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B and Th cell response to Ag *in vivo*: implications for vaccine development and diseases

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While vaccines have been the major medical intervention in human history that fundamentally reshaped our life-expectancy, the global COVID-19 pandemic reinforced public awareness about the critical need for further advancement of vaccine development. Multiple groups have published on improved and directed efforts to develop vaccines—efforts that are informed by the most up-to-date understanding of the immune system and its variability, as well as by advances in biotechnology. This century has seen a dramatic increase in targeted vaccines that were developed using these modern approaches to combat both infectious and noninfectious diseases.

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Multiple decades of studies have spanned a wide spectrum: on one end, the focus is on the fundamental aspects of the adaptive immune system, which is responsible for initiation, progression, and persistence of humoral immune responses to foreign antigens (Ags); and the other end focuses on the development of vaccines to elicit desirable antibody (Ab) responses to provide protection against multiple pathogens. These immune responses consist of a carefully choreographed sequence of events occurring in both time and space. The space, or anatomy, of the response is an essential element as it makes possible the myriad cellular and molecular interactions that must occur. The immune system has its own organs, tissues, as well as specialized anatomical niches within these organs and tissues that facilitate the growth, maturation, and development of immune cells. These spaces provide controlled microenvironments in which immune cells interact in a coordinated fashion, enabling lymphocyte activation, differentiation, and acquisition of effector function, as well as the maintenance of memory cell populations. One of those critical interactions is the communication that takes place between B cells and specialized CD4+ T lymphocytes, T follicular helper (Tfh) cells. Cognate help provided by Tfh cells is an essential element of robust humoral immunity. In 2000, these cells were first described in human tonsils (J Exp Med. 2000 Dec 4; 192(11):1545-52; J Exp Med. 2000 Dec 4; 192(11):1553-62) and were subsequently found in other specialized locations within lymphoid tissues. Ensuring optimal activation of Tfh cell responses is now being considered as a promising approach toward developing improved vaccines. Tfh cells are just one of many types of specialized T helper lymphocytes that support the development of protective immunity. Within the B cell compartment, we also find specialized subsets including the following: plasmablasts, long- and short-lived plasma cells, and memory cells. Each one has their own important role to play in protection against foreign pathogens.

This special issue of *Immunological Reviews,* "*B and Th cell response to Ag in vivo: implications for vaccine development and diseases,*" involves a broad and ambitious topic aimed at bringing together current knowledge in B and Th cell immune responses (including their interactions) that are essential for development of long-lived humoral protection. The issue also includes up-to-date information about multiple factors that are critical for targeted vaccine development. The special issue will touch upon the challenges in generating broadly neutralizing immune responses against rapidly mutating viruses (e.g., influenza) and dysregulation of B/Th cell responses associated with

universal diseases such as autoimmune disease and cancer. It will also discuss how advancement in the vaccine field broadens its focus from conventional pathogens to various intervention therapies. The reviews included in this issue will describe multiple factors that affect B and Th cell recruitment in response to Ag, B cell competition in germinal centers (GCs), and differentiation into memory cells and Ab-secreting long-lived plasma cells, persistence of the antibody-secreting cells, control of B cell responses by Tregs, and molecular dysregulations associated with autoimmunity and B cell cancers. From the vaccine-focused perspective, the reviews will discuss the modulation of B and Th cell immune response by virus-like particles (VLPs) and adjuvants, as well as the immune-response variability that occurs due to aging and various genetic factors. Speaking of genetic factors, years of research have clearly demonstrated that allelic variation in the human leukocyte antigen (HLA) locus has significant effects on both the antibody response and the development of T helper activity in response to both infection and vaccination. In recognition of the current SARS-CoV-2 pandemic that has captured the attention of the global research community, the volume includes an article describing the veritable flurry of studies that have been conducted over a few short months to understand the role of genetic variation, including variation in the HLA region on SARS-COV-2 infection and COVID-19 clinical outcomes. That article also touches on the work currently being done to examine the effect of viral genetic variation on infection and disease severity.

The generation of broadly neutralizing Ab responses against pathogens requires recruitment of multiple Ag-specific B cell clones into T-dependent immune response that can give rise to germinal center (GC)-experienced class-switched memory B cells and long-lived plasma cells (LLPCs). However, recruitment of individual B cell clones into GCs depends on multiple factors, including Ag valency, biophysical properties and amount, cellular/molecular context, and duration of Ag acquisition by B cell and the timing of T cell help. The review by **Turner et. al. [1]** attempts to bring these factors together in the context of spatiotemporal microanatomy of B-cell activation to suggest that Ag distribution and the timing of the initial B-Th cell contacts may influence clonal repertoire of B cells recruited into primary immune response. Other critical factors and considerations are covered in **[8]**. This first article also highlights the fact that B cells may go through more than one round of Ag-dependent activation *in vivo* and raises a few still unresolved questions in the field concerning B cell activation vs tolerance fate *in vivo*.

