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Microbial Immunosuppression

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1. Introduction

Immunosuppression is a condition characterized by immune dysfunction at either cellular or humoral levels [1]. Defective cellular levels include alterations in neutrophils, monocyte/macrophage, and natural killer (NK) cells for innate immunity or alterations in B or T lymphocytes for adaptive immunity [2, 3]. In contrast, immune dysfunction at the humoral level is largely due to alteration in soluble factors mediated by complement or chemokines for innate immunity [4] or due to alteration in antibodies or cytokines for adaptive immunity [5]. Most of these alterations are congenital in nature as evidenced in patients with primary immunodeficiency diseases. The defective compartment of the immune system determines the proclivity of the invading pathogens and the contracted infection is usually disseminating. Consequently, the inflicted immunosuppression is permanent unless reconstituted by immunoglobulin transfusions or bone marrow transplantation. On the other hand, secondary immunosuppression may be internal as a consequence of excessive adenosine release [6] into the extracellular space as evidenced in multiple organ failure (e.g. pancreas, kidney, liver) or it might be externally induced by a number of causal agents including infectious pathogens, immunosuppressive drugs, antimicrobial drugs, and anti-neoplastic drugs. The causal, pathophysiology, and methods used to evaluate immunosuppression due to pathogens are the focus of this chapter.

2. Immunosuppression induced by primary infections

Acquired immunosuppression due to pathogens is primarily caused by viruses that invade the cellular compartment of the immune system. The condition is seen in limited population of both humans and animals. In humans, it is caused by pathogens that selectively infect lymphocytes such as infection of T cells with human immunodeficiency virus (HIV) types I & II [7], or infection with human T-cell lymphotropic virus types I & II [8-10]. Human B lymphocytes, on the other hand, are prone to infection with Epstein-Barr virus (EBV) [11]. In animals, however, direct infection of immune cells that lead to immunosuppression is seen in cats infected with feline leukemia virus (FeLV) [12], cattle infected with bovine leukemia virus (BLV) [13] or in chickens infected with Marek's disease virus (MDV) [14] or infectious

bursal disease (IBD) [15] virus. The striking feature in all of these infections is that immunosuppression is latently developed following viral replication that leads to lymphocytes depletion. Consequently the inflicted host develops immune anergy with increased susceptibility to opportunistic infections. Summary of the causal agents and the target cells involved in the induction of immunosuppression are presented in Table 1.

Causal agent	Host	Immune target cells	Disease	Immunologic sequelae
HIV-1&2	Humans	CD4+ T-cell	AIDS	- CD4 cells depletion; - Immune dysfunction; -IRIS after treatment with HAART
HTLV-1	Humans	CD4+ T-cell	ATL; HAM/TSP	↑ IFN-γ; ↑ TNF-α.
HTLV-2	Humans	CD8+ T-cell	Neuropathy	Immunosuppression
EBV	Humans	B cells	IMN; BL; HD; XLL; OHL	Immunosuppression
FeLV	Cats	CD4+ T-cell	Leukemia	Immunosuppression
BLV	Cattle	B cells	Leukemia; LS	Immunosuppression
MDV	Chickens	CD4+ T-cell	Marek's disease Marek's lymphoma	Immunosuppression
IBDV	Chickens	B cells	IBD	Immunosuppression

HIV= human immunodeficiency virus; AIDS = acquired immunodeficiency syndrome; IRIS= immune reconstitution inflammatory syndrome; HAART= highly active antiretroviral therapy; HTLV= human T-cell lymphotropic virus; ATL= adult T-cell leukemia; HAM/TSP=HTLV-1-associated myelopathy/ tropical spastic paraparesis; EBV= Epstein-Barr virus; IMN= infectious mononucleosis; BL= Burkitt's lymphoma; HD= Hodgkin's disease; XLL= X-linked lymphoproliferative syndrome; OHL= oral hairy leukoplakia; FeLV= feline leukemia virus; BLV= bovine leukemia virus; LS= Lymphosarcoma; MDV= Marek's disease virus; IBDV= infectious bursal disease virus; IBD= infectious bursal disease

