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Trends in basic immunology research – 2001 and beyond

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The immune system is primarily involved in protection against pathogens and opportunistic organisms. Similar to a nation's defence organization, the immune system involves different components. This diversity allows the immune system to defend against different types of attacks by microbes. The past century has witnessed tremendous progress in understanding the components and mechanisms involved in the immune response. This article attempts to highlight areas of active research in basic immunology in the coming years.

THE mechanisms by which vertebrates have devised survival strategies to protect themselves from pathogens and opportunistic organisms constitute the subject of immunology and the past century has witnessed tremendous strides in the growth and establishment of this field^{1,2}. This transition from an 'esoteric' science of undefined factors and mechanisms to 'mainstream' science has been due to the development of defined reagents: monoclonal antibodies, cDNAs and the use of genetically modified mice harbouring targeted mutations in immune function-related genes. Although it is hazardous to predict the future, an attempt is made here to list some of growing areas of immunology in the coming years (Box 1). The knowledge obtained in these basic immunological pursuits finds applications in several other areas of applied immunology and disease pathogenesis; however, not all aspects have been addressed in this article due to limitations of space.

The two main arms of the immune response are innate

and adaptive (Figure 1). The innate arm is evolutionarily conserved, acts early and constitutes the first line of defence. The adaptive arm is evolutionarily recent and the immune response is relatively delayed (compared to the innate system), to generate a specific response towards a particular antigen. This specificity is conferred by antigen-specific receptors on B cells and T cells. The past few decades have witnessed tremendous progress in under-

Box 1. Broad areas of active research in basic immunology

1. Studying the components and mechanisms involved in the innate immune response. Understanding the mechanisms by which the innate response modulates the adaptive immune response.
2. Events leading to activation, proliferation, death and homeostasis in lymphocytes (T cells, B cells and NK cells).
3. Mediators and mechanisms involved in the interaction of lymphoid and non-lymphoid cells under normal, pathogenic and aberrant (e.g. autoimmune, allergic, etc.) conditions.
4. Characterization of cells and mechanisms involved in immunological memory.
5. Genomics and the immune response: Genes involved in immune defects/modulation of immune responses and the role of genetic polymorphisms in the immune response, disease resistance and susceptibility.

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standing the molecular basis of adaptive responses via the elucidation of the genes and structures of the B cell receptor (BCR) and the T cell receptor (TCR) (Box 2). However, less is known of the innate arm of the immune system, which recognizes microbial components. For example, lipopolysaccharide (LPS), a component of Gram-negative bacteria, activates B cells and macrophages. Also, LPS is responsible for endotoxic shock, resulting in hypotension and multi-organ failure³. A better understanding of the mediators and the mechanisms involved in endotoxic shock is required as this information may lead to the development of therapeutic strategies^{3,4}. We are beginning to understand the mechanisms by which components of bacterial cells induce immune responses, especially the role of TOLL-family proteins⁵ and additional proteins⁶. Surprisingly, bacterial DNA containing non-methylated CpG dinucleotides stimulates immune cells⁷. On the other hand, vertebrate DNA contains mainly methylated CpG that is non-stimulatory. The stimulatory capacity of bacterial DNA is extremely potent and certain groups are attempting to use the 'adjuvant capacities' of these sequences in DNA vaccines⁸. Further, work will reveal the nature of receptors involved in specific recognition of bacterial DNA⁹, the cell biology of its endocytosis and finally, the mechanisms by which unmethylated CpG DNA triggers immune effector functions. Therefore, the mechanisms by which microbial cells induce the innate system, as well as the manner in which they may modify the adaptive immune response will be an area of active investigation.

