The Major Players in Adaptive Immunity

2. Cell-mediated Immunity

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Part 1, Humoral Immunity, *Resonance*, Vol.14, No.5, pp.455–471, 2009.

Keywords
Immunity, immunoglobulins, immunodeficiency, B-cell receptor, T-cell receptor, recombinase, antibody diversity.

Our immune system, by and large, does a fine job in protecting us from opportunistic and infectious microbes, potential carcinogens and allergens. It is therefore crucial to understand the organization of the immune network. This article focuses on some important features and key players involved in adaptive immune response. The first part of the article dealt with the humoral immune response mediated mainly by immunoglobulins produced by the B cells. The second part deals with T cells, the Major Histocompatibility Complex (MHC)-encoded molecules, and Recombination Activating Genes (RAG) responsible for generating diverse B-cell receptors (BCR) and T-cell receptors (TCR). With the advent of newer and smarter infectious agents, it is important to understand the working of the immune network as more research in this area may facilitate the development of better protective strategies.

Cell-mediated immune response, the major component of the immune system, involves cell-cell contact. T cells are essential for the cellular immune response. They influence several immune processes such as cytokine production to help B cells produce antibodies, macrophage activation, rejection of foreign tissue, killing of tumors or infected cells, delayed-type hypersensitivity and T_{DTH} reaction (an example of which is the use of PPD antigen to detect previous exposure to *Mycobacterium tuberculosis*). A subset of T cells known as T_{reg} cells lowers the risk of autoimmunity in the periphery. However, in some cases, this mechanism is not foolproof and T cells may mediate autoimmune diseases. For example, autoreactive T cells form inflammatory lesions along the myelin sheath of nerve fibres ultimately destroying it and causing multiple sclerosis (*see Box* 2 in Part 1).

Properties of T Cells

There are two main types of T cells based on their TCR: γδ and αβ. The former express the γδ TCR and are present abundantly in the skin, intestinal and epithelial layers. However, they constitute a minor percentage of peripheral T lymphocytes in blood. These cells are capable of recognizing a broad range of peptide and non-peptide antigens but not necessarily in the context of MHC. Major T-cell responses are mediated by T cells expressing the αβ TCR, which recognizes peptides presented by MHC molecules on antigen presenting cells. It is important to point out that the TCR is distinct from the BCR in that it does not bind antigen alone but only when it is presented by self-MHC molecules. This attribute known as *MHC restriction* was first described by P C Doherty and R M Zinkernagel for which they were awarded the Nobel Prize in 1996 [4].

TCRs belong to the Ig superfamily and there are four TCR multigene families each encoding α, β, γ or δ chains. In humans, α and δ gene segments are located on chromosome 14 and the β and γ segments on chromosome 7. The generation of functional TCR molecules occurs as a result of rearrangement of V and J segments of the α and γ chains and V, D and J segments of the β and δ chains. Each α and β chain has an amino terminal variable (V) and a constant (C) region much like an antibody. Note that the δ-TCR genes are located within the α-TCR gene complex; therefore, the δ-TCR genes are deleted during α-TCR chain rearrangements. In addition each chain has a transmembrane region of 21 or 22 amino acids and a very short 5–12 amino acid cytoplasmic tail. The mechanism is similar to immunoglobulin gene rearrangement and occurs during T-cell maturation in the thymus. However, there is no evidence for somatic hypermutations to occur in the TCR, unlike the BCR, during T-cell maturation.

T cells are the only cells in the body to express TCRs, which are associated with a set of signaling proteins known as CD3. This complex consists of five invariant polypeptide chains which form two heterodimers (γε and εδ) and one homodimer (ζζ). The cytoplasmic tails of the CD3 chains contain special immunoreceptor tyrosine-based activation motifs which interact with adaptor proteins that play important roles during signal transduction. Apart from the TCR–CD3 complex, T cells express on their surface several other receptors and ligands, the important ones being the CD4 and CD8 co-receptors. T cells express either CD4 or CD8 and are accordingly divided into T-helper (T_H) or T-cytototoxic (T_C) subsets respectively. In general, $CD4^+$ T cells recognize peptide/MHC class II whereas $CD8^+$ T cells bind to peptide/MHC class I molecules (*Figure* 1). Both CD4 and CD8 belong to the immunoglobulin superfamily and CD4 is a monomer while CD8 is a heterodimer of α and β chains. These co-receptors perform two functions: first, their extracellular domains bind regions on the MHC molecule thus strengthening the MHC–TCR/co-receptor interaction. Second, their intracellular domains associate with