Table 1. Common lymphotropic infections associated with immunosuppression

i. **HIV infection:** In HIV infection, immune dysfunction is likely due to combinatorial effects resulting from infection of immune cells (CD4+ T cells, macrophages, dendritic cells) with HIV, uncontrolled viral replication that impairs antigen presentation, increased mutations in *env* protein gp120 that leads to virus tropism and survival, increased activation of T helper cells by alloantigens, increased apoptosis by activated CD4+ T helper cells, down-regulation of CD4+ synthesis with functional impairment, and perturbation of cytokine pathways [7,16-19]. These immunologic defects can be partially restored in HIV patients treated with highly active antiretroviral therapy (HAART) [20]. Despite a reduced viral load and improved CD4+ T cells count, a paradoxical response known as immune reconstitution inflammatory syndrome (IRIS) has been evolved in HIV patients treated with HAART [21-23]. The induction of IRIS is worsened in HIV patients with preexisting opportunistic infections [24]. In essence, the severity of IRIS depends on CD4+ T cells count (≤ 100-200 cells/μl), degree of lymphocyte apoptosis or proliferation, and the degree of viral suppression and immune recovery after the initiation of treatment with HAART. All of these factors constitute a challenge to HIV vaccine development [25]. In animals, however, paradoxical immunosuppression associated with IRIS is rarely encountered due to the short life span of infected animals and variations in the care and management of sick animals compared to humans.

ii. **HTLV infection:** In HTLV infection, the virus preferentially infects CD4+ T cells and causes their transformation into malignant lymphoma *in vitro*. The majority of HTLV-infected patients are asymptomatic and few are carriers that may develop a chronic illness through time. The virus has 2 unique genes, *tax* and *rex*, in addition to the standard retroviral genes (*gag*, *pol*, and *env*) that play a central role in lymphocytes transformation. The HTLV-1 tax gene product is known to stimulate viral mRNA synthesis, interleukin (IL)-2 production, and IL-2 receptor (R) expression which are key elements for lymphocytes proliferation and transformation into malignant cells [9, 10]. The aberrant changes in T cells function during the transformation process may contribute to immunosuppression. However, in some patients, the humoral antibody response to HTLV antigens may be detected in sera of infected patients indicating that HTLV may not be the primary causes of all T cell lymphomas. In addition to T cell leukemia, some carriers of HTLV-1 may develop an inflammatory disease of the central nervous system called HTLV-1- associated myelopathy/tropical spastic paraparesis (HAM/TSP). Patients with HAM/TSP have increased HTLV-1 provirus load and increased numbers of HTLV-1-specific cytotoxic T lymphocytes (CTL, CD8+ T cells) that were restricted to the HTLV-1 tax protein. However, the HTLV-1-specific CTL of these patients have been demonstrated to produce IFN-γ and TNF-α that promote inflammation. Therefore, HTLV-1 tax-specific CTLs play a major role in the immunopathogenesis of HAM/TSP.

iii. **EBV infection:** Primary EBV infection causes infectious mononucleosis, a self limiting and silent disease in most inflicted patients. The virus exclusively infects B cells than any other cell type and persisted within the carrier's B cells to establish latent infection. *In vitro* EBV infection of human B lymphocytes has been demonstrated to induce B cell immortalization and proliferation [26]. The process carries the viral genome indefinitely and used for the generation of various lymphoblastoid cell lines. In addition to its B cells involvement, EBV infection has been demonstrated in epithelial cells of

nasopharyngeal carcinoma as well as in the epithelial layer of oral hairy leukoplakia (OHL), a benign exclusive lesion in HIV individuals [11]. Despite its various clinical manifestations and lymphoid cells activation, EBV infection is common in immunocompromised patients. The control of EBV infection has been attributed to CTL (CD8+ T cells) [27] and the consequent immunosuppression is multifactorial effect.

iv. **FeLV infection:** Infection with FeLV is usually asymptomatic and is species-specific. Persistent infection emerges in carrier's cats and correlated well with persistent viremia that last for months [12]. The virus infects primarily T lymphocytes and spread to other lymphoid tissues including bone marrow and glandular epithelium. This broad infection lead to the development of leukemia, lymphoma, and non-regenerative anemia in persistently infected cats. Immunosuppression in pet cats showed suppressed antibody and T cell responses, prolonged allograft rejection times, thymic atrophy, and depletion of the paracortical zones in lymph nodes.

