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Application of Therapeutic Vaccines in the Treatment of Canine and Feline Cancers

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Abstract: The application of immunology and nanotechnology personalized immunotherapy in medical field has ushered in transformative changes in veterinary oncology. This paper will discuss the application of therapeutic vaccines in the treatment of canine and feline cancers. A substantial body of research indicates that therapeutic vaccines not only enhance antigen delivery but also activate robust T-cell responses and favorably modulate the tumor microenvironment. In the field of canine and feline oncology, nanoparticle-based vaccine platform has emerged as a novel strategy that improves antigen delivery and enhances cellular uptake, thereby regulating the tumor microenvironment and demonstrating significant potential in boosting immunogenicity and overall therapeutic efficacy. Concurrently, personalized vaccine offers precise identification of tumor antigens (TAs) to activate targeted T-cell responses. Unlike conventional treatments, these vaccines can be adjusted to accommodate the unique tumor features of each companion animal, substantially improving therapeutic outcomes. Early preclinical and clinical studies reveal that personalized vaccines prolong progression-free survival, reduce tumor burden, and inhibit metastatic lesions, offering new avenues for managing refractory cancers. Although challenges remain in clinical translation and large-scale application, interdisciplinary collaborations continue to advance this field, bringing unprecedented hope to the treatment of cancer in companion animals.

Keywords: Therapeutic vaccines, Tumor microenvironment, Nanotechnology, Personalized immunotherapy, Veterinary oncology

1. Introduction

Over recent years, the incidence of cancers in companion animals, particularly in canines and felines, has been steadily increasing. Tumors, as a critical pathological condition that significantly affects animal health and longevity, have emerged as an increasingly severe challenge in veterinary medicine. Advances in molecular diagnostics and imaging modalities have enabled the detection of tumor lesions at earlier and more precise stages, thereby stimulating the exploration of innovative and efficient therapeutic strategies. Although conventional treatments such as surgery, radiotherapy and chemotherapy can delay tumor progression to some extent, their limitations including high systemic toxicity, incomplete eradication of neoplastic foci, and high recurrence rates. This necessitates the development of novel treatment approaches. Among these, therapeutic vaccines have demonstrated considerable promise by activating the host immune system to elicit targeted antitumor responses and establish durable immune memory.

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Therapeutic vaccines operate via mechanisms that differ from those of prophylactic vaccines. They deliver tumor-associated antigens (TAAs) or neoantigens to antigen-presenting cells (APCs), thereby activating cytotoxic T lymphocytes (CTLs) to directly attack tumor cells. Immune responses are crucially regulated by the tumor microenvironment (TME). The immune-suppressing properties of TME impedes the activation and proliferation of CTLs, consequently compromising vaccine efficacy. Therefore, current research endeavors are not only aimed at enhancing antigen presentation but also at integrating immunomodulatory factors to optimize the TME and promote effective antitumor immunity.

Nanomaterials-based methods can be used to design new therapeutic vaccines for canine and feline cancers. For instance, nanoparticle-based carriers and viral vectors have been shown to improve markedly both antigen stability and targeted delivery efficiency. In preclinical studies involving canine malignant melanoma, squamous cell carcinoma, and other cancers, these novel technologies have yielded notable improvements in immunogenicity and therapeutic efficacy. Concurrently, personalized vaccines have introduced a novel paradigm in the treatment of cancers in companion animals. Given the marked genetic heterogeneity observed in canine and feline cancers, genomic and proteomic technologies can be used to develop bespoke vaccines tailored to the unique antigenic profiles of individual tumors. Personalized vaccines can significantly enhance CTL responses and improve clinical outcomes, underscoring their pivotal role in precision medicine. This has been further substantiated by recent multicenter clinical trials. One such trial demonstrated that canines treated with a personalized vaccine protocol exhibited significantly reduced tumor volumes and prolonged overall survival [1]. In felines, a positive correlation was observed between vaccine-induced immune responses and improved clinical outcomes.

Therapeutic vaccines constitute a novel and highly showing potential approach for the treatment of cancers in canines and felines. By leveraging advancements in nanotechnology and personalized immunotherapy, therapeutic vaccines have the potential to significantly enhance the health and quality of life of companion animals afflicted with cancer. This paper will elucidate the immunological mechanisms underlying therapeutic vaccines for canine and feline cancers, discuss recent clinical research progress, evaluate their therapeutic efficacy, and emphatically discuss the current applications and future prospects of personalized vaccines in veterinary oncology.

