Basic and clinical immunology

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Progress in immunology continues to grow exponentially every year. New applications of this knowledge are being developed for a broad range of clinical conditions. Conversely, the study of primary and secondary immunodeficiencies is helping to elucidate the intricate mechanisms of the immune system. We have selected a few of the most significant contributions to the fields of basic and clinical immunology published between October 2001 and October 2002. Our choice of topics in basic immunology included the description of T-bet as a determinant factor for T_H1 differentiation, the role of the activation-induced cytosine deaminase gene in B-cell development, the characterization of $CD4^+CD25^+$ regulatory T cells, and the use of dynamic imaging to study MHC class II transport and T-cell and dendritic cell membrane interactions. Articles related to clinical immunology that were selected for review include the description of immunodeficiency caused by caspase 8 deficiency; a case series report on X-linked agammaglobulinemia; the mechanism of action, efficacy, and complications of intravenous immunoglobulin; mechanisms of autoimmunity diseases; and advances in HIV pathogenesis and vaccine development. We also reviewed two articles that explore the possible alterations of the immune system caused by spaceflights, a new field with increasing importance as human space expeditions become a reality in the 21st century. (J Allergy Clin Immunol 2003;111:S813-8.)

Key words: *Immunology, immunodeficiency, autoimmunity, HIV, space immunology*

Basic and clinical research related to immunology has expanded to involve many different biomedical fields in addition to primary immunodeficiencies and allergic disorders, including autoimmunity, infectious diseases, neoplastic disorders, and transplantation. We reviewed the biomedical literature published from October 2001 to October 2002 and chose some of the most significant contributions in basic and clinical immunology. Because of space limitations of this article, we do not pretend to cover all the relevant immunologic research that we found published in that period, but we present what we consider most relevant to the readers of the Journal.

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Abbreviations used
AID: Activation-induced cytosine deaminase
IVIg: Intravenous immunoglobulin
Vif: Virion infectivity factor
XLA: X-linked agammaglobulinemia

BASIC IMMUNOLOGY

Commitment of T_H1 and T_H2 cells

Helper $CD4^+$ T cells further differentiate into T_H1 or T_H2 cells, which have been characterized by cytokine secretion patterns that activate either cellular or humoral immunity, respectively (Fig 1). T-bet is a transcription factor that has been shown to induce T_H1 differentiation, suggesting that IL-12 is a secondary stimulus (Table I).[1] Finotto et al[2] provided additional support to the relevant role of T-bet by showing that mice homozygous for the T-bet deletion spontaneously demonstrate respiratory disease similar to asthma, a condition associated with T_H2 cells. In a follow-up article, Szabo et al[3] presented conclusive evidence that $CD4^+$ T cells from the same T-bet–deficient mice do not differentiate into T_H1 cells and are not able to synthesize IFN-γ, secreting instead increased amounts of two T_H2 cytokines, IL-4 and IL-5. This deficiency was not seen in $CD8^+$ T cells, suggesting that they may have a different regulatory mechanism for IFN-γ synthesis. T-bet may be a target for the development of immunoregulatory drugs.

The role of dendritic cells in determining the T_H response was explored by studying the effects of histamine on dendritic cells.[4,5] Histamine receptors H1 and H2 were found on the dendritic cell surface, where they mediated chemotactic activation, downregulation of IL-12 production, and stimulation of IL-10 secretion. These results suggest that histamine may modulate the immune response and favor the development of a T_H2-type response, establishing a connection between hypersensitivity types I (anaphylaxis) and IV (delayed hypersensitivity).[4,5] Furthermore, dendritic cells from atopic individuals produced reduced amounts of IL-12 in response to CD40 ligation relative to healthy individuals.[6] A novel strategy to induce T_H1 commitment from a T_H2-type response through manipulation of dendritic cells was developed by Bhatia et al.[7] With a mouse model for allergy, they delivered an allergic peptide obtained from dust mite to dendritic cells by coupling the peptide to scavenger receptor ligands. They were able to modulate the immune response to increase the production of IFN-γ and to downregulate the production of IL-4 and IL-5 when T cells were stimulated with dust mite antigen in vitro.

