Helping the Fight from Within: Immunotherapy in Soft Tissue Sarcoma

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The immune system is the body's natural defense mechanism against infection and disease. Cancers including soft tissue sarcoma, arise from an abnormal cell within the body. The immune system can potentially recognize tumor cells as abnormal and effectively target and eliminate cancer.

Immunotherapy is a method of treatment which uses various components of the immune system to fight against disease. One of the advantages of using immunotherapy in cancer is the fact that the immune system is inherently designed to attack only specific cells, which theoretically reduces the chances of "collateral damage" to normal cells, minimizing side effects. The immune system also has memory and can re-attack if the eliminated targets return later on (e.g. recurrence). There is even evidence that the immune system can naturally adapt to changes in tumor cells!

In the last few decades, the scientific and medical community has learned much about the interaction between the immune system and tumor cells. For a number of cancers such as melanoma and lung cancer, immunotherapy is quickly becoming standard of care treatment. Although historically, one of the earliest attempts at cancer immunotherapy was carried out in sarcoma patients (by Dr. William Cooley, 1890s), we have only recently started to re-explore the use of the immune system to treat sarcoma. This article will cover the basic principles of the immune response against cancer, the major strategies for cancer immunotherapy, and then focus specifically on immunotherapy in soft tissue sarcoma.

The Immune Response: "An army against the enemy"

If tumor cells are the enemy, the immune system is a natural army of cells and weaponry that are available to fight against this enemy. The immune army indeed has different types of soldiers that have distinct roles. At the frontline, there are cells that form the innate immune system (e.g. natural killer or NK cells), which nonspecifically attack "foreign" cells that lack the appropriate signals indicating "self." In contrast, the adaptive

immune system recognizes a specific enemy based on a unique identifier on the surface of the cell, made up of proteins or peptides (parts of proteins), known as an antigen. Antigen can be thought of as an identifiable piece of clothing on a cell. Antigen is often something abnormal (e.g. mutated), different and not typically found on any other cell in the body. Cancer cells often have abnormal antigen on their surface. Both innate and adaptive immune responses are important in the elimination of tumor cells; however the unique specificity of the adaptive immune system is particularly advantageous for immunotherapy.

At the center of the adaptive immune response in cancer is the dendritic cell or DC **(see Figure)**. DCs patrol the tissue environment and can pick up antigen from tumor cells. DCs then "educate" other immune cells types such as B cells and T cells to help them recognize tumor antigen. This process typically occurs within the regional lymph nodes, which are analogous to immune training centers. B cells, when educated, transform into plasma cells which produce antigen-specific antibodies, similar to homing missiles. T cells are foot soldiers which directly attack tumor cells that display the targeted antigen. There are two major classes of T cells – CD4 and CD8. CD8 "cytotoxic" T cells come in direct contact with tumor cells and in fact, have molecular weapons to kill tumor cells, such as perforin and granzyme. CD4 "helper" T cells mostly provide support (… supplies and food) for CD8 T cells and the other soldiers in the adaptive immune response. Subgroups of both B and T cells that are educated against the enemy remain after the attack, even after the enemy is gone, to become long-term memory cells.

Unfortunately, tumor cells also have their own mechanisms to block and even undermine the immune response. Tumor cells might no longer display antigen ("change clothing") and at that point become unrecognizable to the adaptive immune cells. Tumor cells can also directly secrete products (e.g. TGF-beta, IL-10) that can slow down the oncoming immune soldiers. There are even traitors that exist in this fight, immune cells that are recruited over by the tumor cells. These pro-tumor immune cells, including regulatory T cells, tumor associated macrophages, and myeloid derived suppressor cells **(Figure)**, have the capability to not only slow down but can even kill the anti-tumor immune cells. Finally, despite any original intentions to attack tumor cells, through various mechanisms, the adaptive immune response can "surrender" and quickly convert to become tolerant of the tumor.

Immunotherapy: "Helping the fight from within"

If chemotherapy attempts to directly attack the tumor enemy, immunotherapy supports and/or pushes the immune army to do the fighting. The major recent strategies for

immunotherapy in cancer are 1) vaccines, 2) adoptive cell therapy, and 3) immune checkpoint blockade. All of these strategies focus on the antigen-driven adaptive immune response. It is important to keep in mind that a variety of other immunotherapeutic strategies exist and many more are in active development. Another consideration is that immunotherapy can potentially still be combined with the traditional treatments for cancer: surgery, radiation therapy, and chemotherapy. For example, surgery can remove the bulk of the visible tumor and in theory, immunotherapy can be used after surgery to clean up any remaining enemy cells left behind. Radiation therapy can help to kill the enemy cells, release tumor antigen and help initiate an adaptive immune response.

