**LEADING ARTICLE**

**Immune modulators**

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Immune system modulator is a substance that stimulates or suppresses the immune system and may help the body fight cancer, infection, or other diseases. There are two types of Immune modulators specific such as monoclonal antibodies, cytokines, and vaccines, affect specific parts of the immune system and nonspecific such as BCG and levamisole, affect the immune system in a general way. It is a part of immunotherapy, in which immune responses are induced, amplified, attenuated, or prevented according to therapeutic goals therefore immune modulators used as treatment strategies in many diseases. Recently compounds derived from natural products have demonstrated their effectiveness as therapeutic agents in different areas, such as metabolic disorder, cardiovascular diseases, inflammation, and neurological disorders. Natural products, like herbal medicines, fatty acids, and probiotics, also are implicated in the regulation of immune function [1,2].

Immunomodulatory regimen often have fewer side effect, than existing drugs including less potential for creating resistance when treating microbial disease. Cell-based immunotherapies are effective for some cancer. Immune effector such an lymphocyte, macrophage, dendritic cells, natural killer cell (NK cell), cytokines T lymphocyte (CTL), etc work together to defend the body against cancer by targeting abnormal antigens expressed on the surface of tumor cell. In this article we aim to reveal the various ways in which the immune system can be manipulated to suppress unwanted immune response in the form of auto immunity, allergy, and grafted rejection, or to stimulate protective immune response against tumor or infection diseases.

Unwanted immune response occurs in many states such as autoimmune diseases, transplant rejection and allergy. The goal of treatment in all cases is to avoid tissue damage and prevent disruption of tissue function. Conventional immunosuppressive drugs meaning natural or synthetic-small molecule compound can be divided into served different categories, it's included.

1. Corticosteroid a powerful anti-inflammatory drug, its regulate the expression of many genes, with a net anti-inflammatory effect. First they reduce the production of inflammatory mediators, and Nitric oxide. Second, they inhibit inflammatory cell migration to sites of inflammation by inhibiting the expression of adhesion molecules. Third, prompt the death by apoptosis of leukocyte. All of the above action of corticosteroid can be induced by activate the expression of anti-inflammatory gene. The adverse effect include fluid retention, weight gain, diabetes, bone mineral loss and thinning of the skin [3].
2. Cytotoxic drug which used as immunosuppressant's are azathioprine, cyclophosphamide and mycophenolate. These drugs interfere with DNA synthesis, and their major action is on tissues in which cells are continually dividing. Developed to treat cancer. Azathioprine interferes with CD28 co-stimulation in T cell thus promoting T-cell apoptosis. Mycophenolate is the newest addition to the family of cytotoxic immunosuppressive drugs azathioprine and mycophenolate are less toxic than cyclophosphamide. Cyclophosphamide is a member of nitrogen Mustard family which was developed as chemical weapon [4-7].

 There were three non-cytotoxic alternative to the cytotoxic drug are available an immuno-suppressants and widely used to treat transplant recipients. These are cyclosporine A, tacrolimus and Rapamycin. Cyclosporine A is a cyclic deca peptide derived from a soil fungus found in Norway ***Tolyphocladiumin flatum***. Tacrolimus is a macrolide compound from the filamentous bacterium ***Streptomyces tusukabaensis*** found in Japan. Rapamycin another macrolide, is derived from ***Streptomyces hugroscopius***, found on Eastr Island. All these compound exert their pharmacological effect by binding to members of a family intracellular protein known as immunephilins, forming a complex interfere with signaling pathway important for clonal expansion of lymphocyte so they inhibit lymphocyte and some granulocyte response. Cyclosporin A and Tacrolimus inhibit T-cell activation by interfering with serine threonine –specific phosphatase Calcineurin. Rapamycin has different mode of action from either cyclosporine A or tacrolimus. Like tacrolimus, Rapamycin bind to the FKBP Family of immunophilius, but the Rapamycin: immunephilins complex does not inhibit Calcineurin activity but instead it inhibits a serine/threonin kinase known as mToR (mammalian target of Rapamycin) which involved in regulating cell growth and proliferation. MToR is activated downstream of various growth factor signaling pathways, and becomes associated with either of two proteins, Raptor (regulatory associated protein of mToR) and Rector (Rapamycin- insensitive companion of mToR). The complex Rector, influences cell adhesion and migration by controlling the actin cytoskeleton. One recently introduced drug manipulates immune responses by regulating the migration of immune effector cells to the sites of graft or of autoimmune disease. Fingolimod (FTY720), a sphingosine-1. Phosphate analog, is a newer drug that causes that retention of effector lymphocytes in lymphoid organs, thus preventing these cells from mediating their effector activities in target tissue. Fingolimed was approved for treatment of multiple sclerosis and has promise in the treatment of kidney graft rejection and asthma [8-10].

