes in our circulation and become rapidly mobilized to eliminate microbes and necrotic cells in areas of infection or inflammation.[18] Despite having a brief half-life and lacking proliferative potential, neutrophils have the ability to synthesize and release immunoregulatory factors, thereby helping the recruitment of DCs and monocytes that not only complete innate clearance of invading microbes, but also initiate more specific adaptive immune responses.[4] Neutrophils are generated in the bone marrow from specific granulocyte–monocyte precursors that undergo proliferation and maturation in response to