Vaccines introduce the immune cells to antigen directly. The concept is similar to vaccines given for other diseases, such as the flu, or with childhood immunizations. With cancer vaccines, either a specific antigen can be introduced as the target – a red scarf (e.g. NY-ESO-1); or it can be very broad – all of the clothing worn by the enemy (e.g. autologous whole tumor lysate). The vaccine-introduced antigens are then picked up by DCs to educate B- and T cells, initiating the adaptive immune response. Frequently additional boosts are given along with vaccines to help support this induced immune response (e.g. GM-CSF, TLR agonist). In some vaccine strategies, modified DCs, already focused on recognizing specific tumor cells – ones that have been to specialized training camps, in the laboratory - are given to the patient.

Adoptive cell therapy is a complex process of essentially bringing in a separate and often modified immune army to help fight tumor cells. Adoptive cell therapy using T cells was developed for the treatment of metastatic melanoma by Dr. Steven Rosenberg at the US National Institutes of Health. Immune cells that are already fighting within tumors removed by surgery are isolated, enriched and expanded in large numbers in the laboratory before being reintroduced back into the patient. The more modern variations of this immunotherapy strategy (e.g. CAR T cells) modify and optimize the T cell receptor, the instrument used for recognition by the T cell for antigen recognition, before reintroducing these immune soldiers back into the patient.

Immune checkpoint blockade is simple in concept and works by revitalizing the exhausted T cell foot soldiers that are present and already fighting within the tumor. Once educated to antigen and ready to attack, over time certain signals (e.g. CTLA4, PD-1) on the T cell naturally appear which causes the T cell to stop the attack. This immunotherapy strategy removes these stop signals, without any direct impact on the tumor cells themselves. The identity of the actual tumor antigens being targeted by the T cells is not

known per se and in fact, immune checkpoint blockade likely revitalizes all exhausted, fighting T cells which collectively represent a multitude of antigens.

The Potential for Immunotherapy in Soft Tissue Sarcoma

Soft tissue sarcoma is unique among cancers in that there is tremendous diversity and heterogeneity of subtypes. In other words, from the standpoint of the immune army, there are many types of enemies to attack. Research and development of immunotherapy as a treatment for sarcoma is therefore challenging, especially given the overall rarity of this disease. Some sarcomas may be easy enemies to defeat by the immune army, others are much harder. To date, there is no single, dominant immunotherapeutic strategy that has proven to be particularly effective; however there is an abundance of ongoing research and some promising recent data.

There is certainly strong rationale to explore immunotherapy in sarcoma. Genetic mutations in tumor cells result in abnormal proteins/peptides that are ideal antigens to target. Although the frequency of genetic mutations in sarcoma is not as high as in other cancers (e.g. melanoma), a modest percentage of subtypes do have them, some (e.g. leiomyosarcoma, radiation induced sarcoma) more frequently than others. Genetically, many subtypes of sarcoma have characteristic translocations which are shifts and recombinations of portions of chromosomes. These translocations can lead to abnormal proteins/peptides in the tumor cells that could also potentially serve as targetable antigens. In myxoid liposarcoma and synovial sarcoma specifically, tumor cells have been shown to display NY-ESO-1, which is a particularly suitable antigen target for immunotherapy. Regardless of genetic changes, several sarcoma subtypes clearly have immune cells already naturally fighting within the tumor. A prominent example of this comes from the work done by our group (Dr. William Tseng) in well differentiated / dedifferentiated liposarcoma. In these tumors, the immune system has even established small training camps for the adaptive immune response, similar to lymph nodes! The presence of natural, tumor-infiltrating immune cells suggests that strategies such as immune checkpoint blockade may be effective. In fact, our work showed that the majority of the foot soldiers (CD8 T cells) found in liposarcoma do express PD-1 and are likely “exhausted.”

