Using the Body's Own Natural Defenses to Better Fight Cancer

By Ian Sturgill

Cancer is the second leading cause of death in the United States -- second only to heart disease -- according to the Centers for Disease Control and Prevention.[1] Although certain risk factors like diet, lifestyle, and family history may increase the likelihood of developing a form of cancer, anyone can get cancer at any point in life. This makes receiving a cancer diagnosis an unpredictable yet life-altering event. Further, the effectiveness of cancer treatments depends on a wide range of factors, including the particular type of cancer, the stage of disease progression at the time of treatment, and the variability in individual patient responses. While some types of cancer are easily treatable if detected early, others like glioblastoma – a type of brain cancer – do not respond well to conventional therapies. As a result, many research labs, including the one that I work in, are turning towards new treatments that have the potential to modify an individual's own immune system to better fight off cancer.

This is where cancer immunotherapy comes in. Cancer immunotherapy is a rapidly growing field of medical research that is changing the landscape of cancer treatment, promising to ultimately be capable of healing even those who suffer from what are thought to be terminal diseases. This type of immunotherapy is centered on the concept that the immune system is the single greatest tool that can be used to identify and destroy cancer cells because it already participates in anti-cancer activities. Similarly to how cells of the immune system can stop an infection by killing bacteria, they can also kill cancer cells through a process termed immunosurveillance. This is a continuous process in which immune cells recognize specific components on cancer cells that are distinct from normal, healthy cells. These differences allow for targeted killing of cancer cells with less likelihood of also killing healthy cells. In contrast, chemotherapy and radiotherapy—among the most commonly used conventional therapies—can be very harmful to normal cells and can result in extreme toxicity due to DNA damage and resultant cell death. Depending on the strength and location of the toxic side effects, the patient could experience very serious and even life-threatening complications from the treatment itself.

It should come as no surprise then that our lab is one of many around the world that are excited about the promises of immunotherapy. One of our research projects involves investigating the therapeutic potential of manipulating the interactions between immune cells and a subset of particularly resilient cancer cells called cancer stem cells (CSCs). We can do this by using a drug that causes cancer cells including CSCs to express a larger amount of proteins that interact with immune cells, thereby increasing the likelihood that the immune cells can recognize and kill them. What makes CSCs such a high-priority target is that they are significantly more

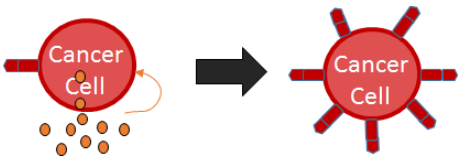

Figure 1. A small molecule drug (yellow) enters a cancer cell and causes it to express more proteins on its surface that will interact with immune cells.

resistant to both chemotherapy and radiotherapy, meaning that they are primarily responsible for cancer relapses. While those therapies tend to destroy the rest of the cancer, the CSCs remain there relatively unharmed. CSCs are more resistant to these therapies because they are generally in a slower-growing state than the other cancer cells. It is the faster-growing cells that are most susceptible to therapies that work by causing damage to DNA because the effects of DNA damage are most potent during cell replication. CSCs are also thought to be responsible for metastasis, which is the movement of cancer to new locations in the body and which makes treatment far more challenging. Metastasis can also create more negative health effects for a patient. For example, metastases to the lungs can eventually make breathing more difficult. Due to these characteristics, CSCs are an attractive target for any new therapy that seeks to have long-term efficacy.

Now we can look at the other side of the interaction. The immune cells that we use to target CSCs are called natural killer (NK) cells. Our strategy is to get these cells by processing blood from a patient and to then grow and activate those cells outside of the patient's body. Activated NK cells can initiate a process of cell death when they interact with certain specific proteins on the surface of target cells. In order to enhance this cell-cell interaction, we stimulate cancer cells with a small molecule drug called bortezomib, which causes the cells to express stress signals that the NK cells will recognize. At this point, the cancer cells are primed to interact with NK cells and we can add the NK cells to the system, leading to the targeted death of the cancer cells, including the CSCs. This combined therapeutic approach with bortezomib and NK cells has seen relative success so far in mice, and we are optimistic about the future of this and other cancer immunotherapies.

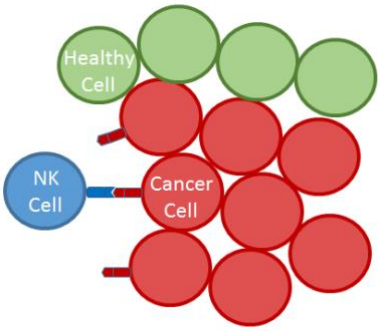

Figure 2. An NK cell (blue) comes into contact with a cancer cell (red) that expresses a particular protein on its surface. The NK cell can then destroy that cancer cell. Healthy cells (green) are less likely to be affected.

Reference

1. https://www.cdc.gov/nchs/fastats/deaths.htm