

Nobel Prize in Physiology or Medicine – 2018

Arunika Mukhopadhyaya

The Nobel Prize in Physiology or Medicine for the year 2018 was awarded to James P Allison of the United States and Tasuku Honjo of Japan for their immense contributions towards the application of immunotherapy for the treatment of cancer. To understand the ramifications of their discovery, we must first understand how the immune system works.

Immune Response

Our body's defense against a wide array of diseases is governed by the immune system. The immune system exerts two lines of defenses known as (1) innate immunity and (2) adaptive (acquired) immunity. Innate immunity is the body's first line of defense, very quick but non-specific, whereas adaptive immunity takes time to kick in, but it is very effective, specific and displays memory.

T cells form the cellular arm of adaptive immunity. T cells are generally of two types – $CD4^+$ T cells and $CD8^+$ T cells. Generally, T cells remain inactive in the body. Upon activation, $CD4^+$ T cells act as a helper cells and aid other cells in exerting immune responses such as antibody production by the B cells. On the other hand, $CD8^+$ T cells upon activation, become cytotoxic T lymphocytes or CTLs, which can directly kill the infected cells. For cancer immunotherapy, both the helper cells and CTLs are desired for optimal responses. However, the problem is that T cells do not get activated directly by the antigens; they need signaling from antigen presenting cells or APCs. Dendritic cell (DCs) are the professional APCs. DCs can regulate T cell activation in various ways. DCs exist in two forms: immature DCs and mature DCs. The ability of DCs to regulate immunity is dependent on DC maturation. In the steady-state, DCs generally remain imma-



Arunika Mukhopadhyaya is Associate Professor in the Department of Biological Sciences at the Indian Institute of Science Education and Research Mohali. After receiving a PhD from the National Institute of Cholera and Enteric Diseases, Kolkata, she pursued her postdoctoral research at the Albert Einstein College of Medicine, New York, USA. She joined IISER Mohali in 2009. Arunika Mukhopadhyaya is a cellular immunologist, and her team works on understanding the immunobiology of host-pathogen interaction processes.

Keywords

Immunotherapy, immune checkpoint, cancer, T cells, lymphocytes, immunity, antigen presenting cells, dendritic cells.



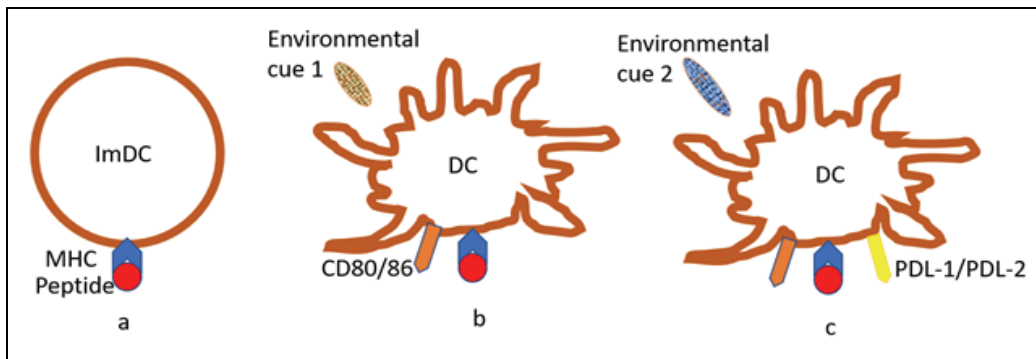


Figure 1. Dendritic cell (DC) activation and maturation by environmental cues leads to surface expression of co-stimulatory (CD80, CD86) and co-inhibitory molecules (PDL-1, PDL-2, etc). (a) Immature DC (ImDC) can present peptide-antigen via MHC, (b) Mature DC expresses co-stimulatory molecule, (c) Depending on the environmental cues maturation also leads to the expression of co-inhibitory molecule by mature dendritic cell.

ture, but once they get a cue from the environment regarding a diseased condition, DCs undergo maturation (*Figure 1*). Maturation of DCs leads to the surface expression of various molecules (*Figure 1*). While immature DCs can capture antigens, process them and present them via the major histocompatibility complex (MHC) molecule to the naïve T cells, this presentation provides only signal 1 (MHC-peptide and TCR interaction; see *Box 1*), and leads to T cell tolerance in terms of deletion, or generation of the suppressive T cells known as the regulatory T cells (Tregs), or T cell anergy, i.e. a state of unresponsiveness (*Figure 2*). With maturation, DCs express higher amounts of co-stimulatory molecules (CD80, CD86) which interact with CD28 on the T cell surface, and provides signal 2 (see *Box 1*) along with signal 1 (*Figure 2*). These interactions lead to T cell activation and generation of T cell helper response and/or CTLs [1, 2].

