Fall 2018

Immune Checkpoints in Cancer Treatment

Matthew A. Cherubino
Gettysburg College

Follow this and additional works at: https://cupola.gettysburg.edu/student_scholarship

Part of the Cancer Biology Commons, Cells Commons, and the Hemic and Immune Systems Commons

Share feedback about the accessibility of this item.

https://cupola.gettysburg.edu/student_scholarship/677

This open access poster is brought to you by The Cupola: Scholarship at Gettysburg College. It has been accepted for inclusion by an authorized administrator of The Cupola. For more information, please contact cupola@gettysburg.edu.
Immune Checkpoints in Cancer Treatment

Abstract
Despite the human immune system, cancer thrives in an extremely hostile environment. Cancer is the second most common cause of death in the U.S. with about 600,000 deaths every year, and cancer is expected to surpass heart disease as the most common cause of death in the U.S. Immune checkpoint inhibitors are a novel and promising therapeutic for treating cancer in its late stages.

Keywords
immune checkpoints, immune checkpoint inhibitors, cancer, ipilimumab, nivolumab

Disciplines
Cancer Biology | Cell and Developmental Biology | Cells | Hemic and Immune Systems

Comments

Creative Commons License

This work is licensed under a Creative Commons Attribution 4.0 License.
Immune Checkpoints in Cancer Treatment
M. Cherubino
Department of Biology, Gettysburg College, Gettysburg, PA

Overview
Despite the human immune system, cancer thrives in an extremely hostile environment. Cancer is the second most common cause of death in the U.S. with about 600,000 deaths every year, and cancer is expected to surpass heart disease as the most common cause of death in the U.S. Immune checkpoint inhibitors are a novel and promising therapeutic for treating cancer in its late stages.

Background
The human immune system evolved to detect and respond to antigens, or foreign insus, that the immune system does not mount an immune response. For example, when MHCI is non-presenting, a T cell receptor (TCR) will not bind to MHCI, thus no interaction occurs (see Figure 1.). For a long time, many researchers hypothesized that transformed cells, cancerous cells derived from within normal cells, the host cell to disguise its insult from the immune system. Researchers now believe that in many cases, this hypothesis is false.

Figure 1. No interaction between a normal, untransformed cell and a cytotoxic T cell.

Figure 2. Immune response suppressed by immune suppression pathway.

Figure 3. Immune response enabled by blocking of the immune suppression pathway.

Figure 4. Immune response suppressed by immune suppression pathway, despite immune checkpoint cancer treatment.

The invention of ipilimumab, the first successful immune checkpoint inhibitor, marked the inception of a new era in cancer treatment. Immune checkpoint inhibitors like ipilimumab and nivolumab (anti-PD-L1) block the immune suppression pathway by mimicking the suppressive ligand and binds to either PD-L1 or CTLA-4 (see Figure 3.). While the binding of these antibodies is irreversible, thus allowing the bonded CTL to be uninterrupted as it carries out instructions from the costimulatory pathway. The resulting clonal expansion of CTLs specific to the cancer antigen leads to a robust immune response to the cancer cells. The randomness of which molecules bump into other molecules is a critical component to the success or failure of immune checkpoint cancer treatments. After all, both PD-L1 and CD80/CD86 and their mimicking antibodies bind irreversibly to their respective PD-L1 or CTLA-4. Although several minor factors influence the probability that a protein will meet its ligand, the process is largely random.

Given 1 PD-L1, 1 PD-L1, and 4 anti-PD-L1, what is the probability that the immune suppression pathway will be blocked? What is the probability that the pathway will be active?

PD-L1 may bind to PD-L1 to activate the immune suppression pathway, or it may bind to one of the four anti-PD-L1 ligands to block the pathway.

In an environment with many transformed cells, some are likely to survive. The daughter cells of the survivors do not inherit PD-L1, and are thus vulnerable to the effect of the drug.

Figure 5. Phase III study compares the living proportion treated with ipilimumab plus dacarbazine (blue) and the living proportion treated with ipilimumab plus dacarbazine (yellow), both versus the status quo.