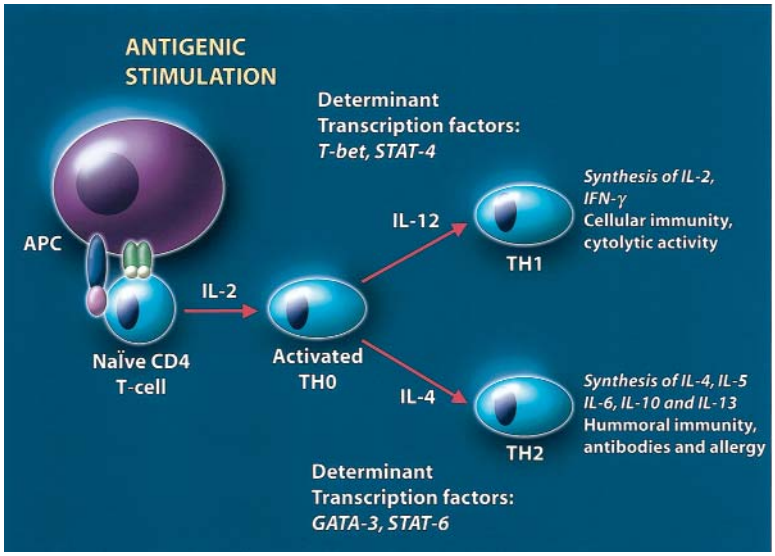

FIG 1. T-helper cell differentiation. CD4+ T-cells differentiate into T_H1 or T_H2 type, depending on antigenic and cytokine stimuli. Specific transcription factors are required to be activated for each pathway: T-bet and signal transducer and activator of transcription *(STAT)* 4 for T_H1 cells and GATA-3 and STAT-6 for T_H2 cells. *APC,* Antigen-presenting cell.

T_H2 cytokines (IL-4, IL-5) from mononuclear cells of patients allergic to dust mites were shown to be inhibited by lactic acid bacteria.[8] This inhibitory effect was dependent on the antigen-presenting cell (monocytes) and required the involvement of IL-12 and IFN-γ. These findings may have significance for evaluation of the hygiene hypothesis of allergic disease.

The activation-induced cytidine deaminase gene

The diversity and maturation of antibody specificity is generated through several processes, including V(D)J (variable, diversity, joining) recombination, somatic hypermutation, gene conversion, and class switch recombination. Although the molecular events that occur in V(D)J recombination are well established, the other processes are still not clear. Several articles have described that the activation-induced cytidine deaminase (AID) is essential for these events. It is known that the AID is required for somatic hypermutation and class switch recombination and is also responsible for the autosomal form of hyper-IgM syndrome (as reviewed by Ballow[9]). Martin et al[10] expressed AID in hybridoma cells, showing that hypermutation can be induced regardless of location (germinal centers). Arakawa et al[11] showed that AID was also involved in gene conversion by studying chicken B cells made deficient in the AID gene. These cells were able to undergo gene conversion only when the AID gene was reintroduced to the cells. When B cells are stimulated to induce class switch recombination but not somatic hypermutation, AID induces point mutations in the switch region, confirming the involvement of AID in these two processes.[12] The mechanism of hypermutation induced by AID seems to occur by the deamination of cytosines to generate uracils in the B-cell DNA. This event may generate transitions and transversions when the lesion is repaired by DNA polymerases.[13] Thus AID appears to be a master element for generating antibody diversity, and further elucidation of molecular mechanisms will define exactly how AID targets the variable genes and how all these activities are performed by one protein.

New mechanisms in the innate immune system's response to bacterial infection

Lactoferrin is an iron-binding protein known to inhibit bacterial growth, probably by sequestering iron essential for bacterial metabolism. In this capacity, lactoferrin is a significant component of our innate immune system. A new mechanism of action of lactoferrin was described by Singh et al,[14] who demonstrated that without lactoferrin bacteria move and twitch only until their first division and start to pile up to eventually form microcolonies and resemble a biofilm. When lactoferrin was added, the bacteria continued to move and remain at low density on the surface. This study suggests that bacteria move toward an environment rich in iron and that lactoferrin thus prevents bacterial colonization. The significance of this work in the development of drugs for the prevention of bacterial infections needs further evaluation. Lactoferrin prevents the development of bacterial biofilms but does not eradicate them. The innate immune system also contains antimicrobial peptides in the skin aspect of a host defense mechanism, cathelicidins and β-defensins. These antimicrobial peptides of the skin build up in concentration in inflammatory conditions of the skin. When two such inflammatory conditions of the skin, psoriasis and atopic dermatitis, were compared, there were significantly lower concentrations of cathelicidins and β-defensins in the skin from patients with atopic dermatitis,[15] possibly contribut-

ing to the propensity of patients with atopic dermatitis toward development of skin infections, particularly with *Staphylococcus aureus*.

