



The Innate Part of the Adaptive Immune System

Sophie Hillion^{1,2} · Marina I. Arleevskaya³ · Patrick Blanco⁴ · Anne Bordron¹ · Wesley H. Brooks⁵ · Jean Yves Cesbron⁶ · Srinu Kaveri⁷ · Eric Vivier⁸ · Yves Renaudineau^{1,3,9} 

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Abstract

The innate immune response provides a first line of defense against common microorganisms and, for more complex and/or recurring situations where pathogens must be eliminated, an adaptive immune response has emerged and evolved to provide better protection against subsequent infections. However, such dichotomy has to be reevaluated because innate B cells (e.g., B1 and marginal zone B cells) and the newly described innate lymphoid cells (iLC) have been found to exhibit innate-like properties, such as antigen internalization, regulatory B cell functions, and helper T cell activities. In addition, the production and function of natural antibodies (nAbs) by innate B cells and their capacity to activate the classical complement pathway constitute additional important mechanisms at the junction of innate and adaptive immunity as well as the recent integration of platelets into the innate immune spectrum. There is no doubt that these mechanisms present an advantage in immunity and homeostasis particularly during the first years of life, but arguments are arising to consider that these precursors may have detrimental effects in a variety of autoimmune/inflammatory diseases, allergies and cancers, as well as in response to immunotherapy. Accordingly, and as presented in this special issue of Clinical Reviews in Allergy and Immunology, a better comprehension of the key molecular and cellular actors implicated at the crossroads of the innate and adaptive immune response represents a new challenge in our understanding of the immunological and immunopathological responses.

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✉ Yves Renaudineau
yves.renaudineau@univ-brest.fr

Sophie Hillion
sophie.hillion@univ-brest.fr

Marina I. Arleevskaya
marleevskaya@gmail.com

Patrick Blanco
patrick.blanco@chu-bordeaux.fr

Anne Bordron
anne.bordron@univ-brest.fr

Wesley H. Brooks
wesleybrooks@usf.edu

Jean Yves Cesbron
jean-yves.cesbron@ujf-grenoble.fr

Srinu Kaveri
Srinu.Kaveri@crc.jussieu.fr

Eric Vivier
vivier@ciml.univ-mrs.fr

¹ UMR1227, Lymphocytes B et Autoimmunité, Univ Brest, Brest, France

² Laboratoire d'Immunologie et Immunothérapie, CHU de Brest, Brest, France

³ Central Research Laboratory, Kazan Federal University, Kazan, Russia

⁴ Laboratoire d'Immunologie et Immunogénétique, CHU Bordeaux, Bordeaux, France

⁵ Department of Chemistry, University of South Florida, Tampa, FL, USA

⁶ Laboratoire d'Immunologie, CHU Grenoble Alpes, Grenoble, France

⁷ INSERM, Université Paris Descartes, Sorbonne, Paris, France

⁸ INSERM, CNRS, Centre d'Immunologie de Marseille-Luminy, Aix Marseille Université, Marseille, France

⁹ Laboratory of Immunology and Immunotherapy, Brest University Medical School Hospital, BP 824, F-29609 Brest, France

Introduction

The evolutionary processes leading to the adaptive immune system, which originated approximately 500 million years ago with the appearance of vertebrates, has evolved within the context of a preexisting innate immunity. This evolution includes (i) variable lymphocyte receptors, as detected in lymphocyte-like cells from lampreys, the most primitive vertebrate, and the precursors of the T and B cell receptors [1]; (ii) immunoglobulin (Ig)M as the first antibody isotype and the complement fraction C1q that binds to IgM/IgG-antigen complexes and in turn activates the classical complement pathway [2]; and (iii) the emergence of new cellular pathways downstream of innate pathways (e.g., Toll-like receptors [TLR] and interferons [IFN]), which became possible due to epigenetic plasticity (e.g., DNA methylation), new transcription factors (e.g. STAT3), and specific cytokine genes [3–5].

Despite the acquisition of a response based on long-term memory with the emergence of the adaptive immune system during vertebrate evolution, the intermediate cellular subsets of such evolution have been maintained including in humans. They have the particularity of being highly represented during the first years of life, a time when the adaptive immune system becomes functional, but later on their presence at high levels may be deleterious in the context of allergy, autoimmunity, and cancer. As a consequence, it is important to better characterize these actors which is the purpose of this special issue.

