Immunotherapy: Basic Concepts and Applications

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بسم الله الرحمن الرحيم

(قالوا سبحانك لا علم لنا إلا ماعلمتنا

إنك انت العليم الحكيم)

صدق الله العظيم

Dedication

I dedicate this work to my family, my husband, and my daughters, whom without their sincere emotional support, this work would have never been completed.

Acknowledgment

In these few lines, I would like to thank **ALLAH** the almighty, for granting me:

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Abstract

Immunotherapy refers to treatment strategies based upon modulating the immune system either by activation or suppression to achieve a prophylactic or therapeutic goal. Strategies that enhance the immune response include active and passive ones. The active includes vaccination and adjuvants, adoptive T cell therapy, mAb therapy, NK cell therapy as well as cytokine therapy.While passive immunotherapy includes antibody replacement therapy.

Strategies that diminish the immune response,on the other hand, include anti-inflammatory agents (steroids and NSAIDs) as well as immuno-suppressive measures for RA, bronchial asthma and graft rejection.

Strategies that alter the immune response include pre-emptive measures as Rh Ig therapy and antibiotic therapy, as well as modification of ongoing diseases by cytokines and allergy desensitization.

Finally, immunotherapy also includes targeted therapy that targets one type of cell or antigen without injuring other cells. This review highlights the different modalities of immunotherapy with special concern on cancer.

- ***Keywords***: Immunotherapy, Activation, Suppression, Cancer vaccines, Targeted therapy.

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List of Abbreviations

APCs: Antigen presenting cells.

AID: Activation induced deaminase.

AICD: Activation-induced cell death.

ADCC: Antibody dependent cellular cytotoxicity.

Ags: Antigens.

AD: Antibody deficiencies.

ALT: Alanine transaminase.

AST: Aspartate transaminase.

BCR: B cell receptor.

BCG: Bacillus calmette-Guerin.

BSC: Best supportive care arm.

CD: Cluster of differentiation.

CCR: Chemokine receptor.

CRP: C reactive protein.

CTLs: Cytotoxic T lymphocytes.

CMI: Cell-mediated immunity.

CpG: Cytidine-phosphate-guanosine dinucleotide.

COPD: Chronic obstructive pulmonary disease.

COX: Cyclo-oxygenase.

CEA: Carcino-embryonic antigen.

CLL: Chronic lymphocytic leukemia.

CTLA-4: Cytotoxic T-cell associated gene-4.

DCs: Dendritic cells.

DNA: Deoxy-ribonucleic acid.

DMARD: Disease modifying antirheumatic drugs.

EGFR: epidermal growth factor receptor.

FDCs: Follicular dendritic cells.

Fc: Fragment crystallization.

FDA: Food and Drug Administration.

Fab: Fragment antibody binding.

GM-CSF: Granulocyte monocyte-colony stimulating factor.

GVHD: Graft versus host disease.

GR: Glucocorticoid receptor.

G-CSF: Granulocyte-colony stimulating factor.

HLA: Human leucocyte antigen.

HIV: Human immunodeficiency virus.

HSC: Hemopoietic stem cells.

HCV: Hepatitis C virus.

HDAC2: Histone deacetylase-2.

HDN: Haemolytic disease of the newborn.

HPV: Human papilloma virus.

HD: High dose.

HSPs: Heat shock proteins.

INF-γ: Interferon-γ.

IR: Immune response.

Igs: Immunoglobulins.

I.D: Intradermal.

ICAM: Intercellular adhesion molecule.

IVIG: Intravenous immunoglobulins.

IgG: Immunoglobulin gamma.

IgM: Immunoglobulin Mu.

ITT: Intension-to treat.

Kb: Kilo base.

LABAs: long-acting β_2-agonists.

LPS: Lipopolysaccharides.

LFA-3: Leucocyte function-associated antigen-3.

LAK: Lymphokine activated killer cells.

LTs: Leukotriens.

MHC: major histo-compatibility complex molecules.

MQs: Macrophages.

MAC: Membrane attack complex.

mAbs: Monoclonal antibodies.

mHRPC: metastatic human refractory prostate cancer.

MUC-1: Mucin 1.

MVA: Modified vaccinia Ankara.

NF-κB: Nuclear factor-κB.

NK cells: Natural killer cells.

NHL: Non Hodgkin lymphoma.

NSAIDs: Non steroidal anti-inflammatory drugs.