The adaptive immune response can be subdivided into two types—the humoral response that is mediated by the secretion of immunoglobulins by B cells and the cellular immune response that is mediated by T cells. Cytotoxic T cells are responsible for killing infected cells, whereas T helper cells produce interleukins (IL), the 'hormones' of the immune system, and modulate B cell responses. Unlike B cells which recognize epitopes on native antigen, T cells recognize peptides presented on major histocompatibility complex (MHC)-encoded proteins (Box 2). There are two broad classes of MHC molecules – classical and non-classical. MHC class I and class II proteins belong to the classical group, are highly polymorphic and play a dominant role in the T cell-mediated adaptive

immune response. Interestingly, natural killer (NK) cells, a sub group of cells belonging to the innate arm of the immune response, survey cells for the lack of expression of MHC class I. They are aided in this job by NK receptors¹⁰, which survey cells for MHC class I expression; cells which do not express MHC class I proteins are targeted for lysis. There is a lot to be learnt on how NK receptors mediate this function – in most cases recognition of MHC molecules by NK receptors prevents lysis of target cells; however, in some cases NK receptors activate target cell lysis. The basis for the differential response by NK receptors (inhibition or activation) will be an area of active study. Recent studies have revealed the importance of non-classical MHC molecules which are not very polymorphic¹¹. There are several cell-surface molecules that belong to this category and their function may vary from transporting IgG (neonatal Fc receptor), iron absorption (HFE or the haemochromatosis gene product) and the presentation of glycolipids (e.g. galactosyl ceramide presentation by clusters of differentiation-1 (CD1) to a subgroup of T cells). Although previous work has focused on the more important polymorphic MHC class I and class II molecules, future work on non-classical molecules will reveal their unique functions.

Much progress has been made in understanding the mechanisms by which peptides are generated and bind MHC molecules for presentation to T cells. It is well known that majority of peptides bound to MHC molecules are generated from cellular proteins. Indeed, in the absence of a peptide, cell-surface expression of MHC molecules is low. During infection, a small proportion of peptides derived from the pathogen bind to MHC molecules and are expressed on the cell surface of antigen presenting cells (APCs) (Box 2). On recognition of this peptide/MHC complex via TCRs, specific T cells get activated and proliferate (Figure 2). The components of the MHC class I and class II antigen-processing pathways are well studied and perhaps, additional components and mechanisms involved in crosstalk between these two pathways will be discovered in the future. Although it is possible to predict MHC-binding peptides from a given sequence, the factors that contribute to the generation of 'immunogenic' peptides from a given protein are yet to be understood. In fact, the relative abundance of peptide produced¹² or the best predicted MHC-binding peptide may not generate a good cytotoxic T lymphocyte (CTL) response^{13,14}. There are several possible reasons for this discrepancy – lack of generation of these peptides *in vivo* due to the inability of enzymes to generate this peptide, short half-life of the peptide, inability of the peptide to be transported into compartments for MHC binding, inability to bind the MHC allele expressed by the individual or lack of T cells specific for this peptide/MHC complex. Therefore, key progress needs to be made in understanding the rules involved in the generation of peptides from proteins, the rules that govern the ability of peptides to be

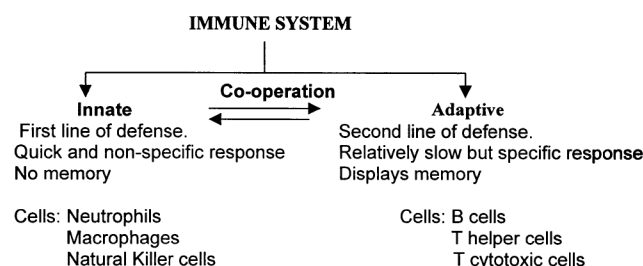


Figure 1. Simplistic view of the immune system.

Box 2. Brief explanation of immunological terms

Adjuvant: A substance which enhances the immune response to an antigen.

Antigen presenting cells (APCs): Dendritic cells, Langerhans cells, macrophages, B cells, etc. that digest cellular or pathogen-derived proteins and present peptide–MHC complexes to T cells. During an immune response, these cells express high levels of costimulatory ligands on the cell surface. High levels of MHC-peptide and costimulatory ligand expression are important for T cell activation.

Antigenic peptide: Cellular or pathogen-encoded proteins are digested and peptides derived from these proteins are presented on MHC molecules. Specific TCRs recognize antigenic peptides/MHC complexes. Agonist peptides mimic antigenic peptides, whereas antagonist peptides are closely related by sequence to the antigenic peptide, but inhibit the activation of specific T cells.