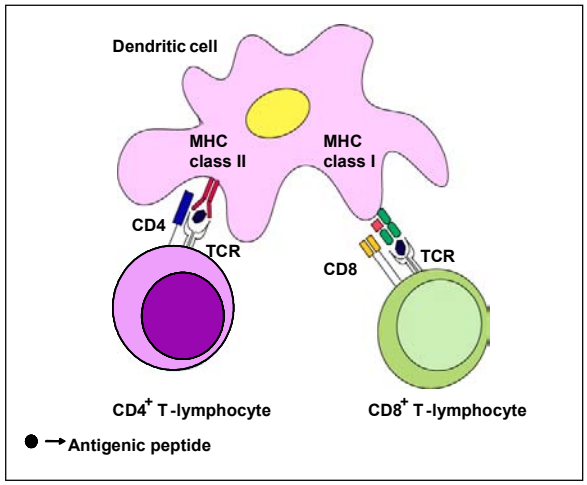

Figure 1. Interaction of an antigen presenting cell with T lymphocytes. Antigen presenting cells process and present antigenic peptides in complex with MHC class I or class II molecules which activate CD8+ or CD4+ T cells, respectively. This figure depicts a dendritic cell (so called due to the presence of 'dendrites') which binds to antigens in tissues and travels to a nearby lymph node to initiate the immune response. Dendritic cells are, perhaps, the most physiological antigen presenting cells. T cells bearing the cognate TCR recognize the MHC-peptide complex and are activated in the proper context to give rise to effector and memory T-cell responses.

Lck, a Src family tyrosine kinase, and this association helps in signal transduction. Mice lacking CD4 do not have MHC-II restricted T cells, produce less IL2 upon activation and are unable to mount an efficient antibody response, i.e., mediate B cell help.

T-cell Activation and Function

After selection in the thymus (see p.617), T cells circulate in the blood and lymphoid tissue until they encounter their cognate antigen. In general, optimal activation of lymphocytes requires two signals: signal 1 is mediated via the specific receptor and signal 2 is through a co-stimulatory receptor. This 'two signal hypothesis' for lymphocyte activation was first proposed by Bretscher and Cohen [5]. It is important to understand that the activation of lymphocytes is context dependent and needs to occur under appropriate conditions to reduce the possibilities of autoimmunity. In case of T cells, activation occurs with the binding of the TCR to its cognate MHC/peptide (signal 1) and the binding of a co-stimulatory receptor with its ligand. The major co-stimulatory receptor in T cells is CD28 which is constitutively expressed. However, the ligands for this receptor, i.e., CD80 and CD86, are greatly induced upon inflammatory conditions. This up-regulation ensures that T-cell activation occurs only when appropriate conditions exist.

Antigen Presenting Cells (APC), such as macrophages and dendritic cells, engulf antigens at the site of infection and migrate to lymphoid tissue where they get activated (increased expression of co-stimulatory ligands, adhesion molecules, etc.) and present processed antigen in complex with MHC to T cells. Naïve T cells (ones that have not previously encountered antigen), upon

binding to the cognate TCR–MHC and co-stimulatory interactions, get activated, secrete cytokines, proliferate and differentiate into effector and memory cells. These reactions usually occur in the peripheral lymphoid tissues and readers will recall that our tonsils become enlarged upon infection due to increased numbers of proliferating immune cells. Activated T cells secrete autocrine growth factors, e.g., IL-2, and divide 2–3 times a day for 4–5 days leading to the generation of a large pool of T cells which either differentiate into effector or memory cells.

