REVIEW ARTICLE

Clarifications for Immunology: Lessons Learnt From Teaching Immunology

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ABSTRACT

Immunology, the study of the immune system and its functions, is a complex subject. Although some immunological terms are descriptive, such as 'T cell receptor' or 'clonal proliferation', others are not as aptly named; inaccurate even and can often be misunderstood or misinterpreted. This article clarifies immunological terms such as 'antigen-presenting cells', 'major histocompatibility complex' and 'neutralising antibodies' and addresses several misnomers to improve understanding of immunology. and It also addresses several misnomers such as Human Leukocyte Antigen (HLA) to improve understanding of immunology We have selected terminologies that may be misunderstood or that can benefit from further thought and discussion. These are lessons we have learnt in a classroom setting from teaching undergraduate level immunology. Accordingly, our commentary may also be of interest to immunology instructors, to consider for their undergraduate teaching. Importantly, this article is not meant as a replacement for immunology textbooks but to be considered as a companion reading material. Immunology like many other life science subjects is constantly evolving. We hope that by sharing our experience on what aspects of immunology require clarification in teaching, it will lead to an overall better understanding and teaching of the subject.
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Introduction

Immunology can be a difficult subject to grasp. Anatomically, it is not restricted to the functions of an organ or two. It also involves numerous cells and mediators that often have redundant functions. Immune cells can also be classified in several different ways, including based on their lineage (myeloid and lymphoid), isolation procedure and morphology (peripheral blood mononuclear cells and polymorphonuclear leukocytes) and immunological features (innate and adaptive). These dichotomies are useful but can hinder the reader from studying immunology in an integrated, systemic manner. This is confounded by the fact that there are misnomers and ambiguity in several immunology terminologies, which we attempt to clarify here. Language however cannot be perfect, and many misnomers in immunology owe their names to the historical consequences of their discoveries, such as major histocompatibility complex. Language also evolves, and some immunological terms have changed over time. For instance, chemokine nomenclature has changed from, for instance, IL-8 to CXCL8. Perhaps this commentary will be an initial step to more discussions on nomenclature and categorisation.

This article serves as an aid aid for novice immunology scholars at the undergraduate level, and clinical and non-clinical postgraduate scholars who are revising basic immunology. It is meant for the individual who has gone through basic immunology textbooks but requires better understanding of certain terminologies. It may also be useful for immunology teachers, offering them a perspective of what we have learnt by teaching undergraduate immunology for the past two decades. It is not however a replacement for textbooks nor being current with immunology literature, as the elements and mechanisms of our immunity is becoming increasingly clear to us with the advancement of science and technology

Allergy
Allergy is a type I (immediate) hypersensitivity reaction. It involving involves an IgE-mediated mast cell degranulation that releases inflammatory mediators such as histamine. Antigens that elicit immediate hypersensitivity reactions are known as 'allergens'. Dust mites, animal dander and shellfish are common allergens that cause a type I hypersensitivity reaction. The American Academy of Allergy, Asthma and Immunology designates the term 'allergy' to an overreaction of the immune system due to the production of IgE antibodies (1).

Allergies typically trigger symptoms in the nose, lungs, throat, sinuses, ears, skin and stomach lining. Typically, these include localised itchiness, redness, swelling, as well as increased mucosal oedema and secretion. For some people, allergies also trigger symptoms of asthma. The most severe clinical presentation of an acute systemic allergic response is anaphylaxis, characterized by systemic symptoms including generalised skin manifestations (such as urticaria, swollen lips and tongue), airway constriction (bronchospasm), low blood pressure due to vasodilatation, and severe gastrointestinal symptoms (severe, crampy abdominal pain, repetitive vomiting) (2).

In practice however, 'allergy' and 'allergen' is often used to describe other adverse reactions. For instance, Macy reports that in electronic health records, 'allergies' are often recorded when there is a drug intolerance although it is not necessarily confirmed as an allergy. The author goes on to suggest that 'intolerance' is a better term to use as it makes no presumption that a clinically significant IgE-mediated hypersensitivity has occurred (3). Similarly, an adverse reaction to milk and milk products could be a lactose intolerance and not necessarily an allergy. Similarly, in a review of the literature, Vyles and colleagues noted that 'most allergies in paediatric patients are self-reported and often inconsistent with true allergy' (4). These are indicative of the rather indiscriminate use of the term 'allergy'.