Cellular Innate Response

Innate T Cells

Innate lymphoid cell (iLC) functions include host defense reaction to kill virus-infected normal cells and tumor cells, inflammation, and tissue homeostasis as presented by Guida S and colleagues [6]. The iLC family encompasses three groups: natural killer (NK) cells, lymphoid T inducer (LTi), and helper-like iLC that are considered to be the innate counterparts of T helper cells as they can produce type 1 cytokines such as IFN- γ (iLC1), type 2 cytokines like IL-5 and IL-13 (iLC2), and type 3 cytokines including IL-17 and IL-22 (iLC3). Helper-like iLCs are, in addition, important for maintaining immune and tissue resistance in part by controlling neutrophil accumulation, while they are dispensable for protection against infections. New arguments further support that helper-like iLCs contribute to the development of autoimmune and inflammatory diseases, asthma, and cancer. As a consequence, controlling helper-like iLCs represents a promising therapeutic approach.

Innate B Cells

B1 cells and marginal zone B cells (MZB) are the two main innate B cell (iBC) populations and contributors of natural antibody (nAb) production as reviewed by Hillion S and colleagues [7]. Main functions associated with iBC include the elimination of apoptotic cells and autoantigens from the circulation, primary response to infections, and antigen presentation to T cells in the tissues. Within secondary lymphoid organs and in response to antigenic stimulation, iBC can moreover differentiate into cytokine and antibody-secreting cells. When activated through the TLR pathway, iBC display a regulatory role preventing an exacerbated inflammation. This function is performed by the production of natural IgM and by the anti-inflammatory cytokines IL-10 and IL-35. Although the majority of iBC possess a natural autoreactive repertoire, their role in controlling or promoting a pathogenic response is still debated. Indeed, iBC distribution is quantitatively and qualitatively altered in autoimmune diseases [8, 9], and iBC clonal transformation is suspected to be involved in hematologic malignancies such as chronic lymphocytic leukemia [10].

Platelets

Usually restricted to a coagulation function, platelets should also be considered as components of the innate immune system as claimed by Brillard B and colleagues [11]. Such an assertion is based on the observation that platelets are effective in protecting against pathogens but also in promoting autoimmune diseases as recently highlighted in systemic lupus erythematosus (SLE), the prototypic autoimmune disease. Indeed platelets can express co-stimulatory molecules such as CD40L and release pro-inflammatory molecules (IL-6, IL-12) that prime plasmacytoid dendritic cells (pDC) to produce interferon alpha (IFN α), thereby increasing SLE disease activity. Such activation may be mediated through TLR7 (viruses), reactive oxygen species (inflammation), glycoprotein Ib (antiphospholipid antibodies), Fc γ R (immune complexes), and Fc ϵ R (autoreactive IgE). Regarding IgE and according to their capacity to form immune complexes when autoreactive, a dual effect is observed on platelets and subsequently on the pDC capacity to produce IFN α . On one hand, a protective role is observed for non-autoreactive IgE while, on the other hand, the cross-linking of the autoreactive IgE engaged in an immune complex leads to platelet activation allowing pDC priming and IFN α production. Interestingly, the use of Jak-STAT pathway inhibitors prevents IFN α release, in this model, and controls the disease, at least in mice [12].

Humoral and Complement Innate Response

Natural Antibodies (IgM)

As presented by Maddur MS and colleagues [13], nAb are defined as immunoglobulins present in normal conditions and in the absence of immunization. They belong predominantly to IgM but also to IgG, IgA, and IgE subclasses and provide different functions for protection against pathogens, apoptotic cell clearance control of inflammation and an autoimmune response, and B cell regulation at different steps of selection, development, and activation. B1 and MZB cells are the main producers of nAb that are characterized by their low affinity, multi-reactivity against self-antigens, and for some of them their capacity to recognize evolutionarily conserved epitopes present in foreign antigens like phosphorylcholine.