1. Interleukin-1, another naturally occurring cytokine, has both immune and pro-inflammatory actions. Anakinra is a human recombinant protein and the therapeutic version of a naturally occurring cytokine that competitively blocks the interleukin-1 receptor, thus blocking various inflammatory and immunological responses [11].
2. There are Antibodies produced to interact with cell – surface molecule can be used to eliminate lymphocyte subsets or to inhibit lymphocyte function. The potential of antibodies to eliminate unwanted lymphocytes is demonstrated by anti – lymphocyte globulin one such Ab is Alemtuzumab which is directed at the cell- surface protein CD52 expressed by most lymphocytes it also used to eliminate cancer cells in the treatment of chronic lymphocytic leukemia. Also Rituximab, a chimeric murine/human monoclonal antibody, works by binding to the CD20 antigen found on the surface of B lymphocytes. B-cells are believed to play a role in autoimmune and inflammatory processes, such as those involved in rheumatoid arthritis. A monoclonal antibodies which are specific for various physiological target are being used or under Investigation to prevent rejection of transplanted organs by inhibiting the development of harmful inflammatory and cytotoxic response. There about 19 type of specific antibodies that under development and in clinical trials [12].
3. Methotrexate is the most widely used conventional disease-modifying anti-rheumatic drugs (DMARD) and is considered the “anchor drug” because of its effectiveness and relative tolerability as well as its potential to enhance the effectiveness of targeted immune modulators (TIMs) [13].
4. Many plants for example poplar bud extracts decreased blood glucose levels and insulin resistance and significantly relieved dyslipidemia, oxidative stress, and inflammation in type-2 diabetes mice [14].
5. There are some commonly used drugs have immunomodulatory properties such as statins and angiotensin Converting enzyme inhibitors widely used the prevention and treatment of cardiovascular diseases, can also modulate the immune responses in experimental animals. Statin is widely prescribed drugs that block that enzyme 3-hydroy-3-methylglutaryl-co-enzyme A (HMG-co A) reductase, thereby reducing cholesterol levels. They also reduce the increased level of expression of MHC class 11 molecules in some autoimmune diseases. These effects may be due to an alteration in the cholesterol content of membrane of lymphocyte signaling.
6. The hormone vitamin D3, essential for bone and mineral homeostasis, also exerts immunomodulatory effect, it decrease IL-12 production by dendritic cell and leads to a decrease in IL-2 &IFN-Y production by CD4T cells, and protective effects have been demonstrated in a variety of animal models of autoimmunity [15].
7. Controlled administration of Antigen can be used to manipulate the nature of an antigen –specific responses. This principle has been applied with some success to the treatment of allergies caused by an IgE response to very low doses of Ag. Repeated treatment with increasing doses of allergen seem to divert the allergic response to one dominated by T cells that favor the production of IgG and IgA Abs from B cells. These Abs though to desensitize the patient by binding the small amounts of allergen normally encountered and preventing it from binding to IgE.

Other approaches using antigen to shift the autoimmune T-cell response to a less damaging TH2 response have been more effective in human. The peptide drug glatiramer acetate (copaxone) is approved for treating multiple sclerosis it is a polymer consisting of the four amino acids glutamic acid, alanine, tyrosine, and lysine in ratios that mimic their composition in MBP, and it induces a TH2 type protective response. This manner defined as altered peptide ligands (APLs) in which amino acid substitutions, have been made in specific amino acid in an antigenic peptide that are at the T-cell receptor contact position [16].

1. Cancer is the most common fatal disease and the major problem in treating cancer is controlling metastasis. Curing cancer there for requires that the entire malignant cell be removed or destroyed without killing the patient. An alternative way to achieving this would be to induce immune responses against the tumor that would discriminate between the cell of the tumor and their normal cell counterparts. Immunological approaches to the treatment of cancer have been attempted for more than a century, but it is only in the past decade the immunotherapy of the cancer has shown real promise. Understanding how the immune system promotes and prevent cancer growth has led to new therapies. Monoclonal antibodies have been successfully developed for tumor immunotherapy in several cases, such as anti- CD20 Antibody used to treat B-cell lymphoma [17].
2. Attempts are also being made to develop vaccine incorporating peptides designed to generate effective cytotoxic and helper T-cell responses.CAR T-cell engineered to recognize CD19 expressed on B- cell can be effective treatment for Acute lymphocytic leukemia checkpoint blockade strategies for CTL-A and PD-1 have been approved for treating melanoma, Ipilimumab was the first FDA-approved immune checkpoint antibody licensed for the treatment of metastatic melanoma (MM) and blocks a checkpoint molecule called cytotoxic T-lymphocyte antigen 4 (CTLA-4) and related strategies are being developed for other biologic target to stimulate anti-tumor responses or block inhibitory mechanism, that suppress such responses [18].

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