The review by **Hua et. al. [2]** discusses several features that are critical for the initiation and progression of T-dependent and T-independent B cell responses to foreign Ags, with particular emphasis on Qβ-VLPs (bacterial phage Qβ virus-like particles with encapsulated single-stranded RNA). The review examines the dendritic cell (DCs)-centered dogma of the initial Th cell activation and infers that, in some cases, Ag-specific B cells may play a more important or even more dominant role than DCs as Ag-presenting cells for Th cells (e.g., following immunization with viral-like particles [Qβ-VLPs] or with inactivated viruses, as well as in the course of progressive autoimmune diseases). The review also addresses the role of TLR-signaling in T-independent proliferation of B cells, magnitude and duration of GC responses, and in autoimmunity.

The role of cognate B-T cell interactions during initiation and progression of T-dependent B cell responses is rendered critical. The review by **Biram et. al. [3]** outlines what is known about the temporal dynamics of B-Th cell encounters and their molecular communication, follicular helper T cells (Tfh) that are critical for GCs, and the principles underlying GC B cells affinity maturation and selection. The review touches on the currently evolving understanding of B cell responses at mucosal surfaces, including: secondary lymphoid organs T-independent IgA responses to commensal bacteria and rotaviruses, extensive B cell proliferation in subepithelial dome, and atypical non-cognate T cell help that supports GCs B cells in parallel to the conventional cognate Tfh-cell driven selection that take place in peyer's patches.

While Tfh cell help to GC B cells, which undergo rapid somatic hypermutation, is critical for selection of B cell clones with high affinity to Ag, this process promotes lymphomagenesis and has been known to lead to cancer. The review by **Minz et. al. [4]** takes a pointed view regarding the molecular mechanisms driving Tfh and GC B cell communication in the off-target support of various GC-originated malignancies, such as follicular lymphomas, GC B cell-diffuse large B cell lymphomas, and Burkitt lymphomas. The review provides analysis of the molecular players and signaling pathways responsible for Tfh cells-mediated support of GC B cells, discusses them in the context of malignancy-associated mutations, and suggests potential therapeutic approaches to disable Tfh-GC B cells communication to avert lymphomagenesis.

The major target of vaccination is development of memory B cells (Bmem), which should be reactivated upon infection if preexisting Ab titers are insufficient or suboptimal for pathogen recognition and removal. The heterogeneous populations of Bmem cells in terms of their origin, trafficking, and fate are elucidated in the review by **Dhenni et. al. [5]**. It also provides a comprehensive overview of memory B cell subsets present at various anatomical locations and discusses the microanatomy of Ag and T cell help acquisition by Bmem cells that is very distinct from naïve B cells. Finally, the review describes atypical and autoreactive Bmem cells and their surfacing role in multiple autoimmune diseases.

Another major focus in the vaccine field is generation of long-lived plasma cells (LLPCs);however, while immunizations usually trigger plasma cell (PC) response, variable success is noted in terms of PC persistence. The review by **Robinson et. al. [6]** provides an overview of the up-to-date knowledge about the intrinsic and extrinsic determinants of PC survival and persistence in the bone marrow (BM). The review covers the origins of PC development, PC homing and adhesion in the BM, and their metabolic regulation. In addition, it describes various cells, molecules, and processes that support survival of PCs in the BM niches in a master transcription regulator Mcl1-dependent fashion. Finally, the review discusses various models of PC turnover in the BM and suggests an important role of inflammation for this process.

While vaccine responses should lead to development of memory B cells and LLPCs, triggering B cell responses may also lead to undesirable effects, such as elevated production of IgE class-switched or autoreactive Abs, which may contribute to allergic reactions and autoimmunity. Tregs, particularly their subset called follicular regulatory T cells (Tfr), have been implicated as the cells controlling these processes. The review by **Wing et. al. [7]** provides a detailed overview of Tregs' functions and heterogeneity and of the Treg/ Tfr -mediated control of B cells and Ab responses. It also describes transcriptional regulation of Tfr development, Tfr localization, specificity, their role in affinity maturation and viral infections, and discusses perspectives that target Tfrs in therapies to improve immune responses to vaccines and to avert allergies.

Abbott et. al. [8] reviews current knowledge regarding the factors contributing to the B cell response to complex antigens. These factors include B cell precursor frequency, the affinity of BCR:Antigen binding, and antigen avidity, which can all affect the nature and magnitude of the antibody response. Understanding how these factors affect the B cell response may prove useful in our ongoing search for an effective HIV vaccine, a universal influenza vaccine, and perhaps vaccines targeting SARS-CoV-2 and other coronaviruses.