Most $CD8^+$ T cells differentiate into cytotoxic T lymphocytes (CTL) whose function is to kill infected cells or altered self cells, for example, during cancer. However, $CD4^+$ T cells can either differentiate into T_H1 or T_H2 effectors. The cellular environment is important for this differentiation process as IL-12, which is secreted by activated macrophages and dendritic cells, skews the response towards T_H1 and suppresses the generation of T_H2 effectors. T_H1 effectors secrete pro-inflammatory cytokines such as IL-2, IFNγ, etc. and are responsible for cell-mediated immune responses. IFNγ greatly activates macrophages, induces the cell-surface expression of MHC molecules and enhances immunity against microbial infections. On the other hand, T_H2 effectors provide B cell help and are involved in the modulation of the antibody response: an increased T_H2 response results in high amounts of IgE whereas that of T_H1 shows high amounts of IgG2a. People suffering from allergies produce high amounts of IL-4 and IgE. Various kinds of effector cells (T_H1, T_H2 and CTLs) and their functions are listed in *Box* 1.

Once a T-cell response has been initiated, it is essential to reduce this burst because maintaining a large pool of activated T cells secreting high amounts of cytokines is deleterious to the body. Lowering T-cell activation is performed by separate mechanisms: reduction in T-cell activation and enhancing death of activated T cells. In addition to co-stimulatory receptors like CD28 which enhance activation, T cells also express receptors like Cytotoxic T Lymphocyte Antigen-4 (CTLA-4) which dampen T-cell activation. CTLA-4, unlike CD28, is expressed only post activation and binds the same ligands as CD28 but with a much higher affinity. Therefore, once expressed it is able to compete out CD28 binding and attenuates the activating signal. Scientists are using this information to boost T-cell responses against tumors using antibody to CTLA-4 that prevent the reduction in T-cell activation. However, the clinical applications of this approach need to be studied further.

T-cell death occurs by a process known as programmed cell death or apoptosis and the phenomenon of effector T-cell death is termed as Activation Induced Cell Death (AICD). This process involves binding of a cell-surface receptor known as FasL, which is induced upon T-cell activation, with its constitutively expressed receptor Fas. The importance of Fas-mediated AICD is highlighted in the autoimmune lymphoproliferative syndrome (also known as Canale-Smith syndrome). This disease is usually diagnosed in children who often possess enlarged

Box 1. Different Subsets of T cells

Subset	Function
γ δ T cells	These cells bear the γδ TCR and constitute less than 5% of the peripheral T cell population in humans. They lack CD4 and CD8 co-receptors, are not MHC restricted and may recognize non-peptide ligands. In fact, the predominant γδ TCR bearing human T cells recognizes a phospholipid found in *Mycobacterium tuberculosis*. They are also found in skin, intestinal epithelium and pulmonary epithelium. γδ TCRs do not show much diversity and are believed to be members of the earliest cell-mediated immune system (innate). They are known to secrete several cytokines which may play an immunomodulatory role with regard to protecting the integrity of epithelial tissues.
T_H1	This is a subset of αβ TCR $CD4^+$ effector T cells which arises post activation and their major function is to secrete cytokines such as IL-2, IFNγ, IL-3, TNFβ. The master transcription factors in T_H1 cells are T-bet and STAT4. Cells of this subset influence classic cell-mediated responses such as cytotoxic killing and delayed-type hypersensitivity reactions. The formation of granulomas in tuberculoid leprosy is a classic example of a T_H1 response.
T_H2	This subset of αβ TCR $CD4^+$ effector T cells secrete IL-4, IL-5, IL-10 and IL-13. The master transcription factor in T_H2 cells are GATA-3 and STAT6. Their function is to primarily provide B cell help and aid in the generation of an effective antibody response. The presence of serum Ig in lepromatous leprosy is a result of a predominant T_H2 response.
Cytotoxic T lymphocytes (CTLs)	$CD8^+$ T cells, upon activation, differentiate into CTLs that are MHC class I restricted and kill cancerous cells or cells infected with microbes. CTLs kill by first forming contact with the target cell and then releasing perforins and granzymes which eventually destroy it. They also kill by Fas-FasL interactions (shown to occur in CTL lines which lack perforins and granzymes).
T_{reg} cells	These cells are $CD4^+CD25^+$ T cells which also express the transcription factor FOXP3 (used as a marker for these cells). Their function is to down modulate peripheral T-cell responses probably by secreting suppressive cytokines, IL-10 and TGFβ. In the absence of T_{reg} cells, there is increased autoimmunity, e.g., inflammatory bowel disease, autoimmune diabetes.
T_H17	This is a recently identified subset of $CD4^+$ T cells characterized by their ability to secrete IL-17. The master transcription factor in these cells is RORγ . This subtype is often associated with inflammatory autoimmune syndromes and mice lacking IL-17 show decreased severity of collagen induced arthritis. Also, T_H17 cells are important in protecting against fungal pathogens.

spleen, lymph nodes and large numbers of double negative ($CD4^-CD8^-$) T cells.