Immune Checkpoint

Maintaining homeostasis of immune responses is crucial for host survival. Uncontrolled immune responses can cause tissue damage and autoimmune disorders.

T cells can be activated by co-stimulatory receptors or tolerized by co-inhibitory receptors which send positive or negative signals respectively. Maintaining homeostasis of immune responses is crucial for host survival. Uncontrolled immune responses can cause tissue damage and autoimmune disorders. To prevent this, a balance between co-stimulatory and inhibitory signals is maintained which regulates the breadth and magnitude of the immune

Box 1. Two Major Signals for T cell Activation

T cell activation requires primary (signal 1) and co-stimulatory signals (signal 2) leading to the proliferation and differentiation of naïve T cells into effector cells. This process requires triggering of intracellular signal transduction cascades and new gene expressions.

Signal 1 occurs when the T cell receptor (TCR) binds to a foreign antigen (peptide) on the surface of an antigen-presenting cell (APC) such as, DC or a target cell, along with the major histocompatibility complex (MHC) molecule (*Figure 1*).

Signal 2 occurs when co-activating molecules on the T cell binds to co-stimulatory molecules on the DC, the most important of which are the B7 proteins – B7-1 or CD80 and B7-2 or CD86. B7 binding by T cell co-stimulatory proteins results in T cell activation, whereas a lack of binding results in T cell tolerance.

system. The signals which are necessary for protecting the host from tissue damage, or in other words maintain self-tolerance, are collectively referred to as ‘immune checkpoints’.

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) are two such prominent checkpoints (*Figure 2*).

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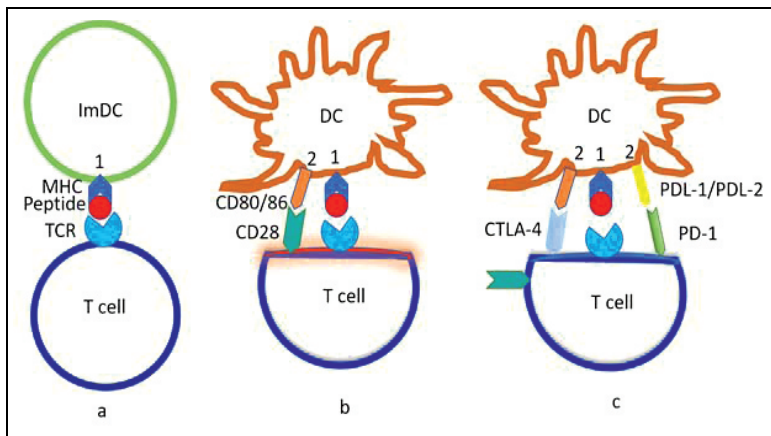
CTLA-4

CTLA-4, a transmembrane glycoprotein is a homolog of CD28 and binds to CD80 and CD86 on DC surface with approximately 20-times more affinity than CD28. Therefore, CTLA-4 inhibits the co-stimulatory signal by outcompeting CD28 for binding with B7 molecules [3]. Furthermore, CTLA-4 can actively remove CD80 and CD86 from the APC surface through the process of transendocytosis [4].

The interaction between CTLA-4 and CD80/CD86 induce inhibitory signaling triggering Treg formation. Treg, in turn, induces the production of more Tregs and suppress the activity of functionally active T cells. Blocking of CTLA-4 increases CD4⁺ T helper cells, indicating that the major inhibitory role of CTLA-4 primarily involves CD4⁺ T cell subset [5].



Figure 2. T-cell activation and regulation depends on the DC maturation state. (a) Antigen presented by ImDC can be recognized by T cell receptor (TCR) which provides only signal 1 and results in T cell tolerance, (b) Both signal 1 and signal 2 (via CD80/CD86 and CD28) provided by mature DC leads to T cell activation, (c) Signal 2 via co-inhibitory molecules (between CD80/CD86 and CTLA-4 or PDL-1/PDL-2 and PD-1) results in T cell tolerance.



PD-1/Programmed Death Ligand 1 or 2 (PDL-1 or PDL-2)