Recently, the Sarcoma Alliance for Research through Collaboration (SARC) and Merck sponsored the first clinical trial of immune checkpoint blockade (anti-PD-1 therapy) in patients with advanced and metastatic sarcoma. The results of this multicenter trial (SARC028) were recently reported at the 2016 Annual Meeting of the American Society of Clinical Oncology. In the soft tissue sarcoma group, although the numbers of enrolled

patients in each subtype was relatively small, no tumor response (shrinkage) was seen in leiomyosarcoma. In contrast, 44% of patients with undifferentiated pleomorphic sarcoma and 22% of those with liposarcoma demonstrated significant tumor response. Further studies are needed. A number of other clinical trials for immune checkpoint blockade, as well as other immunotherapeutic strategies in sarcoma are ongoing.

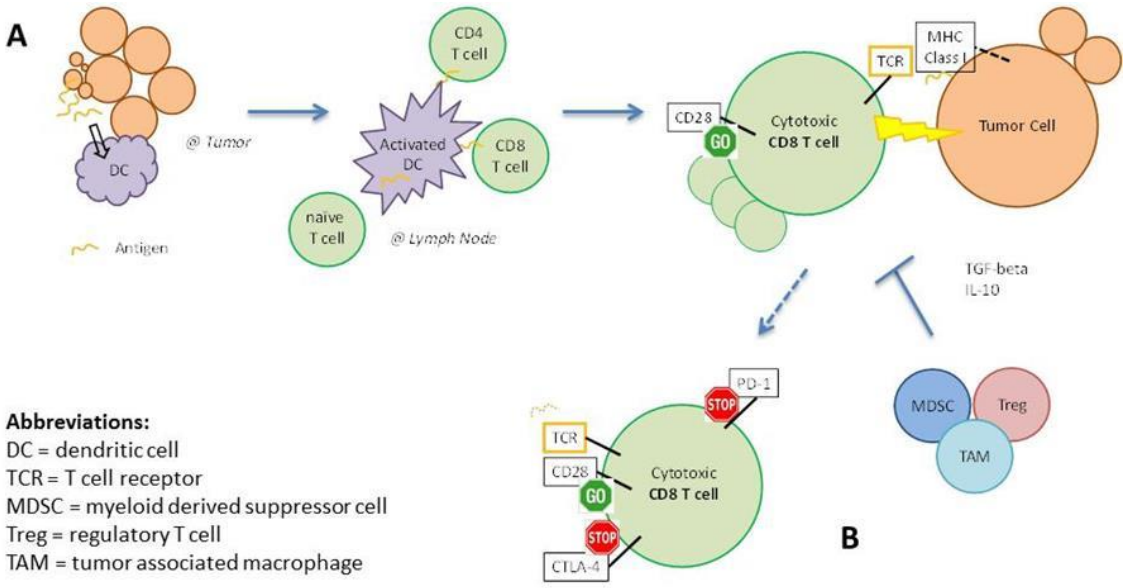
Conclusion

The immune system is a natural army within the body that has the potential to effectively recognize and eliminate the enemy, cancer. In comparison to the traditional treatments available (surgery, radiation therapy, chemotherapy), immunotherapy offers a unique approach to “help the fight within.” Several major strategies for immunotherapy have recently been explored in cancer and have proven to be effective. Further research is clearly needed – not only to study the natural immune response against tumor cells but also the tumor’s own strategies to undermine the immune response. Overall, there is strong rationale and potential for immunotherapy in soft tissue sarcoma. Given the heterogeneity of subtypes, it is very likely that for an immunotherapy strategy (“plan of attack”) to be effective, it will have to be tailored to each distinct sarcoma subtype enemy.

References

Tseng WW, Somaiah N, Engleman EG. Potential for Immunotherapy in Soft Tissue Sarcoma. Hum Vaccin Immunother 2014;10(11):3117-24. PMID:25625925

Figure: (A) Schematic of the adaptive immune response in cancer, initiated by dendritic cell presentation of tumor antigen. Not shown are B cells which, similar to T cells, are educated to target tumor antigen. (B) Mechanisms exist to block and even undermine the immune response.



Dr. William Tseng is a busy surgical oncologist with a specific focus in adult soft tissue sarcoma. He was recruited from MD Anderson Cancer Center to develop the Sarcoma Program at the University of Southern California, Keck School of Medicine. Dr. Tseng provides care for patients with sarcomas of the extremity, trunk and retroperitoneum. He strongly supports a multidisciplinary approach to treatment. Dr. Tseng's research focuses on the immune response in sarcoma and specifically, in well differentiated / dedifferentiated liposarcoma. The goal of his research is to develop new treatment approaches to this disease using immunotherapy. Dr. Tseng is originally from the Los Angeles area and spends his free time with his wife and their Jack Russell terrier / Chihuahua mix.