**The Gut Microbiome: Asset & Liability**

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  Recent studies have shown that a person’s gut microbiome can affect the way they respond to certain cancer immunotherapy drugs. A very effective immunotherapy drug known as a PD-1 inhibitor fights cancer, especially melanoma, by blocking a molecule on T-cells (immune cells) that tumors use to shut the T-cells down (Kaiser). Inhibitors like the PD-1 inhibitor have been very helpful with stopping the progression of different types of cancer like lung, liver, kidney, head, neck, bladder cancer and even Hodgkin lymphoma for years at a time. This drug is beneficial, yet it is only successful in about 25% of patients with certain gut microbiomes. Scientists conducted research on this drug utilizing mice and observing their response to the drug. Antibiotics had a major effect on the mice and patients’ responses to the drug. The mice with different gut microbes did not do well with the PD-1 inhibitor, yet the germ-free mice with no bacteria lingering in the gut responded great to the drug. Patients who were on antibiotics prior to or shortly after taking the immunotherapy drug either relapsed shortly or even died. New studies are currently being done to determine whether manipulating the gut microbiome utilizing fecal transplants or some type of bacterial treatment can help cancer patients respond better to the inhibitor. As of right now, there has been no update on the success of these studies.

**Introduction**

The gut microbiome consists of all of the viruses, bacteria and bugs dwelling in a person’s digestive tract. Microbes within the gut can act as therapeutics. Studies on a patient’s response to immunotherapy drugs seem to rely heavily on the type of gut microbiome a person has. If there is an abundance of good bacteria, the drugs end up being very successful. Patients being on other types of drugs around the same time as taking these immunotherapy drugs have a negative effect on the drug’s impact. The other drugs change the gut microbiome, weaken the immune system and rid the body of needed microbes.

     T cells, known as checkpoint cells help the immune system fight off foreign cells by blocking them from the normal cells ones within. Cancerous cells or tumors often try to utilize these T cells to avoid attack. New drugs like Keytruda, Opdivo, Libtayo, Tecentriq, Bavencio and Imfinzi have been made to target this problem (Mitch). This could have a great effect on cancer patients but there is a fear that the drugs also allow some organs to be attacked. This attack can lead to side effects like itching, nausea, fatigue and even more serious problems. PD-1 is a checkpoint protein found on the T cell; it keeps it from attacking certain cells in the body by binding to a protein found in normal and cancer cells called PD-L1. Sadly, some cancer cells contain a lot of PD-L1, which   help them avoid attack from the immune system. Drugs like the PD-1 inhibitors target the binding of these proteins in order to strengthen the immune system’s response to the cancer cells. Figuring out specifically what is in the gut microbiome that is affecting a patient’s outcome is the key cause of increasing the overall success of these drugs.

**Recent Progress**

Since the PD-1 inhibitor is only successful in about 25% of patients, scientists are trying to find ways to increase this rate of success. In 2015, Immunologist Laurence Zitvogel and his team in France claimed that changing a mouse’s gut microbiome would make the cancerous tumors better respond to checkpoint blockers. Zitvogel’s group analyzed the data of 249 patients with cancer of mainly the lungs, kidney and bladder. About 69 people out of the group had either taken antibiotics right before, during or shortly after starting a PD-1 immunotherapy drug. Most of these patients who had taken antibiotics did not live as long or relapsed shortly after. The antibiotics had disrupted and changed their gut microbiome which made the immunotherapy less successful.

      The team started to look at differences between the patients who did and did not respond well and again used the mice for their studies. For patients that responded well, Zitvogel discovered the presence of *Akkermansia muciniphila*, which helps protect the gut’s mucus lining from diabetes, obesity, etc. The team gave mice that were germ-free and had no gut bacteria fecal transplants from mice that responded well to the PD-1 inhibitors. They concluded that the mice that didn’t respond well could be fed the *Akkermansia muciniphila* in order to become responders. Also, avoiding antibiotics while taking the inhibitors could increase the success from 25% to 40%. Zitvogel’s team also discovered that an immune-signaling molecule called IL12 could help the T-cells. These molecules are released into the gut microbiome in response to the *A. muciniphila*. Further reports on the team’s studies have not been posted, yet a similar team ran tests similar to Zitvogel’s.

      The checkpoint inhibitors strengthen the immune system and allow them it to unleash and attack cancerous tumors, yet people are still not benefiting as they should be. In this study by Immunologist Thomas Gajewski and his colleagues, also utilizing mice, agreed that some people do not have the right mixture of bacteria inside of their gut microbiome. Their studies were the first to look one’s intestines or gut microbiome to the potency or effectiveness of checkpoint inhibitors. Since the tumor cells stimulate the T cells to avoid attack, past researches thought it was linked to a mutation in the person’s genomes. These new studies were hopeful because changing the gut microbiome would be way easier than figuring out how to change a genome. The checkpoint inhibitors can give patient years to live, while shrinking their tumor.

     Gajewski’s team implanted tumors in mice that lacked intestinal bacteria in response to Zitvogel’s observation of a side effect from the PD-1 inhibitors that trigger inflammation of the large intestine. When Gajewski’s team tracked the mice’s response to the drug, it was unsuccessful in the ones that lacked intestinal bacteria. To determine whether certain bacteria were responsible, the team transferred them microbes of *Burkholderia* and *Bacteroides* genera or fed them *Bacteroides-*rich feces from some patients. In both cases, the microbes greatly affected the mice’s response to the checkpoint inhibitors (Cani).

**Discussion**

The research from Laurence Zitvogel and his team are valid. Although they were able to pinpoint certain bacteria that helped strengthen the mice’s immune system and overall gut microbiome, there is still no definite method of making the PD-1 inhibitors successful in 100% of patients. Gajewski and his team confirmed Zitvogel’s studies and confirmed that the intestines inside of the gut also determined the strength of the immunotherapy drugs. There is still not a solution to making sure everyone has the certain gut bacteria needed in order to stop the cancer cells from tricking the T cells to avoid attack. The immunotherapy drugs still have side effects that are greatly harming/affecting patient’s outcome. More studies need to be done outside of mice and in patients to get more details on the side effects in actual humans, in order to come up with a resolution to pinpoint how to rid of them.

     Overall, the results of these studies addressed not only the significance of the gut microbiome in the success of immunotherapy drugs, but also some vital problems the immune system faces when coming in contact with the drugs. The cancerous cells are powerful, but if the side effects can get handled and if scientists find a way to make sure patients have the bacteria needed in their gut microbiome during treatment, these inhibitors will change many lives. As of right now, the inhibitors are beneficial, yet healthy organs and cells are still being attacked, keeping the success rate fairly low.

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