Antibody: Immunoglobulins that specifically bind to antigens and are produced in response to antigen; the specificity of antibodies to different antigens is due to the variable regions present in the molecule.

Antigen: A molecule that elicits the production of antibodies and/or can be processed by APCs to elicit a T cell response.

Apoptosis: Programmed cell death associated with morphologic changes, e.g. nuclear fragmentation, membrane blebbing and release of apoptotic bodies.

Autoimmunity: Abnormal immune response against self-antigens resulting in disease, e.g. systemic lupus erythematosus, rheumatoid arthritis, etc.

B cells: Lymphocytes that mature in the bone marrow in mammals or the bursa of Fabricius in birds and express membrane-bound antibody. On binding antigen, B cells differentiate into plasma cells that secrete antibody molecules.

B-cell receptor (BCR): The B cell membrane-bound immunoglobulin which recognizes antigen and is associated with two signal transducing molecules, Ig α /Ig β .

Clusters of differentiation (CD): Refer to a particular cell surface molecule. Antibodies to different CD molecules are used to denote specific cell populations; for example CD4 is usually present on T helper cells, whereas CD8 is present on T cytotoxic cells.

Costimulation: Optimal activation of T cells and B cells requires signalling via two receptors – antigen-specific receptor (TCR or BCR) and a costimulatory receptor (CD28 or CD19/CD21).

Cytotoxic T cells (CTLs): T cells expressing CD8, on recognition of antigenic peptide/MHC complex, differentiate into CTLs which can kill APCs or target cells.

Immunosuppression: Inhibition of immune responses; some cytokines, e.g. TGF β and IL-10 are known to be immunosuppressive.

Major histocompatibility complex (MHC): MHC molecules are polygenic, polymorphic and inducible with interferon- γ . They were first recognized in transplantation due to the induction of vigorous graft rejections. Genes encoding MHC molecules are located on human chromosome 6 (HLA) or mouse chromosome 17 (H-2). Predominantly, the two types of MHC molecules are class I or class II. MHC class I molecules present peptides generated in the cytosol to CD8⁺ cytotoxic T cells, whereas the MHC class II molecules present peptides degraded in lysosome-like compartments to CD4⁺ T helper cells.

Monoclonal antibody: Produced by a single clone of B-lymphocytes and, hence, possesses the same antigenic specificity.

Mucosal immune system: The mucous membranes lining the digestive, respiratory and urogenital systems are protected by a group of organized lymphoid tissues collectively called the mucosal associated lymphoid tissue (MALT).

Naïve cells: Mature T and B cells that have not encountered antigen; also called unprimed and virgin cells.

T cells: Lymphocytes that express a TCR; most T cells mature in the thymus.

T helper cells: T cells with CD4 expression on the cell surface are called Th cells (Th cells). T helper cells are divided into two populations—Th1 and Th2 subsets. Th1 subset produces cytokines that support inflammation and cell-mediated responses, whereas Th2 subset produces cytokines that help B cells to produce antibodies.

T cell receptor (TCR): The molecule expressed on the surface of T cells that recognizes antigenic peptide/MHC complex via variable regions. TCRs are associated with a group of proteins known as the CD3 complex, which is important for signal transduction.

Thymic selection: A stringent process by which few thymocytes are selected to enter the peripheral circulation as mature T cells. Those thymocytes that can recognize self-MHC molecules are selected (positive selection) and autoreactive thymocytes are eliminated (negative selection).

transported into MHC-binding compartments, the role of additional peptide-binding proteins, the role of flanking sequences in a MHC-binding peptide, etc. Also, progress needs to be made on the mechanisms by which some peptides act as agonists, partial agonists (for example cytotoxicity without cytokine production) and antagonists (a non-functional TCR–MHC interaction)¹⁵.