The Major Histocompatibility Complex (MHC)-encoded Proteins

MHC molecules present peptide antigens to T cells and are encoded in a region of the genome known as the *MHC*, which forms a tightly-linked cluster of genes spanning ~4 million base pairs present on chromosome 6 in the case of humans and chromosome 17 in the case of mice. MHC is designated as the *H-2* complex in mice and the human leukocyte antigen (*HLA*) complex in humans. It is one of the highly gene dense regions of the mammalian genome and plays vital roles during the immune response. G D Snell, J Dausset and B Benacerraf were awarded the Noble Prize in 1980 for the discovery of the MHC and its role during immune responses.

MHC molecules are present on the cell surface and they bind to peptides derived from intracellular proteins. Under normal conditions, MHC molecules bind to peptides derived from host proteins. However, upon infection or conversion of a normal cell to a tumour cell, peptides derived from microbial proteins or transformed proteins bind to MHC molecules and are expressed on the cell surface. These MHC-peptide complexes on the antigen presenting cells are recognized by the appropriate T lymphocytes which lead to production of cytokines and regulation of immune responses by $CD4^+$ T cells or killing of target cells by $CD8^+$ T cells. This mechanism allows T cells to scan for intracellular changes occurring within cells and respond in an appropriate manner depending upon the context. In fact, it is akin to detectives examining the contents of trash cans to get an idea of what is going on inside a house!

The MHC region is divided into three subgroups called class I, class II, and class III. The MHC-I region encodes for heterodimeric peptide-binding proteins known as MHC class I proteins that are expressed on most nucleated cells. MHC class I is composed of a heavy chain that is associated with β_2-microglobulin and a peptide. MHC class I molecules present peptides to $CD8^+$ T-cytotoxic cells. The MHC-II region encodes MHC class II molecules as well as components of the antigen processing pathways. MHC class II molecules are recognized by $CD4^+$ T helper cells and are composed of a peptide and two proteins, α and β chains. MHC class II molecules are expressed only on APCs, e.g., dendritic cells, macrophages, etc.The MHC-III region encodes different immune components, e.g., complement components (C2, C4, factor B, etc.), cytokines (TNF-β, etc.) and also heat shock proteins.

MHC class I and II molecules are polygenic and polymorphic and understanding these aspects are important in order to appreciate their function during immune responses. There are several genes that encode MHC class I and class II proteins, i.e., they are polygenic. There are three genes encoding human MHC class I molecules: HLA-A, HLA-B and HLA-C. Also, there are

three different human MHC class II molecules: HLA-DP, HLA-DQ and HLA-DR. Now there are several variants/alleles in each of these genes in humans and mice, i.e., they are polymorphic. The numbers of alleles for HLA-A, HLA-B and HLA-DR range from 250–500. An individual can have any combination of these alleles in their MHC locus and we inherit two copies of the genome: one from our father and one from our mother. This means that there is a possibility of six different cell-surface MHC class I and MHC class II molecules. Also, MHC class I bind peptides generated in the cytosol, whereas the peptides that bind to MHC class II molecules are generated in the phagolysosome compartment. These different combinations and polymorphisms in MHC molecules ensure that peptides derived from different proteins at distinct cellular locations are likely to be presented by MHC molecules and can be sampled by T cells.

