The Checkpoint Therapy- Helping Your Immune System To Fight Cancer By Unleashing The Brakes On Immune System

*Dr. Madhura Panditrao, ** Dr.Ramesh Kothari,*** Dr. Sunil Mhaske

*Resident, ** Professor and Head, Department of Paediatrics,*** Dean, Dr. Vithalrao Vikhe Patil Foundation's Medical College, Ahmednagar.

Corresponding Author : Dr. Madhura Panditrao

Mail id : madhurapanditrao15@gmail.com

Mobile No.: 9834230632

Address : Department of Paediatrics, Dr. Vithalrao Vikhe Patil Foundation's Medical College, Ahmednagar.

Abstract :

The 2018 Nobel Prize in Physiology or Medicine is awarded to James P. Allison and TasukuHonjo for their discovery of cancer therapy by inhibition of negative immune regulation. In 1996, James P. Allison and coworkers used this accumulated knowledge to demonstrate that antibodies directed against a cell surface molecule on T cells, CTLA-4, is capable of unleashing an immune response, which cured mice of tumors. Prior to this, in the laboratory of TasukuHonjo, a new molecule named PD-1 had been identified. With the aid of biomedical companies, Allison succeeded in developing the new concept with anti-CTLA-4 into clinical therapy for patients with advanced forms of melanoma. The use of antibodies directed against PD-1 and its ligand PD-L1 has now been approved for several cancer forms and this treatment is even more efficacious.

Introduction : Cancer is a common term for a group of diseases caused by uncontrolled cell proliferation and migration.This results in abnormal growth of a tumor mass, first within an organ, then infiltrating adjacent tissues. Eventually, cancer cells can also colonize distant organs via blood or lymphatic vessels, so called metastases, causing morbidity and death. The symptoms, course and prognosis of the disease vary depending on the tissue origin. According to WHO, more than 18 million persons in the world are estimated to be diagnosed with cancer in 2018.

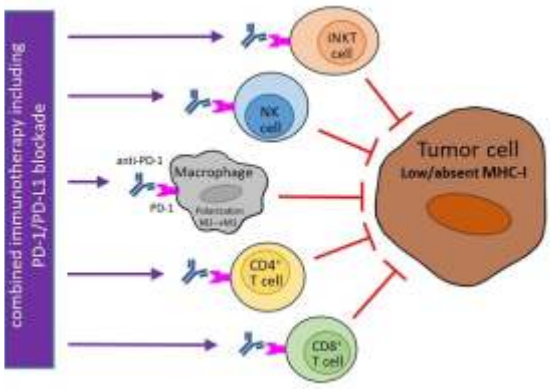
Several discoveries awarded have included infection as an etiological factor (e g Rous 1966, for tumor-inducing viruses; zurHauzen 2008, for Human Papilloma virus as a cause of cervical cancer); and the relation between cellular and viral genes in pathogenesis (e g Baltimore, Dulbecco and Temin 1975, for integration of retroviral genetic information into DNA; Bishop and Varmus 1989, for the cellular origin of viral oncogenes). Despite this remarkable progress, the incidence of cancer is rising in most countries of the world, partly due to an increased life span and improved diagnosis; one out of three will develop the disease and one of 6 will die of cancer.[1]

Tight control of our body's natural defences is just as fundamental as the immune response itself – it means any foreign or damaged cells (including tumour cells) can be destroyed while ensuring healthy cells aren't attacked. Key to this control are T cells, a type of white blood cell, that recognises 'non-self' entities such as bacteria and viruses, as well as the body's healthy cells, using receptor proteins on their surface. 'Brakes' on the surface of T cells essentially halt activation of the immune response when it's not needed. The foundation of Allison and Honjo's Nobel-winning work rests upon the concept of harnessing the immune system to attack tumour cells by inhibiting two specific brakes – called CTLA-4 and PD-1 – to switch on our immune response. It's been the most successful attempt yet to rid cancer patients of life-threatening tumours and, ultimately, the disease itself. This intricate balance between accelerators and brakes is essential for tight control. It ensures that the immune system is sufficiently engaged in the attack against foreign microorganisms while avoiding the excessive activation that can lead to autoimmune destruction of healthy cells and tissues.[2]

Discussion : CTLA4 (cytotoxic T-lymphocyte-associated protein 4), also known as CD152 (cluster of differentiation 152), is a protein receptor that, functioning as an immune checkpoint, downregulates immune responses. CTLA4 is constitutively expressed in regulatory T cells but only upregulated in conventional T cells after activation – a phenomenon which is particularly notable in cancers.[4] It acts as an "off" switch when bound to CD80 or CD86 on the surface of antigen-presenting cells. CTLA4 is homologous