If these adverse reactions are all considered 'allergies', it is a concern that both patient and clinician may not understand and manage the condition correctly . using evidence based therapeutic strategies.

It is important for both clinician and patient to understand the nature of the hypersensitivity as it influences the patient's history taking, investigations, and management. For this reason, a diagnosis of allergy goes beyond signs and symptoms and requires detailed clinical history-taking and tests such as the skin prick test. In 2009, the World Allergy Organization wrote a position paper titled 'Recommendations for Competency in Allergy Training for Undergraduates Qualifying as Medical Practitioners' (5), which states the essential need for undergraduates to understand Gell and Coombs I–IV hypersensitivity reactions as "…a lack of appropriate education and training in allergy at the undergraduate level leaves many medical graduates with low baseline knowledge and skills in the science and practice of allergy.' Being clear on the pathogenic mechanisms of allergies also helps students of nutrition and dietetics to distinguish a food allergy from a food intolerance. A sensitivity to milk is not automatically an 'allergy'.

Allergic contact dermatitis
Allergic contact dermatitis (ACD) is a form of contact dermatitis which is is a type IV hypersensitivity

The term 'allergic' within the 'ACD' can mislead readers into assuming it is a type I hypersensitivity. Type IV hypersensitivities are mediated by antigen-specific T cells while type I hypersensitivities are mediated by IgE-mediated degranulation of mast cells. ACD is often contrasted clinically with irritant contact dermatitis (ICD). Skin damage in ICD is the result of an irritant causing a localised inflammatory response mediated by the innate immune system.

Anti-CD28
Using anti-CD28 as an example, 'anti-CD28' simply means a monoclonal antibody that is specific binds to the receptor CD28. The term 'anti-' simply denotes that it is an antibody. However, because 'anti-()' also carries the meaning of 'against' and 'opposed to' in the English language, the immunology scholar may mistakenly assume that 'anti-CD28' carries the connotation that the antibodies have blocking or inhibitory activities on CD28. This is not necessarily true. The immunology reader must determine this separately, as an anti-CD28 can be an antibody that binds to CD28 to block its function, activate its function, or merely to detect its presence.

Antibodies in hypersensitivities
Hypersensitivities are an excessive, injurious immune reaction. There are four main types of hypersensitivity reactions, classified based on their pathologic immune mechanism (Table I).

Table I: Classification of hypersensitivity types.

Type of hypersensitivity	Alternative name	Immune mechanism	Mechanism of tissue damage
Type I	Immediate	Th2-mediated response produces IgE antibodies that crosslink on mast cell receptors, causing their degranulation.	Inflammation caused by the release of inflammatory mediators such as histamine, serotonin, proteases and cytokines by mast cells and eosinophils.
Type II	Antibody-mediated	IgM and IgG antibodies against antigens expressed on cells or extracellular matrix.	Opsonisation and subsequent phagocytosis of cells Inflammation caused by complement- and Fc-mediated activation of leukocytes Interferes with cell function by blocking or stimulating receptors
Type III	Immune-complex mediated	IgM and IgG antibodies that bind to soluble antigens to form immune complexes.	Deposition in tissue leading to inflammation caused by complement- and Fc-mediated recruitment of leukocytes.
Type IV	T cell-mediated	$CD4^{+}$ T helper cells and $CD8^{+}$ cytotoxic T cells	Cytokine-mediated inflammation, macrophage activation and direct target cell killing.

Type II hypersensitivity is also known as A‘antibody-mediated hypersensitivity . It occurs due to the binding of antibodies to antigens on a cell's surface or on extracellular matrices. The damage caused by the hypersensitivity is on the cell or tissue that expresses the particular antigen. The term 'antibody-mediated hypersensitivity' however may cause the immunology reader to inadvertently overlook that antibodies are also implicated in the immunopathology of other type I and type III hypersensitivities. The distinction is that in type I hypersensitivity, although IgE is involved, it is histamine, leukotrienes and other mediators that go on to mediate the tissue damage. A type III hypersensitivity, the pathology is due to the formation of immune complexes that are deposited in various tissues.