One of the areas that have been greatly influenced by studies on the MHC is tissue transplantation. The reason for this is that ~10% T cells are capable of recognizing and being activated by closely related MHC molecules known as allo-MHC. Given that MHC molecules are extremely polymorphic, this aspect causes problems for recipients during tissue transplantation. T cells from the recipient will 'attack and reject' donor tissues expressing non-self MHC molecules, eventually leading to destruction of the graft tissue. However, kidney and bone marrow transplants are performed on a regular basis these days. The ability of the donor transplant to survive in the recipient depends on the matching of MHC class I and class II molecules. HLA typing (*Box* 2) is performed to determine and maximize the possibility that the recipient will

Box 2. Typing of HLA

HLA typing can be performed using several methods:

a) Mixed lymphocyte reaction: The peripheral blood lymphocytes of the potential donor and recipient are mixed in the same culture. Cells in one of the two populations are treated with X-ray irradiation or mitomycin to prevent cellular proliferation from donor or recipient. If the HLA is different between the two populations, T cells will recognize and high levels of proliferation will be observed. If the HLA antigens of the donor and recipient match, proliferation will be greatly reduced.

b) Microlymphocytotoxicity: This technique uses the principle of complement-mediated lysis of cells. Ig against specific HLA types are added to the isolated lymphocyte culture. This is followed by addition of complement. If the respective antigens are present on the lymphocyte surface, a specific Ig binds to them. Complement proteins bind to the antigen-antibody complexes and subsequently lyse cells.

c) PCR-amplification: This technique is rapid and accurate. Oligonucleotide primers are designed to specifically bind and amplify certain HLA alleles. The amplified product can be detected by gel electrophoresis. The amplified product can further be sequenced to identify the exact amino acid sequences encoded.

accept the transplanted tissue. Hence it is essential to find a donor whose HLA matches closely (least antigenic differences) with the recipient. Usually, transplants from closely matched HLA (often within the recipient's family) is performed under the cover of immunosuppressive drugs (to reduce T-cell responses) to maximise the chances of survival of the transplanted tissue.

The diversity of MHC molecules modulates immune responses. In fact, some MHC alleles are associated with resistance or susceptibility to different infectious diseases, such as malaria and AIDS and autoimmune diseases such as diabetes. Some evidence suggests that decrease in MHC polymorphisms within a species can predispose them to infectious disease. In fact, it has been suggested that the reason for the present cheetah population being highly susceptible to viral diseases, compared to other big cats, is the low amount of diversity in their MHC. It is possible that the surviving cheetahs have arisen from a very small breeding stock.

Self-reactive Lymphocytes are Deleted during Development of Lymphocytes

Lymphocytes learn to recognize host proteins as self during development. This aspect was uncovered by P B Medawar (Nobel Laureate, 1960) when his group showed that the immune system could be 'tricked' to recognize an antigen as self only if it was introduced early during development. How does this occur? During development, all B cells with self-reactive receptors are eliminated by selection. The others which survive then circulate in blood and lymph and play a major role in the humoral immune response. This aspect has practical applications: humans with the blood group antigen A posses antibodies against blood group antigen B and vice versa. Those with blood group O possess antibodies to both antigens A and B whereas humans with blood group AB lack antibodies to both A and B. This aspect demonstrates that BCRs to self antigens are eliminated and antibodies to other blood group antigens occur, most likely, due to cross reactivity with environmental antigens. This aspect becomes important during blood transfusions as the antibodies to blood groups A and B are IgM and will clump or agglutinate red blood cells containing the cognate antigen. One can only imagine the major problems that can be caused upon transfusion of the wrong blood type.

T cells develop in the thymus, which is a bilobed structure located above the heart. It was J F A P Miller who made the seminal observation that removal of the thymus in newborn mice led to lower immune responses [6]. Progenitor T cells from the bone marrow begin to migrate to the thymus under the influence of chemotactic factors and differentiate into $CD4^+$ or $CD8^+$ T cells. The process of thymic education involves multiple processes: first, progenitor T cells need to rearrange α- and β-TCR genes to express the $\alpha\beta$ TCR–CD3 complex on the surface. Second, these TCR-bearing cells are 'selected' for two characteristics: a) They should not be self-reactive, and b) they should be able to recognize self-MHC molecules. MHC molecules are

important for T-cell activation and selection of T cells during thymic education. This aspect is important as TCRs are selected by MHC molecules; therefore, mice lacking MHC class I molecules possess low numbers of $CD8^+$ T cells. Similarly, mice lacking MHC class II molecules lack $CD4^+$ T cells. Most developing thymocytes (more than 99%) are unable to meet the stringent conditions required for selection into mature T cells and die; consequently, very few are selected and released into the peripheral circulation.