Naive T cells enter peripheral circulation after undergoing thymic education. These T cells recognize self-MHC–peptide complexes, but much remains to be learnt about the mechanisms by which T cells transduce signals to initiate activation (Figure 2). The mechanisms by which T cells are activated, the maze of kinases and phosphatases and the reorganization of cell-surface proteins into supramolecular activation cluster (SMOCs)¹⁶ need to be refined further. Similarly, the events involved in B cell activation need to be understood. Enhanced knowledge of B and T cell activation may lead to novel drug targets that control immune responses. Lymphocytes require signalling via antigen-specific receptors (BCR or TCR) and a second costimulatory receptor (CD19/CD21 on B cells and CD28 on T cells). The role of costimulation is to amplify the signals received via the BCR or the TCR to elicit an immune response^{17,18}. This is usually true for immune responses to a model antigen (e.g. ovalbu-

min). However, the role of costimulatory receptors appears to be less important in responses to pathogens since they activate the innate immune system, resulting in an inflammatory response¹⁹. This results in high expression of ligands important for costimulatory receptors. CD28 on T cells is a major positive costimulatory receptor, whereas CTLA4 is a negative costimulatory receptor. Activating T cells via the clonally variable TCR and CD28 is required for optimal proliferation, whereas tickling T cells via CTLA4 down-regulates T cell responses. However, CTLA4 can positively costimulate T cell proliferation under some conditions^{20,21}. How does this happen? What is the role of other costimulatory receptors and interleukins (for example, IL-1, IL-6, IL-12, etc.) which can also costimulate T cells? What is the role of the different cell-surface molecules in T cell activation and cytokine production? For example, CD40–CD40L interactions help up-regulate the CD28–B7 responses²². Much needs to be learnt on the signalling pathways and contributions of different cell-surface receptors in lymphocyte activation.

On activation, T cells produce high levels of interleukins and there has been a tremendous amount of work on the identification and characterization of these factors; for example, IL-2, IL-4, etc. play a critical role in the modulation of the immune response. The ratio of these different interleukins results in the dominance of T helper, Th1 or Th2 type of immune responses, which is important in determining immune responses to pathogens and influencing the development of autoimmune diseases and allergic responses²³. The reasons for the predominance of either Th1 or Th2 responses are complex and are in the process of being defined²⁴. For example, the interaction between ICAM1 and LFA1, which are involved in cell adhesion, blocks IL-4 production resulting in down-modulation of Th2 cytokines^{25,26}. Future work will probably focus on the interplay of interleukins with other non-lymphoid cells and there are evidences that suggest that cytokines produced by T cells affect epithelial cells. Although there are tremendous numbers of cells associated with the mucosal system, these lymphocytes are prevented from activation under normal conditions due to the production of immunosuppressive factors (e.g. IL-10, TGF- β , prostaglandin E2)²⁷. An appreciation of the interplay of non-lymphoid cells and lymphoid cells under normal, pathogenic and autoimmune conditions will contribute to our understanding of the immune response. Similarly, an *in vivo* appreciation of the mechanisms by which cells of the immune system (T and B) communicate with each other will hopefully be better appreciated in the future²⁸. Therefore, future research will reveal more about the roles and contributions of different cells and mediators in generating the immune response.

The probability of finding an antigen-specific T cell is extremely tiny, approximately one specific T cell out of a total of ten thousand T cells. However, during infections