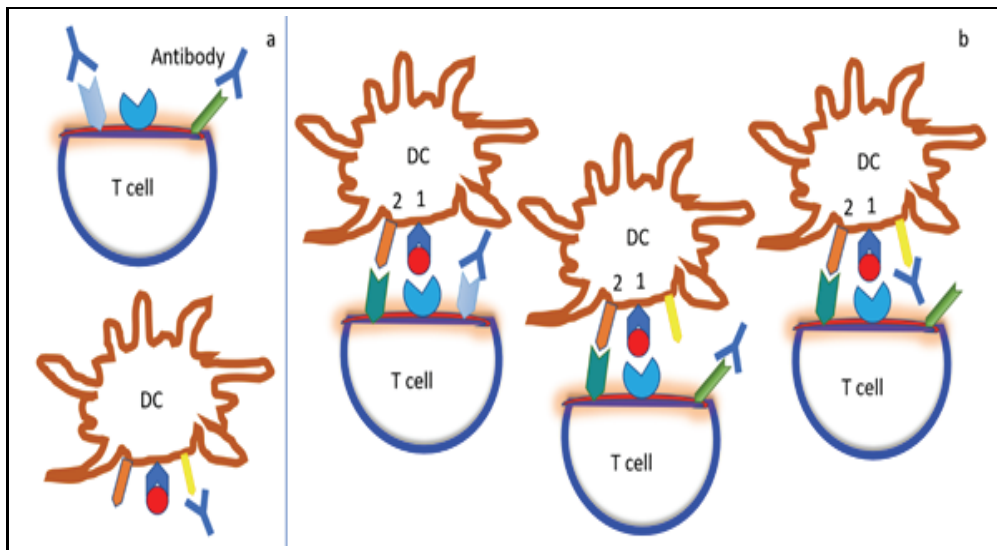
PD-1 is another inhibitory receptor. PD-1 interacts with the ligands PDL-1 and PDL-2 [6]. Signaling through co-inhibitory molecules hijack signal 2 and starts inducing inhibitory signals in terms of Treg formation (CTLA-4-B7 interaction), or T cell death and/or exhaustion (PDL-1/PDL-2 and PD-1 interaction) (*Figure 2*). CTLA-4 is mainly present on Tregs and can also be present even on naïve T cells, but PD-1 is always expressed by the mature T cells.

Blockade of Immune Checkpoints for Cancer Therapy: Allison and Honjo's Discovery

The Nobel Prize in Physiology or Medicine for the year 2018 was awarded to James P Allison of the United States and Tasuku Honjo of Japan for their immense contributions towards the application of immunotherapy for the treatment of cancer. The drugs based on the work of James P Allison and Tasuko Honjo belong to a class called the 'checkpoint inhibitors' [7, 8].

Generally, surgery, chemotherapy, and radiotherapy are the usual procedures employed in the treatment of cancer. However, these treatment measures are often not successful in curing all types of cancers and have major side effects. Employing the body's own immune system to do the job is one of the emerging strategies in

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cancer management.

One of the reasons for cancerous growth is the immune-suppressive environment induced by the cancers. Several studies have demonstrated that the immune-suppressive environment could be due to the induction of suppressive immune checkpoint pathways. This, in turn, led researchers to determine whether abrogation of the key immune checkpoint pathways could induce effective anti-tumor immunity, with respect to the use of the monoclonal antibody to CTLA-4 (*Figure 3*). In this context, CTLA-4 was the first clinically targeted immune checkpoint molecule. Following this, PD-1/PDL-1 pathway (*Figure 4*) has also been targeted.

The binding between inhibitory receptors and ligands are locked by immune checkpoint inhibitors, which, in turn, disrupts the inhibitory second signal (*Figures 2 and 4*). Immune checkpoint inhibitors have recently demonstrated magnificent results in clinical trials, and accordingly, are being used to treat several types of cancer. Some of the approved immune checkpoint inhibitors are the anti-CTLA-4 antibody (Ipilimumab), anti-PD-1 antibody (Nivolumab and Pembrolizumab), and anti-PDL-1 antibody (Atezolizumab).

Figure 3. Manipulation of DC and T cell surface can keep the T cell in activated state. (a) Antibodies can block the inhibitory receptor on T cell surface or ligands on the DC surface, (b) Blocking of inhibitory receptors or ligands let the signal 2 only comes through the co-stimulatory molecules rendering the T cell active.

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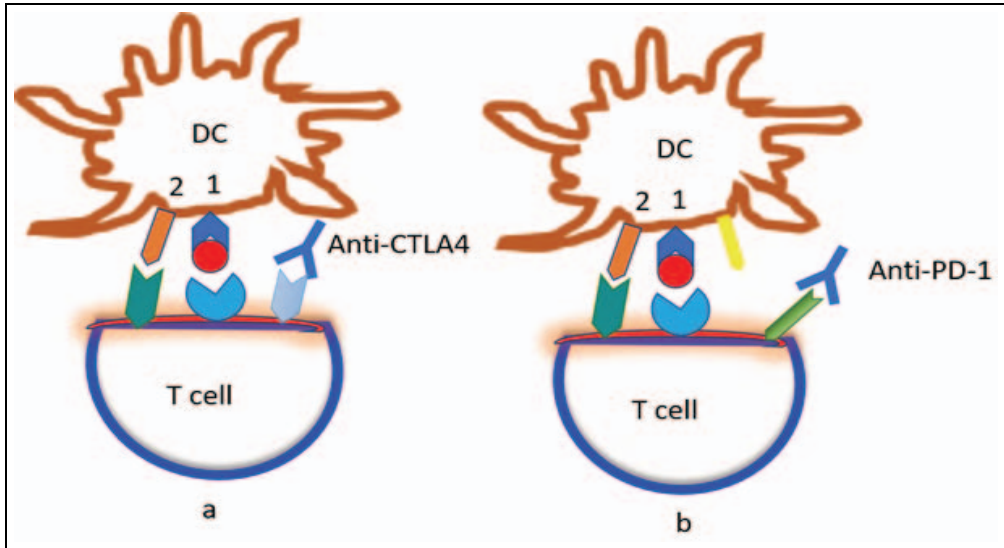