Mutations in transcription factors have led researchers to understand their roles during thymic development. First, mutations in the transcription factor, Tbx1 results in DiGeorge syndrome. These children show developmental defects, including lack of the thymus and, consequently, show reduction in T-cell responses. Not surprisingly, they are highly susceptible to viral, fungal and protozoan infections despite having normal humoral antibody responses. Deficiency in the FoxN1 transcription factor leads to the lack of thymus and greatly reduced hair in mice, which are termed as 'nude'. These mice possess very low numbers of T cells and are useful in tumor studies as they do not reject transplanted tumors (due to the lack of T cells), unlike normal mice. Second, scientists have wondered as to how T cells become tolerized to tissue-specific proteins. It has been shown that a transcription factor AIRE is responsible for the expression of different proteins in the thymus. The deficiency of AIRE leads to multi-organ autoimmune disease known as autoimmune polyglandular syndrome, type 1 (*Box* 3 in Part 1). Given the importance of MHC molecules in selection and activation of T cells, their deficiency reduces numbers of T cells and cellular immunity. Deficiency of transcription factors involved in expression of MHC class II genes, e.g., CIITA, results in an immunodeficiency-like syndrome known as 'bare lymphocyte syndrome'. This disease may also be caused due to lack of expression of transporter associated with antigen processing (TAP), which is important for the transport of MHC class I binding peptides. This aspect is important as MHC class I peptide bound molecules are stably expressed on the cell surface.

Finally, it is possible to reconstitute the entire immune system from pluripotent stem cells that are present in the bone marrow (*Figure* 1 in Part 1). The clinical relevance of this principle is observed in case of patients suffering from lymphoid cancers, who undergo γ-irradiation and anti-cancer drug therapies. As lymphocytes are extremely sensitive to γ-irradiation, this therapy kills both normal and tumor lymphocytes. Consequently, patients are susceptible to infections and are treated with antibiotics. After γ-irradiation treatment, the entire lymphoid system can be reconstituted with MHC matched bone marrow transplants.

RAG, the Enzyme Responsible for Generation of Diversity in Antigen Receptors

As mentioned previously, V, D and J gene segments are assembled randomly to create a diverse repertoire of BCRs and TCRs. The key enzyme mediating this process is RAG which consists

of RAG-1 and RAG-2. As these proteins play an active role only in gene rearrangement, they are expressed exclusively during the development of B cells and T cells. Mice lacking *Rag-1* or *Rag-2* are unable to rearrange and express surface BCRs and TCRs. Consequently, these mice lack mature B and T lymphocytes due to a block in lymphocyte differentiation, a situation resulting in immunodeficiency. This condition, known as 'Ommen's syndrome', is also observed in humans and such individuals are highly susceptible to various infections.

How does RAG recognize BCR and TCR gene segments? This enzyme recognizes a unique DNA sequence called as 'Recombination Signal Sequence' (RSS) flanking each V, D and J segments. Each RSS contains a conserved heptamer and an AT-rich nonamer sequence separated by either a 12 or 23 base pair (bp) sequence, i.e., [7 bp-12/23bp-9bp]. The RAG-1 and RAG-2 proteins act together as a 'heterodimer endonuclease' in initiating the process of receptor gene rearrangement, along with some other proteins. The RAG-1 enzyme is more specific for its targets and contains an Asp-Asp-Glu motif which forms the active site. After recognition of the RSS by RAG, two RSS are brought together and RAG nicks one strand of ds DNA at the end of 7 bp sequence in RSS. The free 3'OH group of the nicked DNA attacks the phosphodiester bond on the opposite strand of signal sequence which generates a hairpin-like structure. Subsequently, some enzymes involved in DNA repair cleave this DNA hairpin at random sites. This cutting generates sites for action of terminal deoxynucleotidyl transferase and other exonuclease which randomly creates diverse, imprecise ends. Finally, the two coding joints are ligated by non-homologous DNA end joining. This latter process is also important for the generation of rearranged BCRs and TCRs, and mutations in DNA-activated protein kinase or Artemis (an exonuclease) lead to immunodeficiency.