OS: Overall survival.

PAMPs: pathogen associated molecular patterns.

PFS: Progression-free survival.

PTX3: pentraxin.

PMNs: Polymorpho-nuclear cells.

PSA: Prostate specific antigen.

PBMC: Peripheral blood mononuclear cells.

PAP: Prostatic acid phosphatase.

PD-1: Programmed cell death 1.

PD-L1: Programmed cell death ligand 1.

PGs: Prostaglandins.

RCC: Renal cell carcinoma.

RNA: Ribonucleic acid.

RA: Rheumatoid arthritis.

Rh: Rhesus factor.

SLAM: Signaling lymphocytic activation molecule.

S.C: Subcutaneous.

SCF: Stem cell factor.

Tat: Tumor-associated antigen to HIV-1.

TNF: Tumor necrosis factor.

TCR: T cell receptor.

TLRs: Toll like receptors.

TH: T helper cells.

TSA: Tumor specific antigen.

TAA: Tumor associated antigen.

Tregs: Regulatory T cells.

TGF: Tumor derived growth factor.

T_{EM}: T effector memory cells.

T_{CM}: T central memory cells.

TERT: Telomerase reverse transcriptase.

TERC: Telomerase RNA component.

TILs: Tumor infiltrating lymphocytes.

TRAIL:Tumor necrotic factor related apoptosis-induced ligand.

VEGF: vascular endothelial growth factor.

XLP: X linked lympho-proliferative syndrome.

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Introduction

Immunotherapy, in medicine, refers to treatment strategies based upon the concept of modulating the immune system either by activation or suppression to achieve a prophylactic or therapeutic goal ***(Rosenberg et al.2008).***

One of the modalities that activate the immune system is vaccination which stimulate the immune system to respond to a specific infectious agent such vaccines use weakened or killed viruses, bacteria, or other germs to start an immune response in the body putting the immune system on alert against these germs thus preventing people from being infected with them ***(Rosenberg et al.2008).***

Also, cancer vaccines were established, they are either designed to work against the known oncogenic viruses, for example, the human papilloma virus (HPV) and hepatitis B virus (HBV) or designed to stimulate the immune system to reject and destroy tumors (True cancer vaccines). It may be conducted by many ways including; adoptive T cell therapy (ACT), using autologus tumor-infiltrating lymphocytes (TILs) ***(Rosenberg et al.2008).***

ACT uses T cell-based cytotoxic responses to attack cancer. T cells that have a natural or genetically engineered reactivity to a patient's cancer are expanded in vitro using high concentrations of interleukin-2, anti-CD3 and alloreactive feeders. These cells are then transferred back into the patient along with exogenous administration of IL-2 ***(Rosenberg et al.2008).***

Another form of cancer immunotherapy utilizes dendritic cells to activate a cytotoxic response towards an antigen. Dendritic cells are

harvested from a patient. These cells are then either pulsed with an antigen or transfected with a viral vector. The activated DCs are then placed back into the patient; these cells will present the antigens to effector T lymphocytes ($CD4^+$T cells, $CD8^+$. This initiates a cytotoxic response to occur against these antigens ***(Rosenberg et al.2008).***

Monoclonal antibody therapy plays a central role in both the recognition of foreign antigens and the stimulation of the patient's immune system to attack the malignant tumor cells and prevent tumor growth by blocking specific cell receptors that are rare or absent on the surface of healthy cells, and which are responsible for activating cellular signal transduction pathways that cause the upregulated growth and division of the tumor cells. Examples include ErbB2 ***(Janeway et al.2005).***

The advent of monoclonal antibody technology has made it possible to raise antibodies against specific antigens presented on the surfaces of tumors, variations exist within this treatment, e.g. radioimmunotherapy, where a radioactive dose localizes on target cell line, delivering lethal chemical doses to the target ***(Janeway et al.2005), (Waldmann et al.2003).***

Immune suppression is needed when normal immune response couldnot be terminated after removal of the initiating antigen, otherwise, autoimmune diseases or allergic diseases will occur. Also immune suppression is required to prevent rejection of the transplanted organ ***(Rotrosen et al.2008).***

Immunotherapy is the only available treatment that can modify the natural course of the allergic disease, by reducing sensitivity to allergens, while other allergic treatments (such as antihistaminics or corticosteroids) treat only the symptoms of allergic diseases ***(durham et al.1999).***