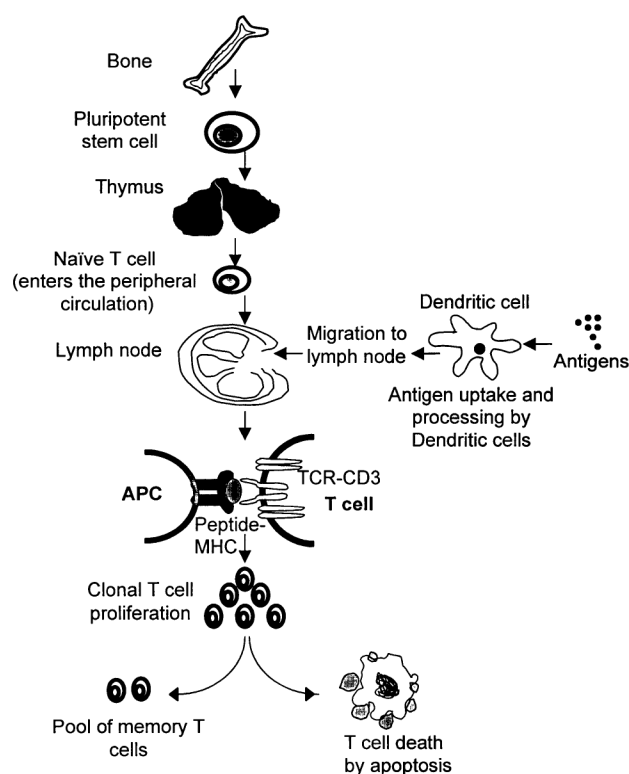


Figure 2. Life history of a T lymphocyte. Majority of T cells enter the peripheral circulation (spleen, lymph node, etc.) after being selected in the thymus. On recognizing antigenic peptide–self-MHC complexes on the surface of APCs (e.g. dendritic cells, macrophages, B cells) specific T cells are activated, produce the autocrine growth factor IL-2 and proliferate. As levels of IL-2 drop, activated T cells undergo apoptosis. However, a small pool of memory T cells remain to fight future battles.

these specific T cells expand greatly ($\sim 10^4$ – 10^5 times) to constitute the bulk of the immune response²⁹. It is dangerous to have such a large number of activated T cells because the large amounts of interleukins or other factors produced by these cells may cause damage to other cells of the body, resulting in immunopathology. As the antigen is cleared the vast majority of such activated T cells undergo apoptosis, although a few memory T cells remain to fight future battles (Figure 2). It is important to emphasize that the immune system has devised mechanisms to down-modulate an acute immune reaction. How does this happen? What are the mechanisms involved in this response? What are mechanisms involved in B cell memory? How does the generation of memory B cells differ from that of memory T cells? These are some questions that need to be addressed in the future.

Lymphocyte death occurs in both thymic and peripheral tissues and this death ensures tolerance and maintenance of immune homeostasis³⁰. Lymphocyte deletion may be triggered via signals through antigen receptors, which recruit death receptor–ligand interactions, e.g. CD95/Fas/Apo-1 and tumour necrosis factor (TNF) receptors into this process³¹. There is a vast amount of information available about the interaction of these receptors with cellular proteins and molecular events of death pathways. However, the regulation of these events, i.e. the decision of the lymphocyte to trigger apoptotic death as opposed to proliferation or survival in response to antigen receptor cross-linking, is as yet unknown. The past five years have seen a tremendous surge in our knowledge of the molecular events that regulate apoptotic death of cells. Caspases, a family of cysteine proteases, have been identified as the key effectors of apoptotic death pathways³². There has also been the delineation of two major apoptotic death pathways involving these death proteases in lymphocytes and other cells. The first is triggered via the death receptors listed above and the second involves the mitochondria. The mitochondrion is a key checkpoint in the death pathway and molecules like cytochrome *c*, apoptosis activating factor-1 (Apaf-1) and a novel flavo protein, apoptosis inducing factor (AIF) are some of the apoptogenic molecules associated with this organelle³³. Interestingly, most of these molecules are located in the intermembrane space (IMS) of the mitochondrion and the coming years should reveal more insights into the movement of these molecules through the outer membrane of undamaged mitochondria in dying cells. Although the primary focus in the field of cell death has been on the role of caspases, molecules like MHC class I and MHC class II, CD2, CD4 and CTL-triggered target cell death appear to be independent of known caspases. Future research in this field should provide a clearer understanding of the physiological significance of these death pathways and perhaps, allow a better manipulation of these events as well. In this context it is interesting to note that recent studies have opened up the intriguing and somewhat unexpected possi-

bility of caspase involvement in the process of T cell activation as well^{34,35}.