Antigen-presenting cells

'Antigen-presenting cells (APCs)' is a term in immunology reserved for cells that present antigens through the class II MHC route. Mainly, these are macrophages, B cells and dendritic cells. The class II MHC route processes extracellular antigens and presents them to CD4+ helper T cells, thus initiating adaptive immune responses (6).

However, the term' antigen-presenting cell' may cause the immunology reader to forget or place less importance on the antigen presentation that occurs via the class I MHC route. . With this, it is feared that the immunology reader may fail to remember that other cells also can perform antigen presentation.

The class I MHC pathway processes proteins in the cytosol (intracellular antigen) and presents them to CD8+ cytotoxic T cells. All nucleated cells can present antigen via class I MHC. This is an equally important defence against viruses, intracellular bacteria and tumour antigens and the class I MHC pathway is just as efficient as the class II at displaying antigens.

The term ‘professional antigen-presenting cells’ of course exists to delineate MHC class II from MHC class I processing. However, confusingly ‘professional antigen-presenting cell’ is also a term used in some immunology references to refer to dendritic cells alone as they are the most effective APC for activating T cells (6). This is partly because DCs express high levels of T cell costimulatory molecules compared to their B cell and macrophage counterparts and because DCs can cross-present antigen to CD8+ T cells for their activation (6) .

Antinuclear antibodies

The term antinuclear antibody (ANA) implies that these antibodies are directed solely against nuclear components (like DNA, histones, nuclear RNA), when in fact, they can have cytoplasmic targets (like mitochondria, Golgi, cytoplasmic actin) and mitotic structures (like mitotic spindle fibre, centriole). A more recently coined term, anti-cell antibody or anti-cellular antibody, is more accurate as it better captures the diversity of these autoantibodies.

Barriers classification

Immunology literature often describes certain immune defences as 'barriers'. These barriers are numerous and often classified as physical, physiological, chemical and biological barriers. Some also use terms such as cellular barriers and anatomical barriers.

The issue with these classifications is that they are restrictive and hinder thought and assimilation of facts. For instance, mucous membranes are considered physical barriers but contain IgA (a chemical barrier). Also, mucous forms a barrier (physical barrier) between pathogens and our epithelial tissues, but it also contains antimicrobial peptides (a chemical barrier). Classifying barriers this way is unnecessarily pedantic and can be done away with. Even more minacious is if the classification is tested in an exam. We rather the immunology scholar appreciate, for instance, that the mucosa of the respiratory system is made up of pseudostratified, columnar epithelium with well-developed cilia. And that the epithelia are tightly adhered to one other at tight junctions. It has secretions that contain mucous, and antimicrobial peptides such as defensins and cathelicidins (7). The mucous, together with the movement of the cilia serves to trap foreign substances and prevent them from moving further down to the alveoli (8). IgA is also present in the airway lumen. This is a far more useful understanding of the immunity of the respiratory system rather than classifying the mucosa as a particular type of barrier.

Importantly, for immunology educators, this can be a discussion point on how to test immunology knowledge in a manner that encourages understanding rather than being unnecessarily pedantic.

Cytotoxic T lymphocyte-mediated killing

Killing indicates an active act. Here, the mechanism is, in fact, inducing cell suicide. When activated, CTLs release the contents of their granules into the target cell. These include perforin, a protein that forms pores in cell membranes and granzymes, that activate the cell's apoptotic pathway to induce cell death.

Distinguish self from nonself

The immunology scholar will know that 'distinguishing self from nonself' indicates is concept of immunity which is to discriminate between foreign and self in order to eliminate foreign antigens and not react to healthy host cells . This concept extends to both the innate and adaptive arms of immunity, although different mechanisms are used by both arms to prevent reactions to healthy cells (6).

