An Immunological Approach to Remedying Cancer

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Cancer often thrives and evades our immune system, bypassing T lymphocyte mediated death. The immune escape mechanism of cancers often involves suppression and antigen blocking systems. A recent discovery of the PD-1/PDL-1 pathway has aided in combination therapy in response to certain cancers. This specific pathway acts as a regulator for T-cell survival and reduces the efficacy of T-cell mediated death towards cancerous tumors. In contrast, an approach towards downregulating this pathway can yield an increased T-cell response. To further increase the amount of T-cells we are able to upregulate and use, we can look upstream and somehow modify the immune process. From recognition and proliferation to activating and deactivating specific genes, we can try and manipulate how we respond to a threat. Dendritic cells are often the look to this due to their role in antigen detection and is a promising route in the creation of "vaccinations" against cancer. Though this field is fairly new in regards to its application to the ever growing diseases that is cancer, there is room for discovery in the detection and response area between the host immune system and cancers.

Introduction

The human body is capable of creating and harboring cancer, so why not focus on immunological approach? When we get sick, the first response is from our immune system. Cells in our body are able to detect the foreign pathogen or entity using many factors, one of which is an antigen. The basics of the immune response consist of Antigen recognition, often by antigen presenting cells like dendritic cells, cellular response by T lymphocytes and B lymphocytes, and then often cell mediated death. In the response to foreign antigens, immune cells are constantly replicated and being tried against the foreign antigen which in this case are tumor antigens. This form of cellular replication is often regulated and consists of many checkpoint areas in order to prevent uncontrolled replication. Cancerous tumor cells often evade the killing stage of our immune system by initiating negative feedback loops which involve inhibitory cytokines, or by presenting ligands that can bind to inhibitory receptors on immune cells, one of which is the PD-1/PDL-1 (programmed death-1) pathway which is upregulated when T-cells become exhausted (Seidel). Modification to host immune cells can allow us to not only avoid tumor cell evasion and successfully eliminate it but open the field up to way more possibilities not limited to cancer immunology.

Recent Progress

Cancer research on the immunological side has shown that modifications of our immune cells can allow for great responses to tumor cells. One such research by John et al. aims to modify T-cells with chimeric antigen receptors (CAR) to determine if it affects the antitumor efficacy. Researchers in this experiment used antigen-specific antigen receptors to transduce their T-cells with after activation. These modified T-cells were then cocultured with tumor cell lines

alongside anti-PD-1 antibodies. The resulting T-cells were then used in mice. The T-cell PD-1 receptors, and various granzymes and cytokines were stained and recorded using flow cytometry in order to quantify the results. Findings from John et al. yielded that the combined efforts of the anti-PD-1 antibodies and CAR T-cells increased antitumor properties, with the antibodies allowing T-cell proliferation to be increased while the enhanced T-cells are able to more effectively target tumor cells. Although the antitumor properties were increased post-combination therapy, the experimenters were able to not able to correlate the localization of the modified T-cells at the tumor site with the increased function and antitumor properties of these cells. The experimenters also tested whether these modified T-cells would affect the host immune system since they were modified outside of the body and may lead to an autoimmune response. The results of this yielded that there was no autoimmunity or tissue damage within the experimented mice. Data was taken from mammary and cerebral tissues due to the tumor cell line HER-2 expressing similar antigens to these tissues (John et al.). This study supports the conclusion that combination immunotherapy using modified CAR T-Cells with PD-1 blockers can enhance its effects on cancerous tumors, which is major. It is important however to note that John et al. stated CAR T-cell therapy alone is not enough to tackle any well-established tumor, but rather in combination with anti-PD-1immunotherapy, allows for an enhanced survival rate.