v. **BLV infection:** BLV infects primarily B cells and persisted to induce their transformation into cancerous cells after long latent periods [13]. In addition to B cells infection, BLV infect cells of the monocyte/macrophage lineage. Infection is usually silent but may progress to persistent lymphocytosis and tumor production. Immunosuppression due to BLV is largely contributed by altered gene expression for the cytokines IL-2, IL-6, IL-10, and IL-12, increased B cells apoptosis, down-regulation of TNF-α and its receptor, and alteration in cells signaling pathway.

vi. **MDV infection:** The pathogenesis of MDV that leads to lymphoma development with consequent immunosuppression [14] involves 4 stages: early cytolytic infection in which the virus spread from cell to cell and B cells were demonstrated as the primary targets for this stage; latent infection in which activated CD4+ T cells are the predominant targets in lymphoid organs as well as schwann cells of peripheral nerves and spinal ganglia; late cytolytic infection is characterized by permanent immunosuppression of T cells; and transformation stage in which T cells lymphoma develop with a dominant expression of Marek's disease tumor-associated surface antigen (MATSA). The resultant immunosuppression caused by MDV infection is largely attributed to loss of effector cells in major lymphoid organs, the bursa of Fabricius and the thymus as well as in bone marrow tissues. Consequently, this cytolytic infection leads to the development of atrophy at the bursa and thymus as well as aplasia in bone marrow cells. Studies by Calnek demonstrated that the degree of immunosuppression may be related to the pathotype of MDV isolates. However, the contribution of host factors in this immunosuppression needs to be elucidated.

vii. **IBDV infection:** Initial infection with IBDV involves lymphocytes and macrophages of gut- associated lymphoid tissues (GALT) followed by invasion of lymphoid follicles at the bursa of Fabricius, the primary source of B lymphocytes in avian species [15]. Since the bursa represents the primary target organ for viral replication, IgM positive B lymphocytes are the target cells for viral lysis. The consequent infection results in bursal atrophy and B cells depletion. Indeed, B cells depletion extends to other lymphoid tissues including the thymus, GALT, and the Harderian gland. Therefore, the production of antibodies will be impaired and the cellular immune response will be diminished in chickens infected with IBDV. The inflicted damage to the bursal tissue coupled with B cells depletion, and loss of T cells function contribute to the

development of immunosuppression in chickens infected with IBDV. Restoration of immunity by adoptive transfer may be possible but no paradoxical inflammatory response has been demonstrated.

3. Immunosuppression induced by bacterial infections

It is well established that infection with some intracellular bacteria may have indirect effects on the immune system with consequent induction of immunosuppression. Among the leading causal agents, *Mycobacterium tuberculosis*, *Ehrlichia chaffeensis*, *Brucella melitensis*, *Coxiella burnetti*, *Bartonella* Sp. and *Nocardia farcinica*. However, in immunocompromised patients, infections with mycobacterial species or agents of bacterial pneumonia are commonly observed in clinical practice. In AIDS patients, disseminated infections with *Mycobacterium tuberculosis* or *Mycobacterium avium* complex are prominent [7, 28]. In contrast, deadly infection with *Nocardia farcinica* [29] has been reported in an immunocompromised patient with type II diabetes and end-stage renal failure. Thus, infection with opportunistic pathogens may be more deleterious to the host than infection caused by pathogens that primarily induce immunosuppression. In general, the underlying mechanism of immunosuppression due to bacteria varies according to the host-parasite cellular interactions, and the elicited host immune mediators that cause a shift in the balance between Th1 and Th2 responses. For instance, sustained production of transforming growth factor (TGF)-β has been associated with immunosuppression in patients with chronic brucellosis [30] or tuberculosis [31]. Further, other mechanisms exist for pathogens induced immunosuppression and they are largely attributed to a defective interaction between the microbe (bacteria, viruses, fungi, or protozoan parasites) and cells of the immune system (macrophages, dendritic cells, lymphocytes, natural killer). Support for this notion stems from the ability of certain intracellular pathogens to prevent phagolysosome biogenesis, inhibition of cellular autophagy, and inhibition of antigen presentation [28, 32-35]. The prototype models for these mechanisms have been established by several investigators who studied the interaction of *Mycobacterium tuberculosis* with the macrophage [36]. In essence, the induced immnuosuppression is the target of several microbial virulence factors in an effort to establish a disease process at their predilection sites. Major virulence factors associated with bacterial infection include toxin production, polysaccharide or polypeptide capsule formation, and secretion of degradative enzymes that promote tissue invasiveness, proteineous pili and mucosal adhesins. Individuals with prolonged immunosuppression offer a rich environment for microbial growth, replication, and pathogencicity conduction. Consequently, the resulting disease will be much exacerbated due to microbial abundance and invasiveness secondary to shift in balance between proinflammatory and anti-inflammatory factors of the host. Therefore, activation of the antimicrobial activity of leukocytes as well as induction of immune cytokines (interferon (IFN)-γ, interleukin (IL)-12, IL-2 and tumor necrosis factor (TNF)-α) are crucial elements in the restoration of cellular immunity [3] in patients with secondary immunosuppression due to bacteria.

