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Modulation of Immune System for More Effective Attacks against Pathogens

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Changsha, Hunan, China - The idea of "driving" the immune system to attack specific diseases is not a new concept, yet for the past century desirable results have remained elusive. Fortunately, a modern understanding of the way the immune system functions along with the progress made in the development of aptamers has allowed for the realization of much more successful treatment.

Just like all systems in the body, the immune system is constantly conversing. It is stimulated through various signals but also has a series of checks in place to keep offensive attacks from causing significant harm to itself (autoimmunity). In order to harness the power of the immune system effectively and safely, one must understand these stimuli.

The four broadest strategies for harnessing the power of the immune system are: stimulation of immune system and guided attacks against pathogen, inhibition of immunosuppressors, inhibition of costimulators, and coupled immunotherapy with current first-line treatments.
Depending on the disease, various strategies will have more success than others, with some cases needing a combination of strategies. Below, "guided attack" and "inhibition of immunosuppressors" strategies will be broadly discussed.

Guided Attacks

The immune system is often very effective at keeping pathogens at bay. However, it is an evolving game where pathogens evolve to try to outsmart the immune system while the immune system constantly learns to adapt.

In this game of tit-for-tat, our best ally (our immune system) sometimes could use outside help. Veraptus is aiding the immune system by stimulating and directing the immune system to attack pathogens or cancer cells.

After fighting off a new infection, the immune system makes a memory of the infection so it can respond more quickly the next time. However, when new infections are met, the immune system needs time to react and recognize the infection as a threat. These infections can wreak havoc while the immune system learns to adapt. For really aggressive pathogens (i.e. MRSA or anthrax) this adaptive time required may not be fast enough, allowing the pathogen to become a lethal force against the host.

When time is of the essence, aptamer-linked immunostimulators can be used in order to tag these unknown pathogens. Aptamers are single strands of nucleic acid that can be made target specific to an array of targets. The immunostimulators that are attached to the aptamer are innately recognized by the human immune system. The immune system immediately recognizes these molecules as "tasty treats." Once the aptamer binds to the pathogen to which it has been programmed, the immune system goes into action, eating the "tasty treat" and subsequently the pathogen as well. This approach can be used to attack cancer, bacterial infections, parasitic infections, and viruses.

Modulating Immunosuppresors

In addition to stimulating the correct pathways to create the proper offense against pathogens, it has been shown clinically useful to also inhibit immune-suppressors that can suppress the aggressiveness of an attack on pathogens or cancer cells. These checkpoints are necessary in order to manage the duration and amplitude of an attack, as well as to insure self-tolerance. However, cancer cells can "hijack" some of these checkpoints, giving protection against tumor-specific T cells and blunting the attack by the immune system. This allows for the cancer cells to divide unchecked or to be destroyed by the immune system at a rate that is not aggressive enough to ablate the cancer cells' growth. By targeting these checkpoints, the brakes on the immune system can be released systematically in order to ramp up the immune system to more effectively attack the pathogen. An immune system that is able to operate without these brakes present have broader and more robust attacks.

Recent clinical trials have shown that inhibiting such checkpoints can be an effective strategy in the fight against cancer. Many researchers and doctors are quite optimistic about the near future role of immuno-modulators in the treatment of cancer. Recently, two targets (CTLA-4 and PD-1) have been of the most interest to researchers and doctors due to the amount of positive clinical data that has been collected. Both of these ultimately deliver a negative signal for the immune system when activated. Doctors have been targeting these checkpoints in the treatment of melanoma and have achieved durable responses.

Preclinical research shows there are other targets of interest that can be beneficial in the management of cancer as well as targets we can monitor in order to better diagnose patients or create more effective treatment. For instance, relatively higher proportions of intratumoral T regulatory cells (Tregs) to tumor-infiltrating lymphocytes (TILs) have been linked to a higher risk of recurrence of cancer. (Shimizu, 2010) These Tregs are immune-suppessors that secrete high levels of TGF-β and express CTLA-4. (Woo, 2002) Proper inhibition of such targets can significantly weaken the cancer cells' ability to evade the immune system.

Outlook

Harnessing the power of the immune system to thwart infections and diseases is still in its nascency. Yet, initial results suggest this to be an effective strategy in the next generation treatment of cancer. Also, with diminishing effectiveness for antibacterials/microbials, novel treatments need to be explored. Through a cocktail regiment of inhibiting certain checkpoints while stimulating and directing the immune system towards specific bacteria, viruses, and cancer, the most burdensome diseases and pathogens can be more effectively managed. In order to be most effective, immuno-guiding drugs coupled with traditional first line therapies (i.e. radiation) should be incorporated into current clinical trials.

References

Shimizu, K. N. (2010). Tumor-infiltrating Foxp3 regulatory T cells are correlated with cyclooxygenase-2 expression and are associated with recurrence in resected non-small cell lung cancer. *J. Thorac. Oncol.*, 5, 585–590.

Woo, E. Y. (2002). Cutting edge: regulatory T cells from lung cancer patients directly inhibit autologous T cell proliferation. *J. Immunol.*, 4272-4276.