CD4+CD25+ regulatory T cells

$CD4^+CD25^+$ regulatory T cells were first identified in mice and shown to participate in the development of tolerance and to protect against autoimmune disease.[16] Annunziato et al[17] studied $CD4^+CD25^+$ T cells from neonatal human thymuses. Similar to earlier findings, they found that these cells showed poor proliferative response to allogeneic cells and suppressed the lymphoproliferative response of $CD4^+CD25^-$ T cells. They also discovered that the effect was contact dependent and mediated by cytotoxic T-lymphocyte antigen 4 expression and transforming growth factor β1. These regulatory cells are being explored to improve graft-specific tolerance for transplanted tissues. Taylor et al[18] depleted $CD4^+CD25^+$ cells from donor T cells and administered these cells with skin grafts to study their regulatory effects on graft-versus-host disease. They found that $CD4^+CD25^+$ cells administered in vivo prevented the development of graft-versus-host disease. Graca et al[19] reported that the regulatory cells that infiltrate tolerated skin grafts are able to induce tolerance to third-party mice. They proved that these cells were responsible for the tolerance effect by observing lack of tolerance when the skin graft was depleted of $CD4^+CD25^+$ cells. Although cytotoxic T-lymphocyte antigen 4 and transforming growth factor β appear to be the main mediators of tolerance mediated by $CD4^+CD25^+$ cells, it has recently been shown that the glucocorticoid-induced TNF family–related gene may also play a significant role.[20] This gene is predominantly expressed in $CD4^+CD25^+$ cells, and its stimulation abrogates T-cell–mediated suppression. Removal or antibody stimulation of this gene induced autoimmunity in normal mice.[20] Further exploration of these regulatory T cells and their mechanisms of action may result in novel strategies for prevention or treatment of autoimmune disease.

Dynamic imaging of immunologic processes

New technology is helping us to understand molecular mechanisms that previously had been studied only by indirect means. Real-time confocal microscopy is being used to follow specific protein molecules within cells and to show specific cell to cell interactions. With green fluorescent protein fused to MHC molecules, Boes et al[21] and Chow et al[22] were able to show the trafficking of these molecules in dendritic cells in vivo with explanted lymph nodes. Boes et al[21] constructed transgenic mice that expressed MHC class II molecules fused to green fluorescent protein and showed the distribution of dendritic cells in the skin by confocal microscopy, taking advantage of the high expression of those molecules in dendritic cells. They also showed the intracellular movement of MHC class II molecules and their concentration on the surface on activation. In a subsequent study, by transfecting dendritic cells with gene expressing MHC class II molecules fused with green fluorescent protein, Chow et al[22] also visually showed the pathway that MHC class II molecules travel from intracellular vesicles to the cell membrane after being stimulated with bacterial glycolipids. Miller et al[23] and Stoll et al[24] observed the migration and homing of fluorescent marked T cells into lymph nodes in vivo with single-photon and two-photon microscopy, respectively. With these methods, it was demonstrated that T-cells move without a specific direction for long periods at speeds as great as 25 μm/min. When stimulated with an antigen, however, some T-cells remain stationary in clusters and others move in swarms. Bousso et al[25] studied the interactions of thymocytes with stromal cells and demonstrated that self-antigen presentation increases the interaction time of these cells. These articles present a novel methodology that allows visual observation of immunologic processes.

TABLE I. Key advances in basic immunology

1. T-bet is a transcription factor that is necessary for T_H1 differentiation of $CD4^+$ T cells but not $CD8^+$ T cells.
2. Dendritic cells modulate the immune response by producing cytokines to induce T_H1 or T_H2 differentiation in response to diverse stimuli, such as histamine and lactic acid bacteria.
3. The AID appears to be involved in the generation of antibody diversity by participating in the processes of somatic hypermutation, gene conversion, and class switch recombination.
4. Lactoferrin inhibits bacterial colonization by preventing bacteria from forming clumps and biofilms.
5. The skin contains antimicrobial peptides that are decreased in patients with atopic dermatitis, suggesting an explanation for the increased frequency of skin infections in these patients.
6. $CD4^+CD25^+$ T cells induce tolerance to allogeneic skin grafts in mice and may prevent the development of graft-versus-host disease.