Figure 4. Model for inhibition of immune checkpoint as a measure for cancer immunotherapy based on James P Allison (a) and Tasuko Honjo's (b) work. (a) Blocking of the inhibitory receptor CTLA-4 by anti-CTLA-4 antibody allows the co-stimulatory ligands, CD80/CD86, to interact with CD28 leading to signal 2 as co-stimulatory signal, (b) Blocking of PD-1 receptor with anti-PD-1 antibody blocks the interaction between PD-1 and PDL-1/PDL-2 and let the signal 2 come through only co-stimulatory molecules rendering the T cell active.

Checkpoint inhibitors have only been approved for certain types of cancers, and they do not work for every individual patient. Immunotherapy involving checkpoint inhibitors is expensive, costing more than 100,000 USD per year per patient, and it can have severe side effects. However, this immunotherapeutic approach has now become a major strategy in the management of many types of cancers. Immunotherapy with checkpoint inhibitor drugs has been reported to cure even critical stages of cancers where every other therapy had failed.

Allison and Honjo's research is mainly targeted at CTLA-4 and PD-1. But it is interesting to note that there are other checkpoints as well, and a lot more targets are being discovered, accordingly updating our current understanding of the complex interactions at the APC–T cell immune synapses. The intracellular signaling cascades stimulated by many of these checkpoint molecules, such as CTLA-4 and PD-1 are non-redundant. Therefore, the future of immunotherapy of cancer is very promising. Further, the rate of success of cancer treatment may increase by combining different checkpoint inhibitors together and/or combining immunotherapy with other standard treatments of cancer.

Box 2. Glossary of Some Immunological Terms

Immunotherapy: Using immune system for treatment of a disease.

Innate immunity: Defense mechanism present from birth.

Adaptive (acquired) immunity: Defenses acquired during body's subsequent experience with infections/diseases.

T cells: Cells important for adaptive immunity. They recognize antigens via T cell receptors (TCRs).

CD4⁺ T cells: T cells which have CD4 marker (co-receptor) on their surface. Upon antigen exposure, CD4⁺ T cells either become T helper (Th) cells or regulatory T (Treg) cells.

T helper cells or Th: A type of CD4⁺ T cells which mainly help in antibody production by B cells.

Regulatory T cells or Tregs: A type of CD4⁺ T cells that suppress the function of Th cells.

CD8⁺ T cells: T cells which have CD8 marker (co-receptor) on their surface. Upon activation, CD8⁺ T cells become cytotoxic T lymphocytes or CTLs.

Cytotoxic T lymphocyte or CTLs: Cells formed by the activation of CD8⁺ T cells. CTLs directly kill the infected cells.

APCs: Antigen presenting cells. They capture, process and present antigen via surface expressed major histocompatibility complex molecules to be recognized by the T cell receptors.

DCs: Dendritic cells. These are professional antigen presenting cells of the body.

CD28: Receptors present on the T cell surface.

CD80 and CD86: Co-stimulatory molecules. They are also known as B7-1 and B7-2. They are expressed on the surface of APC upon activation, and generally bind to CD28 on the T cell surface, providing activation signal to the T cell.

CTLA-4: Cytotoxic T Lymphocyte Associated Protein 4. It is expressed on the surface of certain type of T cells mainly Tregs. CTLA-4, like CD28, binds to CD80 and CD86 but provides inhibitory signal to the T cell.

PD-1: Programmed death 1. It is a member of the CD28 superfamily. It is expressed on the surface of mature T cells and interacts with PDL-1 and PDL-2 on DCs and provides inhibitory signal to the T cells.

Suggested Reading

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Address for Correspondence

Arunika Mukhopadhyaya
Associate Professor
Department of Biological
Sciences
Indian Institute of Science
Education and Research
Mohali
Sector 81, SAS Nagar
Manauli 140 306
Punjab, India.
Email:
arunika@iisermohali.ac.in

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