In this hypothesis, PD-L1 and anti-PD-L1 bind to each other, and the PD-L1 activation is blocked. The resulting clonal expansion of CTLs specific to the cancer antigen leads to a robust immune response to the cancer cells. With the randomness of which molecules bump into other molecules, the process is largely random.

Conclusions
Immune checkpoint inhibitors, such as ipilimumab and nivolumab, block the suppression pathway of cancer cell interaction with T cells. This model simulates the proliferation of T cells, which can result in a robust immune response to metastatic melanoma, among other cancers. Immune checkpoint inhibitors lead to produce around a 20% five-year survival rate.

Acknowledgments
Special thanks to Robert Garrity for his knowledge and guidance throughout the creation of this project.

Treatment Information
Many immune checkpoint inhibitors are in clinics and development today. These inhibitors extend the life of terminally ill patient or serve as a safeguard according to removal of cancerous tissues. Ipilimumab and nivolumab are most often used to extend life by treating late stage, metastatic melanoma and lung cancer. In a study, ipilimumab plus dacarbazine (a chemotherapeutic) were found to have a five-year survival rate of 18.2% versus the 8.8% five-year survival rate of placebo plus dacarbazine (see Figure 5.). Nivolumab and other immune checkpoint inhibitors offer similar results for their respective cell types. All approved immune checkpoint inhibitors have around a 20% five-year survival rate. Inhibitor cocktails can sometimes lead to better results at the cost of higher toxicity.

Treatment Mechanism
The invention of ipilimumab, the first successful immune checkpoint inhibitor, marked the inception of a new era in cancer treatment. Immune checkpoint inhibitors like ipilimumab and nivolumab (anti-PD-L1) block the immune suppression pathway by mimicking the suppressive ligand and binds to either PD-L1 or CTLA-4 (see Figure 3.). While the binding of these antibodies is irreversible, thus allowing the bonded CTL to be uninterrupted as it carries out instructions from the costimulatory pathway. The resulting clonal expansion of CTLs specific to the cancer antigen leads to a robust immune response to the cancer cells. The randomness of which molecules bump into other molecules is a critical component to the success or failure of immune checkpoint cancer treatments. After all, both PD-L1 and CD80/CD86 and their mimicking antibodies bind irreversibly to their respective PD-L1 or CTLA-4. Although several minor factors influence the probability that a protein will meet its ligand, the process is largely random.

Given 1 PD-L1, 1 PD-L1, and 4 anti-PD-L1, what is the probability that the immune suppression pathway will be blocked? What is the probability that the pathway will be active?

PD-L1 may bind to PD-L1 to activate the immune suppression pathway, or it may bind to one of the four anti-PD-L1 ligands to block the pathway.

In an environment with many transformed cells, some are likely to survive. The daughter cells of the survivors do not inherit PD-L1, and are thus vulnerable to the effect of the drug.

Figure 5. Phase III study compares the living proportion treated with ipilimumab plus dacarbazine (blue) and the living proportion treated with ipilimumab plus dacarbazine (yellow), both versus the status quo.

In this hypothesis, PD-L1 and anti-PD-L1 bind to each other, and the PD-L1 activation is blocked. The resulting clonal expansion of CTLs specific to the cancer antigen leads to a robust immune response to the cancer cells. With the randomness of which molecules bump into other molecules, the process is largely random.

Conclusions
Immune checkpoint inhibitors, such as ipilimumab and nivolumab, block the suppression pathway of cancer cell interaction with T cells. This model simulates the proliferation of T cells, which can result in a robust immune response to metastatic melanoma, among other cancers. Immune checkpoint inhibitors lead to produce around a 20% five-year survival rate.

Acknowledgments
Special thanks to Robert Garrity for his knowledge and guidance throughout the creation of this project.

Literature Cited


Immune Checkpoints in Cancer Treatment. Cancer Treatment Reviews. 2015;5165.10.