In general, the extent of microbial immunosuppression is dependent on the balance of proinflammatory and anti-inflammatory mediators following injury and/or infection, disease duration (acute, chronic), immunocompetence of the inflicted host, dosage rate and treatment regimen of anti-microbial drugs used, and a synergy of these therapy, if exist. The balance between these factors had a major impact on the restoration of immunity and/or disease progression.

4. Immunosuppression induced by opportunistic viral infections

In clinical practice, the most common opportunistic viral infections that were encountered in immnuocompromised patients include, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and human herpesvirus 8 (HHV8). In addition to their primary causes of disease in immunocompetent hosts, these viruses have been detected in blood and lesions of immnuocompromised patients with AIDS, renal and bone marrow transplants as well as in patients with neoplasms [24, 26, 37, 38]. Latency of infection is commonly encountered with these viruses while congenital infection is prominently seen in CMV. Therefore, newborns with immunological defects are at a highest risk of CMV disease. However, infection with HHV8 causes Kaposi's sarcoma, the most common cancer in patients with AIDS. The inflicted immunosuppression due to these viral infections is usually dual in nature and largely attributed to inhibition of T cell responses.

5. Immunosuppression induced by antimicrobial drugs

Although most antimicrobial drugs are safe and effective in patients with infectious diseases, some are toxic to the host cells causing alterations in immune cells function that may lead to immunosuppression [39]. Major immunotoxic effects attributed to antimicrobial drugs include neutropenia and agranulocytosis, autoimmune diseases development, or hypersensitivity reactions. These toxic effects had influenced the therapeutic choice of some antimicrobial drugs despite their clinical interventions. The mechanistic events involved in the alteration of immune cells with consequent immunosuppression are not well established. However, in clinical practice, the antiviral agents, Ganciclovir, Ribavirin, and Zidovudine as well as the antibacterial agents, Chloramphenicol, Rifampicin, Sulfa derivatives, Macrolides (Azithromycin, Clarithromycin, or Erythromycin) and β-lactam (Penicillins, Cephalosporins) antibiotics are leading causes of neutropenia, agranulocytosis, inhibition of phagocyte function, and immunotoxic effects on bone marrow precursor cells. The latter effect is dose dependent and usually diagnosed by adding the patient's serum and the antibiotic drug under investigation to an *in vitro* culture of bone marrow cells. However, in addition to toxic effects on immune cells, some antibacterial drugs or their metabolites have been implicated in allergic reactions as exemplified by the ß-lactam, Penicillin G. The sensitizing capacity of any antimicrobial drug depends solely on its ability to interact irreversibly with tissue proteins to form complexes that provoke immune effector cells. Consequently, an IgE-mediated allergic reaction would be induced and the competence of these patients to mount a specific immune response is paralyzed. Other immunologic caveats attributed to antibacterial drugs include production of immune complexes as shown in drug-induced systemic lupus erythematosus with Isoniazid, Sulfonamides, Streptomycins, and Penicillins or cell-mediated hypersensitivity reactions as shown in contact dermatitis with Penicillins, Neomycins, and Nitrofurantoin. Again, the immunocompetence of patients with drug-induced autoimmune disorders or hypersensitivity reactions would be jeopardized unless reconstituted. In any event, alterations in immune cells caused by these drugs are expected to affect the immune function with consequent immunosuppression. At this stage, the host is more prone to infection with several opportunistic pathogens.

