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VIEWPOINT

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No social distancing in the immune system

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Lymphocytes comprise two major subsets, T and B cells. Some T cells kill infected cells, while others help B cells produce antibodies. Deciphering the interactions between these cells and other cells is crucial to the development of therapeutics and vaccines.

In 1961, the thymus, a long-neglected organ, was shown to have a crucial immunological function: mice lacking a thymus from birth were unable to control infections and to make antibodies in response to certain antigens (Miller, 1961). In 1968, mammalian lymphocyte populations were found to be composed of two distinct major subsets: one, subsequently known as T cells, that developed from lymphoid precursor stem cells within the thymus, and the other, known as B cells, that differentiated in the bone marrow. It was also shown that in many cases, B cells needed cognate help from T cells to produce optimal amounts of antibody to certain antigens (Miller and Mitchell, 1968; Mitchell and Miller, 1968; see figure), and in particular to allow B cells to switch immunoglobulin class from low affinity IgM to higher affinity IgG (Cheers and Miller, 1972).

The identification of T and B cells as the two major distinct subsets of lymphocytes and the discovery of T cell help for B cell responses have had a profound impact in immunology and more generally in medicine (reviewed in Miller, 2020). As a result of the delineation of the "two-cell system," a search was made to determine how T and B cells perceive antigen and how, given their low frequency, they could come close together to interact. This led to the discovery of numerous cytokines and chemokines, and of APCs, like dendritic cells. B cells were shown to recognize native antigenic determinants via immunoglobulin molecules present on their cell surface, but T cells could only perceive APC-processed short peptide fragments in association with the body's own marker molecules, known as major histocompatibility complex, or HLA, in humans (Zinkernagel and Doherty, 1974). Further T cell subsets and their lineage markers were identified in the thymus and in the periphery, notably CD4 T helper cells (subdivided into a range of subsets including Th1, Th2, and Th17 cells, according to their cytokine profiles), CD4 Tfh cells (T follicular helper cells essential for B cell responsiveness and germinal center formation in lymph nodes, Peyer's patches, tonsils, and spleen), CD8 cytotoxic cells needed to control viral infections and kill foreign cells, and CD4 Foxp-3 regulatory T cells (T reg) required for homeostasis and the suppression of inflammatory responses. The deletion of self-reactive cells developing in the thymus and in the bone marrow was shown to be mediated by apoptosis induced by the pro-apoptotic BH3-only protein BIM (Bouillet et al., 2002).

T and B cells were also found in birds, in which B cells are derived from the bursa of Fabricius, a cloacal organ unique to avian species (Cooper et al., 1966), while the existence of T and B cells in humans was inferred from genetic disorders in which patients can make antibodies but cannot control virus infections and other disorders

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in which the opposite occurs (Cooper et al., 1968). Interestingly, the dichotomy of T and B cells is also a feature of jawless vertebrates that use distinct types of cells and molecules to recognize intracellular and extracellular pathogens (Alder et al., 2005).

Many immunological phenomena had to be reinvestigated in terms of the contribution made by either T or B cell subsets. At a basic level, these included the carrier effect in which B cells cannot respond to part of an antigenic molecule, the hapten, without the help of T cells that respond to another part of the same molecule, called the carrier (e.g., Cheers and Miller, 1972), immunological memory, immunological tolerance, and original antigenic sin (where B cells

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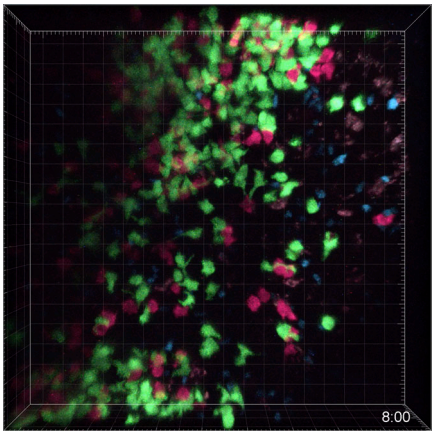

T cell–B cell interactions. Shown are OVA-specific B cells (OB1 cells; green) interacting with OVA-specific CD4 T cells (OT-II cells; red) at the T cell–B cell border, after vaccination against OVA. A few polyclonal B cells are shown in blue in the adjacent follicle. Courtesy of Yu Kato, who provided this single frame image from a multiphoton movie.

respond faster to antigens from a previous encounter than to a second encounter with antigens of a slightly different structure). At a more applied level, there were graft versus host (GVH) reactions, allergies, inflammatory conditions, tissue and organ transplantation, genetically determined unresponsive states, immunodeficiency, and autoimmunity. T cells indeed appear to be involved essentially across the entire spectrum of tissue physiology and pathology, and not just in conditions or diseases considered to be bona fide immunological, but also, to cite just some examples, in tissue repair, in dysbiosis, in pregnancy, in senescence, and in cancer (reviewed in Miller, 2020).