A recent finding is that MHC class I and class II molecules are important in not only selecting T cells in the thymus, but are also important in maintaining naive T cells in the periphery (Box 2). In fact, peripheral T cells transferred into hosts lacking lymphocytes result in proliferation of these newly transferred T cells in a self-MHC-dependent manner, until a certain number of T cells is reached. However, uncontrolled proliferation is prevented. How is this performed? What are the controlling factors (perhaps, cytokines or cell surface receptors) involved in this process? Thus, not only are self-MHC molecules important for selecting T cells in the thymus, but they are also important for their maintenance in the periphery. Intermediate affinity interactions between the TCR and self-MHC molecules help T cells to be positively selected in the thymus and survive in the periphery. On the other hand, high affinity interactions lead to deletion of these T cells in the thymus as they may be auto-reactive (negative selection). However, high affinity interactions in the periphery lead to proliferation of T cells and the effector T cell response and memory²⁹. This scenario is different for memory T cells which do not require self-MHC molecules for survival²⁹. How are these signals perceived differently with different outcomes? Are there any differences between the signals in CD4⁺ Th and CD8⁺ CTL cells? What is the nature of these signals and why and how are these signals perceived differently by T cells? What is the role of costimulation in this process (if any)? These are all questions that are actively being asked by T cell biologists and there is no doubt that this area will be the focus of active research in the years to come.

The molecular basis for the human 'nude' phenotype (immunodeficiency accompanied by baldness) was recently determined. This disease is caused due to a nonsense mutation in the winged-helix-nude transcription factor, which is expressed in skin and thymic epithelial cells³⁶. Genetic mapping has identified several loci known to be important in immune function (e.g. <http://www.jax.org>); however, the precise location of the genes responsible for a variety of immune defects has not been identified. The information derived from the sequencing of the mouse and human genomes will be used by immunologists to identify candidate genes involved in immune-related functions, determine the molecular basis of immune defects and the role of polymorphisms. For example, humans who do not express IFN- γ -receptor are extremely susceptible to infection by bacteria which live in intracellular compartments within a host cell, e.g. mycobacteria³⁷. Recently, the complete sequence and order of genes in the HLA complex was published³⁸. Interestingly, only 40% of expressed genes in the HLA region (the most gene-dense region in humans) code for immune functions. As MHC genes are extremely polymorphic and there are numerous

associations between various genes in the HLA complex to disease phenotype, genome sequence information will make it easier to map, type, functionally analyse and accurately predict patients who may be susceptible to a particular disease. Also, the gene array technique may reveal key molecules that are modulated by the immune response, revising our understanding of immune activation. For example it was thought that naive T cells are dormant; however new information using the array technique shows that naive T cells express large numbers of genes, but the messages of only a few genes increased with T cell activation³⁹. In other words, immunologists will reap the benefits of the tremendous information explosion once the complete mouse and human genomes are available.

Viruses have evolved a variety of mechanisms to down-modulate immune responses, including MHC class I and class II down-regulation and cytokine modulation⁴⁰. Studying the mechanisms by which viruses subvert the immune response may lead to the identification of some potential drug targets. Another promising area of research is the study of mechanisms by which human patients resist viral infections. For example, work on human survivors of HIV⁴¹ and Ebola⁴² has revealed that patients who secrete higher levels of cytokines stand a better chance of survival compared to patients who mount a slow and low cytokine response. This is a fine example on how knowledge of basic immunology helps us to design experiments to understand how some humans become resistant to different viruses in a 'real life' situation. Understanding these host defence factors in a variety of diseases may help us devise mechanisms to fight different kinds of diseases.

The past few decades have witnessed an enormous appreciation of the basic components that constitute the immune system. The coming years will elucidate the identification and roles of cell surface receptors, interleukins and transcription factors. The next decades will probably focus on the signalling components, understanding the system as a whole (crosstalk between different components of the immune system as well as immune/non-immune cell interaction) and immunogenetics will gain importance. Understanding the molecular details involved in an immune response will help to modulate the immune response, which may help in designing more effective therapeutic strategies. There is no doubt that rapid progress will be made in understanding basic mechanisms in immunology in this century; hopefully, some of these contributions will emanate from laboratories in India.

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