Complement

The complement pathway is at the crossroads of innate and adaptive immunity playing a key role in host defense, tissue regeneration, angiogenesis, and homeostasis by removing immune complexes and apoptotic cells. This pathway may be altered when autoantibodies (auto-Ab) targeting complement components are detected as reviewed by Defendia F and colleagues [14]. One example is highlighted by the anti-C1q auto-Ab that are associated with lupus nephritis in SLE and thrombotic events in patients with anti-phospholipid syndrome [15]. In vitro, anti-C1q auto-Ab are able to inhibit the clearance of apoptotic cells, and can result in IFN α overproduction by pDCs.

Immunotherapy

With the development and use of monoclonal antibodies (mAb) in clinic, mechanisms implicated and controlling complement activation have gained in attraction in order to improve therapeutic responses as presented by Bordron A and colleagues [16]. To this end, several strategies can be proposed. First, the use of fresh serum, concomitant with the use of mAb, intended to restore innate or acquired complement deficiency. Second, a technological strategy based on optimization of the mAb to improve its capacity to activate the classical complement pathway that could be achieved by selecting an epitope close to the plasma membrane and not affected by the cellular inhibitory mechanisms or by promoting better fixation of C1q. Third and finally, developing strategies to control soluble and cellular complement regulators.

The TLR Pathway, Jak Inhibitors, and Epigenetic Plasticity

TLR Pathway

Expressed at the surface of innate immunity cells (e.g., dendritic cells, macrophages, NK cells, platelets), adaptive immunity cells (e.g., T cells and B cells), and non-immune cells exposed to the external environment (e.g., epithelial, endothelial cells, and fibroblasts), Toll-like receptors (TLR) are implicated in the recognition of molecules that are broadly shared by pathogens. As a consequence, TLR are primarily required for host defense but when chronically activated, the TLR/IL-1R dependent pro-inflammatory cytokine response participates in the development of autoimmune diseases such as rheumatoid arthritis (RA), and this supports a role for endogenous or exogenous activators as described by Arleevskaya MI and colleagues [17]. There is in addition, an ongoing debate as to whether infectious events predispose to RA or there are alterations in the immune system that increase the susceptibility to infections; both explanations are reported with herpes simplex viruses (HSV) [18–20]. With regard to bacteria that contribute to the development of RA, this would include the presence of the main periodontitis agent *Porphyromonas gingivalis* in the oral cavity and a gut dysbiosis capable of impairing the balance between pro- and anti-inflammatory immune responses.

JAK Inhibitors and Epigenetic Plasticity

Sjogren's syndrome (SjS) is an inflammatory autoimmune disorder, which is characterized by epithelial cell activation and destruction involving redox dysregulation concomitant with a pro-inflammatory interferon signature. Using a cellular model, Charras A and colleagues [21] have tested and demonstrated the ability of two JAK inhibitors (JAKi), AG490 and ruxolitinib, to alleviate the oxidative stress induced by hydrogen peroxide (H₂O₂) by controlling the phosphorylation of STAT3.

Another result from this study is the observation that JAKi reverse the oxidative stress and interferon capacity to trigger DNA demethylation. This is based on the observation that JAKi block the upregulation of ten-eleven translocation 3 (TET3) enzyme and increase 5-hydroxymethylcytosine levels in a human salivary gland epithelial cell line stimulated with H₂O₂, IFN- α , or IFN- γ . DNA demethylation in salivary gland epithelial cells represents the major epigenetic process reported in SjS, and differences in methylation mostly affect genes regulated by IFN and the oxidative stress pathways [22, 23]. Lymphocytic infiltration in salivary glands inversely correlates with the level of DNA methylation in epithelial cells, supporting the concept that JAKi may be exploited to reverse the abnormal interplay between activated epithelial cells and lymphocytes in SjS to form ectopic germinal centers [24–26].

Altogether, these findings establish the molecular basis for the therapeutic promise of JAKi in SjS.

Conclusions

Our understanding of the innate lymphoid and B cells (iLC/iBC) has advanced from viewing these cells as spectators rather than actors to a heterogeneous subset of cells that display diverse functions in response to stimuli. Pathway gene analysis indicated that many of the modulated genes involving innate and iLC/iBC responses are related to a limited number of pathways including interleukin/JAK/STAT, oxidative stress, and TLR signaling pathways. As a consequence, understanding the molecular events underlying innate and iLC/iBC activation will be critical in generating targeted therapeutics with applications in autoimmunity, allergy, and cancer.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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