T and B cells are crucial to control infection by viruses such as influenza and SARS-CoV-2. Tfh cells enable B cells to produce potent neutralizing antibodies, and CD8 T cells kill virus-infected cells. In the case of SARS-CoV-2, a detailed study of the differentiation markers on CD8 T cells during the infection has revealed that the virus may have compromised T cell activation. Prior vaccination using a more effective delivery system may therefore be useful to provide an essential CD8 T cell response (Habel et al., 2020).

For influenza vaccination, inactivated influenza virus containing virus envelope hemagglutinin and neuraminidase proteins is used to activate B cells. However, the resultant strain-specific antibodies are only seasonally effective. One possible way of obtaining longer term protection, not requiring annual vaccination, would be to stimulate CD8 T cells to relatively conserved peptides from the inner virus core using a live attenuated virus infecting dendritic cells covering major HLA types.

Antibodies have been the basis of all successful vaccines against acute infections, but not against chronic infections such as malaria, HIV, and tuberculosis. In these, a more efficient activation of antigen-specific CD8 T cells could be worthwhile.

Immune enhancement may occur with certain vaccines (e.g., against dengue) and may either be due to antibody-dependent enhancement or Th2 cell–based enhancement, sometimes termed immune deviation. In the former case, the constant portion of the antibody molecule binds to the Fc receptor on an APC, which enhances viral entry into the target cells and subsequent replication within them. If Th2 cells are activated, a dysregulated response inducing immunopathology may result, as occurs, for example, in allergic diseases. Thus, more research is needed to understand the circumstances that lead to such reactions.

CD8 T cells show markers of exhaustion in cancer and chronic infections. Blocking the activity of inhibitory receptors has reinvigorated the T cell response to some cancers (reviewed in Miller and Sadelain, 2015) and could perhaps also be used in viral infections such as SARS-CoV-2.

Targeting some of the many cytokines or cytokine receptors is bound to have some influence in modulating unwanted effects associated with various immune responses, as is already being shown, for example, in severe COVID-19 disease using anti–IL-6, anti–TNFR-2, or anti-GMCSF. Given that SARS-CoV-2 neutralizes IFN1, a role for intranasal administration of this cytokine early in the infection could be worthwhile. There can, however, be redundancy in the action of cytokines and their receptors.

Researching the microbiome will have an immense impact on our understanding of immune-mediated conditions such as inflammatory bowel dysfunction and allergies. Many intraepithelial "unconventional" T cells (γδ T cells) lie in close proximity to the microbiota and deserve further intensive study.

T reg cells are essential to maintain tolerance by suppressing the activity of self-reactive T cells that have slipped through thymus censorship mechanisms (Hori et al., 2003). Targeting T reg cells to augment their activity in autoimmune disease has been shown to be beneficial in animal models. On the other hand, T reg cells can also impair immune responses to infections and cancer. To use these cells in a therapeutic setting, there is therefore a need to understand the details of the signaling pathways that determine their expansion or contraction.

The BH3 mimetic drug, venetoclax, has been used successfully for the therapy of intractable chronic lymphocytic leukemia (Roberts et al., 2016). This suggests that it might be possible, in the case of autoimmune diseases, to conjugate other similar agents, such as an MCL-1 inhibitor (Kotschy et al., 2016), to an antibody that would bind it to self-reactive T and B cells but spare the T reg cells.

Spectacular success has recently been obtained in the immunotherapy of cancer. Monoclonal antibodies made by B cells have had good results, notably herceptin in HER2-positive breast cancers, while melanomas and other tumors have regressed following the targeting of inhibitory checkpoints on tumor-infiltrating T cells. Chimeric antigen receptor T cells (CAR T cells), engineered by fusing the activating chain of the T cell receptor with the antigen-binding site of antibody molecules, have shown impressive clinical outcomes, especially in B cell malignancies (reviewed in Miller and Sadelain, 2015). Further refinements of this technology are needed to overcome immunosuppression in the solid tumor microenvironment, for example, by deleting the TGFβ receptor from the CAR T cells to prevent them from being suppressed. Given the extreme cost, time, and compromised function of autologous CAR T cells, allogeneic "off-the-shelf" CAR T cells are the future. To prevent GVH reactions, the CAR can be inserted into the TCR α chain locus, TRAC, thereby replacing the endogenous TCR. Alternatively, γδ T cells or natural killer T cells might be used because their restricted repertoire precludes GVH reactions. Loss of MHC Class I by β2m gene deletion should prevent host rejection in outbred populations. Further modifications to improve CAR T cell function and longevity include deletion of checkpoint inhibitors (e.g., PD-1 and PD-1L) and addition

of multiple CARs to mitigate cancer escape through mutation of the nominal target.

In conclusion, recent advances in our understanding of adaptive immune responses are leading to promising new therapeutic approaches for treating some forms of cancer and autoimmune diseases. However similar advances in chronic infections and allergic diseases await a deeper understanding of the diverse responses that T and B cells and their subsets exhibit in different circumstances.

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