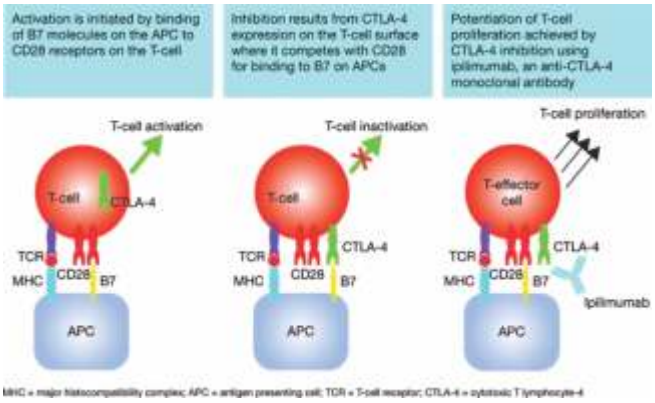
to the T-cell co-stimulatory protein, CD28, and both molecules bind to CD80 and CD86, also called B7-1 and B7-2 respectively, on antigen-presenting cells. CTLA-4 binds CD80 and CD86 with greater affinity and avidity than CD28 thus enabling it to outcompete CD28 for its ligands. CTLA4 transmits an inhibitory signal to T cells whereas CD28 transmits a stimulatory signal. CTLA4 is also found in regulatory T cells (Tregs) and contributes to their inhibitory function. T cell activation through the T cell receptor and CD28 leads to increased expression of CTLA-4. Blocking of CTLA-4 would strengthen the T cell anti-tumor response, even pre-established tumors were found to be sensitive and rejection was followed by durable tumor immunity.[3]

Programmed cell death protein 1, also known as PD-1 and CD279 (cluster of differentiation 279), is a protein on the surface of cells that have a role in regulating the immune system's response to the cells of the human body by down-regulating the immune system and promoting self-tolerance by suppressing T cell inflammatory activity. This prevents autoimmune diseases, but it can also prevent the immune system from killing cancer cells.PD-1 is an immune checkpoint and guards against autoimmunity through two mechanisms. First, it promotes apoptosis(programmed cell death) of antigen-specific T-cells in lymph nodes. Second, it reduces apoptosis in regulatory T cells (anti-inflammatory, suppressive T cells). PD-1 inhibitors, a new class of drugs that block PD-1, activate the immune system to attack tumors and are used to treat certain types of cancer.The PD-1 protein in humans is encoded by the PDCD1 gene.PD-1 is a cell surface receptor that belongs to the immunoglobulin superfamily and is expressed on T cells and pro-B cells.PD-1 binds two ligands, PD-L1 and PD-L2 Figure A).[4]



After the initial studies showing the effects of CTLA-4 and PD-1 blockade, the clinical development has been dramatic. We now know that the treatment, often referred to as "immune checkpoint therapy," has fundamentally changed the outcome for certain groups of patients with advanced cancer. Similar to other cancer therapies, adverse side effects are seen, which can be serious and even life threatening. They are caused by an overactive immune response leading to autoimmune reactions, but are usually manageable. Intense continuing research is focused on elucidating mechanisms of action, with the aim of improving therapies and reducing side effects.

Ipilimumab is the first approved drug to block this inhibitory interaction. It uses a type of protein called an antibody, which binds directly to CTLA-4 so that there is no space for an interaction with CD80/86. This removes a natural check on the immune response and allows the body to mount a more effective battle against cancer cells (see Figure 1B). The exact mechanism of Ipilimumab action is still under active investigation and likely involves the regulation of a whole host of immune processes, including the destruction of your body's immune cells that are known to dampen the immune response.[5] It is the first treatment to improve overall survival in patients with metastatic melanoma, with 10% of patients showing decreased tumor size in a recent study. Much like ipilimumab, an anti-PD1 drug called Nivolumab boosts T cell activity by binding to the T cell's PD-1 to block this inhibitory interaction. Because of its high clinical promise and the successful path previously paved by the ipilimumab, the FDA has fast-tracked the review of anti-PD1, and physicians are hopeful it will become available for expanded use soon. Antibodies are also in development to block the PDL1 found on cancer cells.[6,7]



While there are still unanswered questions in the field, immune checkpoint blockades have demonstrated that sometimes one of the best defenses against cancer cells may be your body's own army of immune cells bolstered by therapies that keep cancer cells from bypassing their response.

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