In the topics of immune tolerance, lymphocyte development and autoimmunity, the concept is discussed with the knowledge that self-reactive cells can be created by receptor diversity and majority of them are eliminated (9). On the off chance that the immunology reader is reading without scrutiny, he or she may misinterpret the term 'distinguishes' or ‘discriminates’. It may be mistaken for an active process; that a lymphocyte actively recognises both self-antigen and foreign antigens and proceeds then to only ambush foreign antigens. This is not the case. LLymphocytes are clonal and - each lymphocyte is specific for onea particular antigenic determinant or epitope. One lymphocyte may be specific for a bacterial epitope, while another for a self-antigen epitope. Lymphocytes specific for a self-antigen epitope are controlled via the process of tolerance, both central tolerance and peripheral tolerance. Central tolerance occurs in immature lymphocytes, self-specific lymphocytes die by apoptosis , a process known as clonal deletion. Lymphocytes that are not specific for self are allowed to live. In mature lymphocytes, the immune system employs various other strategies to prevent attacks on self, including clonal anergy and regulatory T cells. A failure of tolerance leads to autoimmunity and can result in autoimmune diseases. All in all, the concept of ‘distinguishing self from nonself’ should not be misunderstood as just one singular action.

Human Leukocyte Antigen

Human leukocyte antigen (HLA) is the human's major histocompatibility complex (MHC). The name HLA indicates it is only expressed on leukocytes. However, HLA Class I is present on all nucleated cells. Names and terminologies often are the starting point for a student to decipher their function and characteristics. In this context, HLA is not a particularly useful name.

Also see Major histocompatibility complex.

Lymphocyte maturation and lymphocyte activation

In immunology, the maturation and activation of lymphocytes allude to several specific proceedings and outcomes (Table II). 'Maturation' and 'activation' as standalone terms can be quite ambiguous, and the immunology scholar must discern each process's biological events.

Table II: A summary of lymphocyte activation and maturation.

	Lymphocyte maturation	Lymphocyte activation
Goal/ Outcome	Establishing a repertoire of antigen-specific lymphocytes that are MHC-restricted (for T lymphocytes) and tolerates self-antigen.	Activating B and T lymphocytes to perform their effector function that confers immunity.
Location	Occurs in the bone marrow for B lymphocytes Occurs in the thymus for T lymphocytes.	Occurs in secondary lymphoid organs such as the lymph nodes, tonsils, spleen.
Antigen exposure	Occurs before antigen exposure.	Occurs after antigen exposure.
Involves	Expression of antigen-specific receptors (the BCR and TCR) and necessary co-receptors Self-tolerance mechanisms.	Recognition of antigen Binding of costimulatory signals to their ligands.

B and T cell maturation, it involves the generation of a repertoire of lymphocytes with antigen-specific receptors and equipped with the necessary coreceptors and cell surface molecules. Simply put, a mature B or T cell is a cell that is equipped to recognise antigens but has not yet recognised antigens. Lymphocyte maturation also indicates these processes occur in the bone marrow and thymus. A mature B or T cell is a cell that is equipped to recognise antigens but has not yet recognised antigens.

Mature B and T cells exit the bone marrow and thymus to reside in lymph nodes, the spleen and other secondary lymphoid organs and recirculate in blood.
One of the main aims of describing lymphocyte maturation is to deliver the following concepts: (i) antigen recognition of lymphocytes stems from a gene recombination process where gene segments are randomly rearranged, and (ii) some lymphocytes recognise self-antigens and are eliminated. These concepts go on to become relevant in topics of autoimmune disease and certain inborn errors of immunity.

B and T cell activation alludes to the concept that immunity is tightly controlled. Activation of B and T cells begins with the recognition of antigens. This is, in fact, true of all cells of the immune system – they have effector function after binding to antigens. However, recognising antigens alone is often insufficient for B and T cells to function. They require a second 'signal' provided by other cells. All in all, it is a 2-step startup system designed to keep the immune system in check.

Uncontrolled activation of lymphocytes would be destructive. Although the term 'activation' is also used when describing macrophages that are 'activated' by the cytokine IFN-γ and by CD40-CD40L interactions, the context differs slightly from lymphocyte activation. Macrophages can for instance phagocytose function without IFN-**γ**, IFN-γ merely provides the cellular signalling to boost their function and therefore it is not necessarily viewed as a control mechanism.