TABLE II. Key advances in clinical immunology

1. Caspase 8 deficiency produces a form of combined immunodeficiency with defects of T-cell activation and decreased B-cell and natural killer cell function.
2. Progressive neurodegeneration was found as a possible rare side effect of IVIg administration.
3. A 33-mer gluten peptide was found to be the primary antigen for celiac sprue.
4. Cytokine alterations and increased susceptibility to infection found in an animal model suggest that spaceflight conditions may induce immunologic dysfunction.
5. CEM15, a cellular protein that is necessary to permit replication of Vif-containing HIV strains, has been described.
6. HIV preferentially infects HIV-specific memory CD4 T cells.

CLINICAL IMMUNOLOGY

Primary immunodeficiencies

A new primary immunodeficiency disease has been described that involves a deficiency of caspase 8, an enzyme that participates in apoptosis (Table II).[26] Heterozygous mutations of CD95 (Fas), CD95 ligand, and caspase 10 (all aspartate-specific cysteine proteases involved in apoptosis) cause most cases of autoimmune

lymphoproliferative disease, which is characterized by defective apoptosis of lymphocytes, lymphadenopathy, spleno-megaly, and autoimmunity. Interestingly, instead of autoimmune lymphoproliferative disease, the caspase 8–deficient patients and their family members had defects in T-cell activation, B cells, and natural killer cells. To explain this difference in phenotype from that of autoimmune lymphoproliferative disease, it was postulated that caspase 8 may participate in lymphocyte activation processes independently of CD95.

A newly reported cohort of 73 patients with X-linked agammaglobulinemia (XLA) has extended the understanding of the natural history of that disease.[27] Most of the patients were receiving intravenous immunoglobulins (IVIg). Interestingly, IgA was originally present at normal levels in 3 patients, as IgM was in 5 patients, but declined with time. The most significant complication of XLA was chronic lung disease as a result of repeated bouts of pneumonia (39 of 73 patients). There were no reports of autoimmune or neoplastic diseases in this cohort of patients with XLA, except for lung disease. The course of these patients during IVIg therapy was relatively benign, a finding that stresses the importance of early detection and prompt treatment to avoid complications.

Carvalho et al[28] studied PBMCs from patients with recurrent vaginal candidiasis to study the possibility of a cytokine deficiency. They found that mononuclear cells from these patients produced relatively low or absent levels of IFN-γ on stimulation with *Candida* antigen. This downregulation of PBMCs in response to *Candida* was specific, because the patients' PBMCs could respond adequately to stimulation with tetanus toxoid or purified protein derivative. Carvalho et al[28] suggested that specific immunosuppression may be responsible for increasing susceptibility to Candida infection in this disorder.

IVIg

IVIg is widely used for replacement therapy in patients with primary immunodeficiencies and as an anti-inflammatory agent in certain immunologic diseases. Busse et al[29] reviewed the clinical histories of 50 patients with a diagnosis of common variable immunodeficiency who were receiving IVIg. There was a reduction in the number of patients who had pneumonia develop after IVIg was started (from 84% to 22%). This study documents the benefits of IVIg in patients with immunodeficiency.

The side effects of IVIg therapy include anaphylaxis, fever, aseptic meningitis, and kidney failure. Progressive neurodegeneration was found in 14 patients in a multicenter study of patients with primary immunodeficiency who were receiving IVIg.[30] No evidence of an infectious cause was found in these patients, suggesting the possibility of a new rare complication of IVIg therapy. Ziegner et al[30] therefore have recommended careful monitoring for neurologic changes in patients being treated with IVIg.

Autoimmune disease

Antibodies and T cells are thought to be the mediators of most autoimmune diseases that attack body organs and systems. In the case of type 1 diabetes mellitus, however, the immune mechanism has not been well defined. Some animal models of this illness require the presence of B cells to produce disease. Martin et al,[31] however, reported a case of diabetes type 1 in a 3-year-old patient with XLA, demonstrating that this disease can occur in absence of B cells and autoantibodies and suggesting that efforts to develop immunologic therapies should be directed toward control of the cellular response.

