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Perspectives for the development of therapeutic Tasmanian devil facial tumor diseases

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Abstract. The Tasmanian devil facial tumor disease is an emergent transmissible cancer. The Tasmanian devil is the only unextinct member of the genus, and now only lives in Tasmania, Australia, and is known as the "Tasmanian Devil". Tasmanian devil facial neoplasia is a contagious cancer. Since 1996, the disease has been afflicting in Tasmanian devils. In 2006, scientists looked at the cancer cell chromosomes of Tasmanian devils and found that the cancer could be transmitted through bites between Tasmanian devils. It has two different types of DFT, including DFT1 and DFT2. Since the trend of extinction was discovered in 2009, researchers have tried to find a way to save the animal. The knowledge about the tumor and the devil is also learned deeper. Vaccination, including prophylactic vaccine and therapeutic vaccine, is one of the possible solutions. The vaccine technology has been developing rapidly since the last century and has already cured or stopped the expression of some deadly diseases both in humans and animals. Introduction of common vaccine technology will be made and their potential application in DFTD will be discussed in this passage. This review introduces the current research status of vaccine& other therapy development for Tasmanian devil facial tumor disease and summarizes the current problems and solutions in this research field. Although the species is facing great danger of extinction, not enough experiments and clinical trials have been carried out to find a way of saving it.

Keywords: Tasmanian facial tumor, vaccine, immunotherapy.

1. Introduction

The Tasmanian devil has been listed as endangered by the IUCN [1]. The cause of its extinction is an epidemic, whose pathogen is different from any other epidemic, that is, the Tasmanian devil facial tumor disease (DFTD). The tumor spread through the species by the animal's habit of biting each other [2]. Large tumors on the face and neck are the disease's hallmark. Most impacted animals will pass away from malnutrition and organ failure as a result of metastasis. Major histocompatibility complex Class I (MHC-I) and antigen presentation mechanism molecules are downregulated by DFTD cells to avoid homorecognition and enter a new host [3]. The presence of additional tumor escape mechanisms is mainly unclear, nevertheless. In order to distinguish it from the first DFTD, the second infectious disease that affects Tasmanian devils was identified in 2014. This cancer is known as DFT2.

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1.1. DFT1

Based on research into demonic immune systems, it has been found that Tasmanian devils have functional cellular and humoral immune systems. The ability of older animals to fight off infections is impacted by the T cell diversity, which has recently been demonstrated to be dramatically reduced between the ages of 11 months and 2 years. Furthermore, Tasmanian devils have the ability to reject skin grafts after transplantation, which suggests that they should have the capacity to develop an immunological response to DFT. To ultimately remove functional MHC Class I from the cell surface, DFT1 cells have down-regulated elements of the antigen presentation pathway, such as 2-m and TAP1/TAP2. This could be DFT1's method of preventing alloreactive T cells from responding non-self between MHC mismatched hosts.

This process is epigenetically downregulated. The adult demon T cell pool was also revealed to be constrained by DFT1 infection, indicating that tumors directly impact the host immune system [4].

1.2. DFT2

Little is currently known concerning the Wild Devil's reactions to DFT2. Numerous DFT3 cancers contained invading CD2+ lymphocytes, which suggests that demons can react to DFT2 tumors, according to Caldwell et al. [5]. Surprisingly, infiltrating lymphocytes, which are immune cells, do not appear to be dependent on MHC Class I expression in malignancies. It is unknown how DFT2 prevents MHC-mismatched hosts from inducing homologous responses of host T cells, and further research is required to understand the immunological escape mechanism of DFT2.

2. Current vaccine development

2.1. Vaccine

One of the biggest advancements in public health over the past century has been the development of vaccines, which have increased life expectancy and saved countless lives. Vaccines, for instance, have successfully eliminated smallpox and considerably reduced the occurrence of a number of dangerous diseases, including polio and measles. Vaccines come in a variety of varieties and have varying designs. However, the underlying idea is the same. This immunological memory, which is the foundation for creating long-lasting defense, is defined by the creation of memory cells and the persistence of antibodies against the same pathogen.