Evolutionary Aspects of the Adaptive Immune System

An interesting observation is that jawless vertebrates (e.g., hag fish and lampreys) do not show any signs of an adaptive immune system, i.e., they lack organized lymphoid organs (such as lymph nodes), the primary B cell response, etc. However, jawed vertebrates clearly show signs of an adaptive immune network. How did the adaptive immune system, a complex network, appear over a short evolutionary time? In general, two events appeared to have catalysed this transformation: first, a transposon carrying the RAG recombinase probably was inserted into an ancestral BCR- or TCR-encoding gene. Transposons contain two essential parts: (i) Transposase, an enzyme which cuts double stranded DNA precisely and helps in excision. (ii) Terminal repeats, a palindromic-conserved sequence which is recognized by the transposase. These ancestral transposons contained RAG recombinase with a function equivalent to transposase. After one such transposition event into the ancestral BCR or TCR genes, the recombinase gene may have excised or deleted or was copied at some other place in the genome. Now, these

terminal repeats which were left in the ancestral BCR or TCR gene became the RSS flanking these gene segments. At the same time, the recombinase gene which got placed elsewhere became RAG-1 and RAG-2. Most likely, the transposon insertion was in a germ cell as both RAG-1 and RAG-2 were inherited as a tightly-linked pair of genes. The RAG proteins cleave the RSS signal very precisely, revealing their original function as a transposase. This information suggests that RSS, RAG-1 and RAG-2 represent the disassembled components of a transposable element. Moreover, some regions of RAG-1 and RAG-2 show similarity with bacterial recombinases and with some DNA repair proteins. Most likely, this machinery was acquired from bacteria by a horizontal transfer and transposition. Subsequently, duplication events may have led to RSS-containing Ig and TCR genes. Second, large-scale gene duplications may have coincided with the origin of vertebrates that led to the emergence of novel molecules, including the MHC. In fact there are suggestions that a fusion between heat shock proteins that are known to bind peptides with an Ig family gene may have led to the emergence of the MHC class I and II molecules.

Concluding Remarks

We are under threat from several sources: newly evolved strains of well-known pathogens (drug resistant microbes or strains with altered tissue specificity) and newer pathogens (e.g., severe acute respiratory virus, Ebola virus). In this respect, the importance of immunology is becoming increasingly evident. The immune system relies on multiple cells (innate and adaptive) and mechanisms (BCR, TCR, MHC, cytokines, killing mechanisms) to protect us. This broad review has highlighted some of the advances in our knowledge of the adaptive immune system; however, there is much left to be learnt on how the body responds and controls different infections. It should be emphasized that the immune system has two faces: for the most part, it protects us from pathogens; however, it is also responsible for autoimmunity. A better appreciation of the multifactorial nature of immune responses (e.g., context dependent, activation state of cells, the amounts and timing of responses, etc.), is required. This aspect is highlighted by the observation that an overly exaggerated response by the host during infections leads to the secretion of very high amounts of cytokines known as 'cytokine storm'. This situation leads to septic shock, an acute inflammatory response, which causes low blood pressure, multi-organ failure and may become life-threatening. This example demonstrates that immune responses need to be balanced and, in the absence of such a balance, the molecules that protect can be harmful under altered conditions. Therefore, proper understanding of our immune system is required to counter the ever-increasing list of smarter microbes, tumors and autoimmune cells and effectors. It is possible that appreciation of these complex mechanisms may help us to devise better and faster therapeutic strategies.

It is also important that the general public becomes more aware and appreciates the complexities involved in immune responses. In fact, the European Federation of Immunological Societies has designated April 25 as Immunology Day (http://www.dayofimmunology.org) to encourage better understanding and dissipation of information. This review is a small step in that direction – with the hope that more young minds will take up the challenges of research in immunology.

Acknowledgments: We thank Profs. R Manjunath, P Sadhale and S Raghavan for patient reading and comments on the manuscript. The encouragement of all members of the DpN laboratory is appreciated. We are grateful to the Government of India agencies (DBT, CSIR, DST and ICMR) for providing research funding to the laboratory.

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Errata

Resonance, Vol.14, No.5, p.464, May 2009.

The correct *Figure* 4 of the article 'The Major Players in Adaptive Immunity – Humoral Immunity'.