Another future application that immunology has on the cancer treatment world includes the possibility of vaccines being a method of transportation for cancer therapies or treatments. Dendritic cell-based vaccines aim to take advantage of the immune system's response pathway where when a foreign antigen or pathogen is detected, dendritic cells are able to catch and use antigens in order to stimulate a T-cell and immune response. In this study, Bulgarelli et al. aims to study the efficacy of dendritic cell based vaccines against metastatic melanoma tumors. These vaccines were produced using autologous tumor lysates or homogenates obtained from patient tumor lesions in preparation. Sixteen patients were intradermally injected every 2 weeks for 4 cycles or until any change was noticed or lysate was gone. Delayed hypersensitivity tests were used to measure responsiveness post vaccination. Biopsies were taken post vaccination in order to gather data. Bulgarelli et al. concluded that 15 out of 16 patients were immunoresponsive and that there was an increase in PDL-1 upon tumor cells that correlates with the increased amount CD8 cytotoxic T-cells within the tumor tissue. granzyme B, a major effector molecule for CD8 T-cells (Bulgarelli et al.) was stained and the experimenters concluded that PDL-1 interfered with the activation of cytotoxic CD8 T-cells. Analysis of pre and post vaccination biopsies yielded the conclusion that dendritic cell vaccination in this study does increase the number of intratumoral T-cells, but not in a significant way as a whole. However, when the data was analyzed based on previous tumor treatments, those who have previously failed immunotherapy treatments did not have a significant change in CD8 T-cells within the tumor pre and post vaccination. Bulgarelli et al. hypothesize that the vaccine effects may have been hindered by the immune escape mechanisms that led to previous immunotherapy failures.

Discussion

The result from these two studies provide a strong and foundational start for future advances in immunotherapy, specifically as a response to cancer. The approaches Bulgarelli et al. and John et al. have taken with their experiments really tackle the collection of diseases that is cancer one step at a time, from the possible idea of a vaccine towards tumors, to the unique escape mechanisms that cancer has against our immune system. In response to our bodies launching an immune attack on the tumors, these cancerous

cells have developed responses to dampen our response. The results from Bulgarelli et al. showcases that a vaccine based off the detection and presentation mechanism in the host's body could increase a response against tumors, but like previously stated. This response is dampened by the tumor itself the more chronic the response is. This leads to the idea of modified response cells such as the CAR T-cells formed and used by John et al. within their study. The CAR T-cells yielded a significant antitumor response towards tumor cell lines as well as increasing the survival rate of mice. Although localization at the tumor site was not concluded in this experiment, this opens up room for development by others. Similar to this study, Bulgarelli et al. hypothesized that previous immunotherapies are often evaded by the tumor cells, and the same could happen to both of these studies, which is shown to a degree. Once again, both of these studies provide a solid footing for immunotherapy and immune response to cancer, but there is still much to be found. One approach for the future should be the continued exploration of immune evasion techniques these cancer tumor cells use in order to prevent being targeting or killed. The main issue that experimenters would have to face in this field would have to be all of the various ways that evasion can occur, not only receptor interactions, but cytokine, phage, detector, and cytotoxic interactions.

Since the nature of cancer is ever changing, there must be a way we can follow these changes and adapt as they happen. The idea of somehow harnessing the mutation strategies that our body's B-cells use to increase antibody affinity could also be an interesting farfetched approach that parallels cancer's mutational properties. There is also the issue of ethics, safety, and fear when we develop this type of technology. When talking about the modification and mutation of host cells, ethics and safety are of utmost importance due to the implications that these products can have on the population they will be used on. Many of which were talked about in Burgarelli et al. and John et al. which mentions the safety of dendritic cell vaccines and the non-autoimmunity inducing properties of CAR T-cells in mice respectively. The idea of fear should also be mentioned, mainly due to the fact that not everyone is in agreeance with the use of vaccines let alone ones that involve modified cells that are allowed to proliferate within their body. There are lots of social and economic issues that arise from this research like cost and efficacy that need to be addressed alongside the actual mechanisms of the treatment itself. There are plenty of roadblocks that are preventing the control and remedy of cancer currently, but hopefully in the near future, there will be more breakthroughs such as the studies above and allow our population to overcome the complication that is cancer.

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