Types of vaccine includes live-attenuated vaccine, whole cell killed vaccine, or parts of the pathogens, like recombinant protein-based vaccines and viral vector-based vaccines. Live attenuated vaccines have the effect of causing relatively little infection. The immune responses that healthy people experience are analogous to those brought on by infections that occur naturally because attenuated pathogens exhibit the same antigens as the original viruses. Because of this, these vaccinations usually produce long-lasting protection after just one or two doses and elicit powerful cell-mediated and antibody responses. The drawback is that it might lead to illness in people with impaired immune systems. Additionally, pregnant women cannot use it [6]. Whole cell-killed vaccines, in contrast, do not include any living or infectious particles, making them disease-free and inactivated. They therefore typically have a favorable safety profile, even in those with impaired immune systems. The drawback of these vaccines is that their immunogenicity and persistence of immunity are typically lower than those of live vaccines, and that further doses or adjuvants might be necessary to increase immunogenicity.

Recombinant protein-based immunizations use particular antigens from the infection rather than the complete pathogen. These fragments, called virus-like particles (VLP), can be composed of proteins, polysaccharides, or even bits of the virus itself.

Certain viral vectors that mimic disease-causing virus particles serve as the basis for viral vector-based vaccines. VLPs don't spread since they don't have a viral genome. Antigenic proteins are more immunogenic than unbound proteins because their native shape is well retained. The human oncovirus (HPV) vaccine, which guards against cervical cancer brought on by these cancer-causing viruses, is the best-known example of VLP [7].

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Adjuvants are also often discussed in vaccines. They are chemicals that enhance and control the immunogenicity of antigens. They are frequently utilized in subunit vaccinations, though, as these vaccines have fewer antigens and lack several inherent components that stimulate the innate immune response in whole viruses, decreasing the chance of efficient downstream adaptive responses [8].

2.2. Vaccine against cancer

The topic of cancer vaccinations has received a lot of attention. Although there is strong biological and preclinical support for the creation of therapeutic cancer vaccines, it has proven challenging to apply this therapeutic strategy in clinical settings. While some cancer patients have the ability to produce an adequate quantity or function of T cells that are specific for an antigen and have exceptional antitumor activity, the majority do not. One way of assuring appropriate levels and activity of immune effectors is therapeutic cancer vaccination. Active immunotherapy of this kind tries to elicit an immune response that will target TAA or TSA. An early conception of a cancer vaccine was inspired by the discovery that certain tumors spontaneously shrank in people with acute infections. Using heat-inactivated bacteria, Dr. William Coley developed a key anti-cancer immunotherapy more than a century ago [9]. Discuss how the congenital immune response to the bacterial product of the non -specificity is transformed into a specific anti-tumor immune response. This is the discovery of the discovery of the antigen to the cell (APC) (dendritic cells [DC]). Peptide reactions derived from primary tumor. This causes such theory that if the antigen derived from tumor is presented to a sufficient immunogenic environment, the relatively safe and effective cancer treatment may target cancer cells due to priority persistent immune force.

2.3. Current development of therapy in DFTD

Only 2 clinical trials utilizing vincristine chemotherapy and doxorubicin and carboplatin [10] have been performed, despite the Tasmanian devil facing an imminent threat of extinction. Despite the frequent discussion of therapeutic vaccines, no clinical trials have been conducted. Researchers that used system dynamics analysis demonstrated that the cancer's rate of transmission sharply decreased, suggesting that it may be changing from an epidemic to an endemic [6]. However, the species still runs the long-term risk of extinction if the sickness is incurable.

2.4. Potential antigens for vaccine development

Immunogenic antigens: The devil's immune system is capable of recognizing HSPS produced from DFTD cancer cells. In devil cell lines, human Ad5 can be transduced to express functional transgenes. This necessitates the continued development of human adenovirus vectors for use in DFTD immunotherapies and vaccinations, as well as potential future vaccines for other marsupial diseases.