Celiac sprue is a common disease characterized by diarrhea and malabsorption, usually controlled by a strict diet devoid of gluten. Patients with celiac sprue have high levels of antibodies against the enzyme transglutaminase, which is highly expressed in the gut and has a high affinity for gluten. Shan et al[32] identified a 33-mer peptide from gluten that appears to be the primary mediator of the intestinal inflammation in celiac sprue. This peptide is stable against known human proteases (gastric, pancreatic, and intestinal). However, it is a good substrate for the tissue transglutaminase enzyme, which converts it to peptide products with enhanced binding capacity to the HLA DQ2 molecule and unique ability to stimulate T cells. Shan et al[32] demonstrated that this protease-resistant gluten peptide induced T-cell proliferation in 14 of 14 patients with celiac sprue. In addition, they also showed that this peptide is readily digested by bacterial prolyl peptidases, suggesting a possible oral peptidase supplement as therapy for celiac sprue.

Space immunology

There has been increasing interest in the study of the biologic effects of spaceflights. Several conditions of spaceflight may influence the immune system, including ionizing radiation, lack of gravity, stress, sleep deprivation, isolation, and confinement. Shearer et al[33] have studied these effects using human subjects isolated in the Antarctic as a model and found increased IFN-γ plasma levels and decreased IL-10 levels relative to subjects not isolated. These results suggest a T-cell response to reactivated viral infections in subjects, with increased viral shedding. Belay et al[34] used a mouse model to study the effects of microgravity in the course of infection with *Klebsiella pneumoniae*. They found increased severity of the infection and difficulty controlling it, with increased mortality. Both studies support the hypothesis that spaceflight conditions may alter the immune system and may increase the susceptibility to infections, and this risk should be placed into consideration.

HIV-1

Although HIV is among the most studied of viruses, its mechanism of pathogenesis still contains unknowns that need to be clarified. One of the accessory HIV proteins, virion infectivity factor (Vif), is required for replication in certain cell lines, called *nonpermissive,* but not in others. Vif enhances acute infection of primary T cells.[35] Sheehy et al[36] have found that nonpermissive cells express a protein of unknown function named CEM15, which possibly interacts with Vif. CEM15 is

present in all nonpermissive cell lines but is absent in permissive cell lines. Expression of CEM15 in a permissive cell transforms it to nonpermissive cell. These findings may lead to the development of new alternatives for anti-HIV therapy with either Vif or CEM15 to suppress replication in acutely infected T cells.

The loss of HIV-specific CD4 T-cell responses has not been satisfactorily explained.[35] Douek et al[37] studied HIV-specific and cytomegalovirus-specific memory $CD4^+$ T cells from 12 HIV-infected patients. These investigators found a comparative increase in proviral HIV DNA in HIV-specific T cells, which could be explained by the prolonged contact of these cells with the virion. Implications of this finding include the risk of increased HIV replication in patients undergoing structured interrupted therapies, which are designed to expand pools of HIV-specific memory T cells.

Development of an effective vaccine against HIV has proved elusive, but several efforts are currently underway. An example of the difficulty of this task is shown by the work of Shiver et al[38] and Barouch et al.[39] It is thought that an effective HIV vaccine should elicit not only neutralizing antibodies but an effective cytolytic T cell response.[40] Shiver et al[38] immunized macaques with different vaccine vectors carrying simian immunodeficiency virus Gag protein and demonstrated that the strongest cytolytic response was achieved with the adenovirus vector. Shiver et al[38] then challenged the vaccinated monkeys with a chimeric simian-human immunodeficiency virus. The monkeys become infected; however, the infection was mild, and they were able to maintain normal T-cell numbers. In a subsequent article, Barouch et al[39] showed that a virus mutant originated to evade the vaccine-induced, virus-controlling cellular immunity in one of the monkeys that received a DNA-based anti-HIV vaccine. Although this finding was disappointing and reemphasizes the need for caution, it might be possible to improve the effectiveness of this vaccine by changing the vaccine antigen, the vaccination strategy, and the experimental design of the study.

CONCLUSION

The pace of new discoveries in the basic and clinical aspects of immunology research has continued to accelerate during this past year. Discoveries of fundamental science, such as the T-bet transcription factor and the cathelicidins and β-defensins, not only hold importance for understanding mechanisms in molecular biology and immunology but are also critical for understanding how these factors contribute to common clinical conditions, such as asthma and atopic dermatitis. Discoveries in the clinical sciences also present this two-part paradigm of advancing molecular science and illuminating possible new treatment programs for clinical diseases. The discovery of the antigenic peptide in celiac sprue, for example, is important for the molecular biologist studying binding of peptides to HLA molecules and for the clinician seeking an oral peptidase to help patients with celiac sprue hydrolyze toxic peptides. This past year has demonstrated again the gains that accrue to science and medicine with publication of outstanding basic and clinical immunology research.

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