Major histocompatibility complex

Major histocompatibility complex (MHC) molecules are membrane proteins that present antigen to T cells. That is the evolutionary role of MHCs, to display peptide antigen for recognition by T cells. The MHC molecules however term were discovered when scientists were studying transplantation in mice. They observed that transplants could survive or be rejected by the immune system - 'histocompatibility' refers to the similarity of antigens between a donor and recipient (10). . Therefore, the name 'major histocompatibility complex' in itself does not refer to the fundamental role of MHC in immunity. Transplantation is a medical invention and not part of the design of our immunity (9).

Neutralising antibodies

The term 'neutralising' can be quite ambiguous and open to misinterpretation. Firstly, antibodies have several effector functions depending on the antibody isotype, pathogen type and infection site. Antibodies that have an effect on inhibiting the infectivity of microbes and or (ii) preventing the damaging effects of microbial toxins are termed neutralising antibodies. For instance, the spike proteins of the SARS-CoV-2 virus are responsible for viral entry into the host. Neutralising antibodies against SARS-CoV-2 would be antibodies against the spike protein. Neutralisation can also be the agglutination of bacteria by antibodies to reduce their infectivity. Similarly, an antibody can bind to a microbial toxin, preventing it from binding to cellular receptors and causing tissue damage. None of these functions require the Fc regions of the antibody; they only require the Fab (fragment, antigen-binding) regions.

A useful exercise is to list what neutralising antibodies DO NOT do. Neutralising antibodies do not opsonise, activate the classical complement pathway, mediate cytotoxicity (through ADCC), or degranulate mast cells. Another useful thing to remember is that the 'neutralising' effect only requires the antigen-binding regions of the antibodies, whilst opsonisation and ADCC are mediated by the Fc (fragment, crystallisable) regions of the antibody binding to Fc receptors on the effector cells.

Importantly, 'neutralising' describes an overall effect of antibodies and not necessarily a type or class of antibodies.

Positive selection

Positive selection is not necessarily a misnomer, but it would be useful for the immunology reader to know that it means slightly different things for B and T cells.

It has to do with B and T cell development within the bone marrow and thymus, respectively. Maturation for these cells involves the expression of antigen receptor genes, expression of functional receptors and differentiation into functional and phenotypic-specific subpopulations. Not all lymphocytes succeed in doing this, and the process of positive selection selects lymphocytes that will be potentially successful in their prospective function.

This is much more defined for T lymphocytes. Positive selection of T lymphocytes is the selection of thymocytes which recognise self-peptide-self MHC complexes (binding to them with low avidity) to develop into mature T lymphocytes that can recognise antigens through MHC presentation (i.e. they are MHC-restricted). This is not required for B cells as they do not require MHC antigen presentation. And so, for B lymphocytes, positive selection indicates the selection of progenitor B cells with functional antigen receptors.

Primary immunodeficiencies

Historically, primary immunodeficiencies were diseases characterised by an increased susceptibility to infections due to a deficient immune system. The word primary was used to indicate that it results from a genetic defect and to contrast it to secondary immunodeficiency.
Primary immunodeficiencies are now known as inborn errors of immunity (IEI) (11). This latest definition allows for the inclusion of malignancies and autoimmune reactions that are now clearly part of the spectrum for

these diseases.

Vaccines
Vaccines are antigenic preparations that stimulate an immune response to confer protection and immunological memory during a subsequent infection.

It is not a misnomer, but the term 'vaccine' has also been used to describe dendritic cell immunotherapy. Dendritic cell vaccines are preparations of dendritic cells that are antigen-loaded with antigens for better stimulation of T cell responses (12). This allows more efficient antigen-presentation and co-stimulation of the patient's T lymphocytes and has been explored for cancer therapy and infectious diseases such as HIV. Importantly, dendritic cell vaccines are discussed in the light of treatment, and not necessarily as a prophylactic.

Therefore, the term 'vaccine' no longer only indicates protection towards infection, nor is it a purely antigenic preparation. In the case of dendritic cell vaccines, it is a cellular preparation.

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