3. DFT vaccine and immunotherapy approaches

3.1. Live-attenuated vaccines

Attenuated vaccinations must be carefully controlled and specified in order to provide the required level of protective immunity without causing clinical disease signs in the host animal. There is a slim risk that the attenuated antigen may revert to its full degree of toxicity, hence a thorough reversion to toxicity safety investigation is necessary. Additionally, when creating vaccine antigens, other infectious agents could be included; these additional infectious agents themselves might have undesirable side effects when the vaccine is utilized in the wild. Live vaccines are frequently the most successful at promoting permanent immunity because they closely resemble the course of an infection in the body. Living DFT cells can be altered ("attenuated") to lessen their propensity to initiate new tumors. For instance, scientists have created DFT cells that can up-regulate MHC-I and trigger the expression of IFN-γ . A potent antitumor response can be induced while also increasing safety by combining overexpression of immunostimulatory genes with "suicide genes" and inhibitory pathways. The possibility of recovery to virulence can be diminished by other attenuation processes, such as tissue culture adaptation to site-

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specific development of strains and pathogens [11].

3.2. Viral vector-based vaccines

Clinical experiments on humans indicate promise for oncolytic viruses that preferentially infect tumor cells. These immunogenic viruses directly lyse the tumor cells, releasing molecules that trigger the migration of effector cells and antigen-presenting cells (APCs) into the tumor microenvironment. Oncolytic virus vectors with altered genes that express "cargo" (such as tumor-specific antigens or cytokines) show potential as immunotherapeutic and preventative agents. In order to reduce the chance of transmission to a secondary host and to restrict replication in the target host, viral vectors are routinely attenuated.

3.3. Recombinant protein-based vaccines

Purified recombinant protein and an immune-stimulating adjuvant are combined in the safest DFT vaccine formulation. Recombinant protein targets can be employed with efficient adjuvants that send out immunogenicity "danger signals" . Thanks to the advancement of recombinant DNA technology, foreign genes may now be placed into expression vectors and then delivered into cells to serve as "production factories" for the foreign proteins that those genes encode. This frequently offers an accessible and reasonably priced supply of infectious pathogen proteins for vaccine development. Several recombinant express systems have been effectively used in vaccine development. Select a few effective expression systems and protein targets, then create an experiment to evaluate the effectiveness.

3.4. Whole-cell killed vaccines

Whole-cell killed vaccines must be 100% virus- and contaminant-free. The cause of previous field outbreaks of issues has been identified as insufficient inactivation. If more dependable inactivation chemicals, inactivation processes, and incompetence testing were applied during the production process, these issues would not occur. Additionally, there is a chance for harm to the persons engaged as well as the environment. Unwanted "foreign" proteins may be present in vaccines produced in tissue cultures, simple media, or eggs, which could compromise their immunogenicity or cause allergy- or reactivity-related issues. Finally, there are restrictions on the way inactivated vaccines can be administered and, consequently, on the type of immunological reaction they might trigger. The vaccination response may be modest, and the time needed to increase the vaccine's overall immunogenicity or efficiency with adjuvants or immune stimulants may be brief.

Because DFT cells can express the whole set of tumor antigens, the whole cell-killed vaccine technique is a suitable place to start. Cloned DFT cells, on the other hand, have spread throughout many species and evolved to be more adept in evading the immune system, resulting in non-immunogenic cells (such as those cells with down-regulated MHC-I expression) that can express immunosuppressive cytokines and checkpoint molecules. Whole cells are also capable of expressing the whole array of self antigens associated with healthy cells. By recognizing normal "self" proteins, regulatory T cells and other tolerance cells can establish an immunosuppressive environment that hinders anti-tumor immunity in mice and humans.

4. Conclusion

DFTD is a severe disease that threats the existence of the species. The down regulation of MHC-I leads to recognition failure. The development of therapy is very limited. Vaccination, as a potential solution have no clinical trails until now. Vaccine technology has been evolving rapidly, as mRNA vaccines have already been made to fight against Covid-19. Though researchers have made some progress in figuring out the mechanism of the DFTD, few have given a design for vaccine development. Here we listed some traditional ways in vaccine development. Hope more research can be carried out in the field to save the Tasmanian devil.

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