The next article in this issue focuses on efforts to create more effective (and broadly reactive) vaccine responses against influenza. **Fukuyama et. al. [9]** argue that antibodies targeting conserved epitopes in the stem region of the HA protein offer broad protection against antigenically divergent influenza strains. Mechanistic-based vaccination strategies that lead to the formation of memory B cell populations producing broadly reactive antibodies may also be applicable to other viral pathogens.

The article by **Frasca et. al. [10]** shifts our attention to the effect of age on immune response to vaccination and infection. They dissect the molecular and cellular mechanisms contributing to immunosenescence, with particular attention paid to defective interactions between T helper cells and B cells and alterations in the microenvironment. One important contributor to immunosenescence is believed to be the accumulation of immune cells with a senescence-associated phenotype. The impact of these cells on immune function is highlighted. Age-related changes in metabolic activity are also enumerated, and their impact on immune dysregulation is also discussed.

Mohsen et al. [11] provide a thought-provoking review regarding the design of vaccine antigens, the delivery of those antigens, and the dynamics of the response. They explore these concepts in the context of highly repetitive virus-like particle antigens, where size and other characteristics can be manipulated to fine tune antigen delivery to lymphoid tissues, thereby shaping desired immune responses.

The next article, by **Schijns et al. [12]**, also deals with the modulation of immune function, but approaches the issue from two different standpoints: adjuvant usage and therapeutic vaccination.

The authors contend that therapeutic vaccination has untapped potential due to the large number of chronic health conditions with immune components. The article begins with a discussion of the indications for therapeutic vaccination and segues into a review of the adjuvants and innate immune responses that may be harnessed for optimal vaccine efficacy. There is a careful consideration of elements necessary for the induction of not only humoral immunity, but also cell-mediated responses, which are all too often ignored or minimized during discussions of vaccine efficacy.

Knight et.al. [13] provide a detailed overview of the difficulties facing the immune response to influenza, covering: immunodominance, viral mutation of both the hemagglutinin and neuraminidase proteins to avoid immune recognition, and immunologic imprinting and original antigenic sin. The authors describe the effects these phenomena have on B cell responses to infection and vaccination, the mechanisms behind those effects, and how to use this knowledge to develop vaccines eliciting protective immune responses with broad or universal influenza strain reactivity.

The final article in this issue focuses on genetic variation and immune response to infection and vaccination. This is a topic that has been extensively reviewed in the scientific literature; because of this, **Ovsyannikova et al. [14]** highlighted the studies focusing on human coronaviruses, including the four seasonal coronaviruses, SARS-CoV, MERS-CoV, and SARS-CoV-2. In the few months since the COVID-19 pandemic began, there has been an explosion of published SARS-CoV-2-specific literature on PubMed and preprint servers, with well over 1,000 manuscripts becoming available every week. It will not surprise our readers to see that this has included a number of reports characterizing viral genetic variation and assessing the impact of both viral and host genetics on infection and disease severity. We fully expect that these intensified research activities will continue well into the future and will provide a wealth of information regarding this novel pathogen. This work will also foster an increased understanding of the dynamic interactions of the immune system in the development of protective immunity.

Collectively, these articles will provide the reader with insights into T and B cell interactions during the development of immune responses to infection and vaccination. This issue also highlights the progress that has been made in understanding the intricate details of immune response and how those insights are currently being used to inform vaccine development. Each article outlines major

areas currently under investigation that are poised to deliver the next set of advances in our understanding of how immunity develops.

1. Turner, Benet, Grigorova

The 2-signals…

2. Baidong Hou

Role of B cell antigen presentation in the initiation of CD4+ T cell response

3. Ziv Shulman

T cell help to B cells: Cognate and atypical interactions in peripheral and intestinal lymphoid tissue

4. Jason Cyster

Tfh cells in GC B cell selection and lymphomagenesis

5. Tri Phan

The Geography of Memory B cells reactivation in vaccine-induced Immunity and in autoimmune disease relapses

6. David Tarlington

How intrinsic and extrinsic regulators of plasma cell survival might intersect for durable humoral immunity

7. Shimon Sakaguchi

Control of foreign Ag-specific Ab responses by Tregs and Tfr

8. Shane Crotty

Factors in B cell competition and immunodominance

9. Tomohiro Kurosaki

Influenza vaccination strategies targeting the HA stem region

10. Bloomberg B.B.

Age-related factors that affect B cell responses to vaccination in mice and humans

11. Bachmann M.F.

The 3Ds in virus-like particles based-vaccines: "design, delivery and Dynamics"

12. Maria Lawrenz (or the last review)

Modulation of immune responses using adjuvants to facilitate therapeutic vaccination

13. Patrick Wilson

Imprinting, immunodominance, and other impediments to generating broad influenza immunity

14. Richard Kennedy

The Role of Host Genetics in the Immune Response to SARS-CoV-2 and COVID-19 Susceptibility and Severity