Immune System Boot Camp: Training Your Body Against Cancer

Abstract

In this review paper we will be discussing the feasibility of using your immune system to fight off cancer growth; this will be explored through multiple avenues, some of these method's being from entirely the host, and some of them being influenced by pathogenic activity. While there are different avenues of the training, the part of the system that is being targeted is constantly the innate system, which in the past was thought to not have memory a as the adaptive immune system does. This was proven to be false, as in recent years the innate system has been able to undergo metabolic and epigenetic rewriting, essentially training them. Hence, the term of trained immunity was coined.[1] The prospect of the topic at hand is monumental, at this point and time, we have no reliable and surefire way of fighting cancer, and we still don't. However, if, in the future, 20 or 30 years down the line, the key to beating cancer was already in our bodies and ready to go, it would be the medical advancement of the century.

Introduction

In recent years the primary approach to treating cancers with immunotherapy has been by targeting the adaptive immune response, due to how the tumor hijacks and takes over its local environment changing genetic content to continue unlimited proliferation.[2] Due to this, it would be a good course of action to try and reverse this genetic change in the system of a host; Kalafati, L et al. worked with the bone marrow cells of lab mice and used the concept of trained immunity with β-Glucan to exhibit anti-tumor activity in the mice, which were injected with B16-F10 melanoma cells.[2] They verified that the adaptive immune system was not a factor in the interaction of β-Glucan by removing those cells from the tested mice. They did acknowledge, though, that they were unable to determine whether Reactive Oxygen Species (ROS) were integral to the training of the production of anti-tumor neutrophils and other granulocytes; they were further unable to differentiate whether type one interferon signaling was involved in the ROS upregulation for the trained neutrophils.[2] The team wants to further research these unresolved mysteries in future studies.

Other studies led by Priem, B et al. focused in also on the trained immunity of tumor suppression but incorporated nanobiologics to do so. Nanobiologics, as described by their team, is the use of nanomaterials that are being changed from natural carrier molecules such as cholesterol and phospholipids. They coupled these with checkpoint inhibitor drugs, which induce or restore the ability of a T cell's ability to produce an effective anti-tumor response, by removing the cell's limiters, or the brakes for the anti-tumor properties.[1] The findings of the team had a positive correlation of bone marrow-avid nanobiologics that suppressed tumor growth and improved the immune system's responsiveness towards checkpoint blockade therapy. Similar to this study and many others, there were limitations, primarily the team was unable to determine the long-term strength of this treatment against the melanomas. And in terms of future applications, the team plans to invest more time and research into unraveling

the durability of this treatment, although it works in the short term, they are unsure if it works in the long term.

Recent Progress

Moving forwards to the more present day we will now be looking into a quite recent publication by Wang, Tao et. al, within this study his team showed an outsourcing of training the body to a pathogen, specifically a quite common one, Influenza A(IAV). Typically scientists have stuck to substances that are found in the body or could be produced synthetically that still have an organic function, Wang and his team decided instead to explore the immunity conference of lung cancer as a result of prior infection of Influenza A in the lungs of a host.[3] They found that injecting the mice with a sublethal dose of IAV which resulted in immune response that caused the mice to recover, which was expected. For the next part of the experiment after 30 days since infection, they were then injected with luciferase-expressing B16 melanoma cells, to induce tumor growth within the lungs. To measure the effectiveness the team had a control group of mice that were uninfected with IAV prior to cancer inoculation, they found that the mice that were prior infected with IAV had reduced tumor signaling in the lung area, and much less visible tumor nodules in the lobes of the lung.[3] To verify that the lack of growth was due to the infection and not the cells not being incorporated into the lungs, they quantified the tumor cells in the lungs at 30 minutes and 24 hours after injection, which showed that the number of cells had comparable early counts between the two groups. Their idea of limited immunity also comes from the phenotype monitoring after the infection, they found that the same anti-tumor phenotype was present at the 60 day and 120 day mark after the initial IAV infection.

Furthermore, to prove like the other studies that this was truly trained immunity and not a subset or combination of adaptive immunity aiding this process, they drained in vivo mice of their T cells, CD4 and CD8 and found that the tumor burden or the frequency of the growths was the same as the prior examined IAV mice. They next reran this testing if the trained immunity is dependent on natural killer cells or interferon-γ(IFNγ). During this they found that removing the natural killer cells didn't have an effect on the IAV mice and their tumor burden, but removing the IFNγ resulted in an increased tumor burden within the IAV mice. Part of this process was testing the efficacy of training in Alveolar Macrophages (AM) in the mice. They then went to inspect human AMs and compare the similarities in the genetic makeup and function. They found that a co-expression of characteristic genes: *PPARG* and *SERPINA1*. This was among other similar expressions of trained immunity that the IAV mice would show after treatment.[3] *The* team hopes to continue this research and that it fosters further investigation into the information learned from the study.

Discussion

While none of these studies have cured cancer and it's still a very prevalent disease that affects so many people globally, every time we make a new discovery on a new way to look into combatting cancer, that's a massive win in the arms race that is cancer development and treatment development. In the first two articles discussed the methodology of treatment was

more based on treatments using biomolecules some of which are organically produced such as the carbohydrates and lipids, and some that need to be obtained from other sources, like the β-Glucan injection. If further explored this is another of the possibilities that could lead to a potential future where we may have to take something akin to an antibiotic to remove cancerous growths. Granted this is probably not how that would come about, it would more than likely be a bit more complicated to produce and obtain. However regardless of that, an overarching theme between all of these studies was that aside from the cancer part, the mice didn't have ill effects from the treatments they were being given, the only thing that was causing them harm, was the cancer. The biggest prospect that these advancements have, would be a move away from chemotherapy and the negative side effect that are associated with the treatment, this would result in a much healthier way to treat someone suffering from cancer than by harming the body with toxic chemicals.

The other methodology that was discussed, the IAV infected mice, are a much more interesting topic, which does raise questions. Specifically, it is mentioned that the mice obtained a sub-lethal dose of the IAV, so it does lead to the question needing to be asked, did the mice need to be given something that barely doesn't kill them to confer this immune response? The hopeful answer would be no, and that similar to a vaccine it would be possible to take the training process of the virus, and make it into a minor reaction that would confer that same limited immunity. Another question that needs to be asked, is that while it had limited effect on induced cancer, and the phenotype was still present after one hundred and twenty days, if there was simply a singular cancer cell that was beginning to form, assuming that the phenotype is a permanent change, would someone never get lung cancer from this knowledge? It's another interesting future to think of where we may receive vaccines for cancers. Due to the recency of this publication, it had time to circulate and be checked for accuracy by others rerunning the experiment. Still, the initial findings seem to be adding to the avenues for types of oncolytic virus therapy.

References

1. Priem, B. et al. Trained immunity-promoting nanobiologic therapy suppresses tumor growth and potentiates checkpoint inhibition. Cell 183, 786–801 (2020).
2. Kalafati, L. et al. Innate immune training of granulopoiesis promotes anti-tumor activity. Cell 183, 771–785 (2020).
3. Wang, T. et al. Influenza-trained mucosal-resident alveolar macrophages confer long-term antitumor immunity in the lungs. Nature immunology 24, 423–438 (2023)