In contrast, immunosuppression induced by immunosuppressant drugs had a profound effect on lymphocytes function [1]. Common drugs used for this purpose include Calcineurin inhibitors (Cyclosporine A or Tacrolimus), glucocorticoids, and Mycophenolate

mofetil. The resultant immunosuppression induced by these drugs led the host to be more vulnerable to opportunistic infections as evidenced in most solid organ- transplants (e.g. kidneys, liver, and pancreas) or cancer patients [40]. In this population of immunocompromised patients, the predominately encountered opportunistic infections include *Mycobacterium tuberculosis*, *Mycobacterium* other than tuberculosis (MOTT), *Aspergillus* sp., *Crptococcus neoformans*, *cytomegalovirus*, and/or *pneumocystis jirovecii* pneumonia.

6. Immunological evaluation of immunosuppression

Despite the application of various treatment modalities for the control of infection in immunocompromised patients, a limited number of methods are available for the evaluation of immunosuppression. Most of the available methods rely on T or B cells function as exemplified by lymphocytes activation and proliferation, cytokines production, leukocytes count and expression, and specific antibody production. Although these methods are well established in several research studies, only ELISA for antibody and cytokine assays and flow cytometry for leukocyte counts and markers expression are commonly used in clinical referral laboratories. However, in routine diagnostic laboratories, none of these methods are approached properly. Therefore, there is an urgent need to scrutinize the fidelity of these methods in the evaluation of immunosuppression in most clinical laboratories. The rationale is to identify the immunocompetence of the host before the institution of any therapeutic intervention [41].

For routine isolation of lymphocytes and monocytes in anti-coagulant-treated blood, density gradient centrifugation [42] is used after lysis of red cells. For the isolation of neutrophils, dextran sedimentation is firstly used for the isolation of leukocytes-rich preparation followed by density gradient sedimentation in Percoll A. In both settings, the viability of leukocytes can be measured by trypan blue exclusion and phenotyping of leukocytes preparation can be established by flow cytometry using the commercially available monoclonal antibodies against leukocyte surface antigens (CD). HLA typing can be conducted similarly. For functional analysis of phagocytic cells (macrophages or neutrophils), limited methods are used including phagocytosis (ingestion), opsonisation (enhanced attachment), and chemotaxis (directed cell motility).

7. Conclusions

Immunosuppression is a sword of two edges; while it is beneficial when intentionally instituted to maintain the life in solid organ-transplants or cancer patients, it is perilous in patients with primary immunodeficiency diseases, patients with HIV infection, and/or patients with multiple organ failure. Therefore, the mediating factors must be scrutinized, the leukocyte counts and function must be stated and the pros and cons of an immunosuppressant medicine must be thoroughly evaluated before being prescribed.

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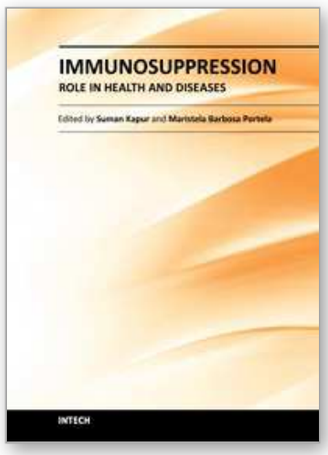

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A need for a book on immunology which primarily focuses on the needs of medical and clinical research students was recognized. This book, "Immunosuppression - Role in Health and Diseases" is relatively short and contains topics relevant to the understanding of human immune system and its role in health and diseases. Immunosuppression involves an act that reduces the activation or efficacy of the immune system. Therapeutic immunosuppression has applications in clinical medicine, ranging from prevention and treatment of organ/bone marrow transplant rejection, management of autoimmune and inflammatory disorders. It brings important developments both in the field of molecular mechanisms involved and active therapeutic approaches employed for immunosuppression in various human disease conditions. There was a need to bring this information together in a single volume, as much of the recent developments are dispersed throughout biomedical literature, largely in specialized journals. This book will serve well the practicing physicians, surgeons and biomedical scientists as it provides an insight into various approaches to immunosuppression and reviews current developments in each area.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

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