2. Immunological mechanisms of therapeutic cancer vaccines

Therapeutic vaccines operate via mechanisms that differ fundamentally from those of prophylactic vaccines. While prophylactic vaccines aim to induce long-term immunological memory to prevent disease onset by priming the immune system with antigens before exposure to pathogens, therapeutic vaccines are specifically designed to target established tumors. The delivery process often involves sophisticated techniques such as nanoparticle carriers or viral vectors to ensure efficient uptake by APCs. This targeted approach aims to boost the body's natural defenses against existing malignancies, offering hope for more personalized and effective cancer treatments.

Once delivered, the antigens are processed by dendritic cells (DCs), which present antigenic epitopes via major histocompatibility complex (MHC) molecules to T lymphocytes. This antigen presentation is crucial for the activation of CD8+ CTLs that directly target and eliminate tumor cells. Moreover, CD4+ helper T cells contribute by enhancing B-cell responses and secreting cytokines that further amplify the cytotoxic response.

A critical challenge in therapeutic vaccine efficacy is posed by the TME. The TME is inherently complex and is often characterized by immunosuppressive factors that hinder an effective antitumor immune response. In many tumors, inhibitory cytokines such as transforming growth factor-beta (TGF-β) and interleukin-10 (IL-10), along with regulatory immune cells including regulatory T cells and myeloid-derived suppressor cells (MDSCs), create a milieu that dampens the activation and

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proliferation of CTLs [2]. When tumor antigens (TAs) are efficiently presented, the immunosuppressive nature of the TME can significantly compromise vaccine efficacy.

Considering the challenges presented by the TME, current research is focusing more on strategies that enhance antigen presentation and also adjust the TME to support antitumor immunity. A promising method includes the co-administration of immunoadjuvants that can counteract inhibitory cytokines and diminish the suppressive effects of regulatory cells. Moreover, the existing researches are striving to integrate multimodal strategies, including emerging technologies such as nanotechnology, personalized vaccine formulations based on tumor neoantigen profiles, and combinational immunotherapies. In the future, these immunoregulatory approaches hold promise for optimizing the TME, thereby providing more effective and personalized immunotherapeutic solutions for canine and feline cancers.

3. Therapeutic efficacy of nanoparticle-based vaccines

3.1. Clinical performance

Recent developments in nanoparticle-based delivery systems have markedly improved the performance of therapeutic cancer vaccines by enhancing both antigen stability and targeted delivery. Liposomal formulations and PLGA nanoparticles have been optimized to encapsulate tumor-associated antigens, protecting them from rapid degradation and enabling sustained release. This controlled release increases the exposure of antigens to APCs and facilitates robust T-cell activation. Parallel to nanoparticle advances, viral vector-based systems have emerged as a complementary strategy for effective tumor antigen delivery. Engineered adenoviral vectors, for instance, are capable of high-efficiency transduction of APCs, leading to elevated expression levels of tumor neoantigens and enhanced CTL activation. Combining nanoparticle carriers with viral vectors may yield synergistic benefits by optimizing both antigen stability and targeted delivery efficiency. In several clinical settings, these technologies have demonstrated improved safety profiles and reduced systemic toxicity, positioning them as promising candidates for future immunotherapeutic strategies.

3.2. Clinical evaluation

Nanoparticle vaccines can significantly improve tumor remission rates and extend survival. For example, in a phase I–II clinical trial for canine malignancies, intratumoral or peritumoral injections of HA-Pt resulted in complete remission in 3 out of 7 dogs with squamous cell carcinoma [3]. Although the administered dose of HA-Pt did not adversely affect renal function, its use was associated with severe adverse effects, including toxic hepatic changes and cardiac arrest. OncoTherad® monotherapy, a novel therapeutic approach for canine malignant melanoma, introduces an antigen delivery system utilizing nanoparticles. This treatment activates Toll-like receptors (TLR) 2 and 4 through a glycoprotein-associated nanostructured inorganic phosphate complex, significantly enhancing interferon (IFN) signaling pathways and promoting the synthesis of IFN-α and IFN-γ. OncoTherad® attenuates the expression of the RANK/RANK-L system, potentially contributing to a reduction in tumor metastases. Clinical data indicate that the treatment cohort achieved positive outcomes, including complete response, partial response, and stabilization of the disease, as well as an overall increase in progression-free survival [4]. However, the absence of large-scale, randomized controlled trials assessing its efficacy and safety in canine malignant melanoma introduces uncertainty regarding the treatment's effectiveness across varied clinical contexts.

The investigators assessed L-MTP-PE as a nonspecific immunomodulator in the treatment of female mammary carcinoma, where 40 cats undergoing total mastectomy were treated with L-MTP-PE. It was found that cats with stage II mammary carcinoma exhibited a significantly longer disease-

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free interval (DFI) compared to those with stage III disease. Nevertheless, overall, the postoperative use of L-MTP-PE did not significantly impact DFI or overall survival (OS). There are still questions regarding the choice of using feline subjects in the study instead of selecting a canine mammary cancer model that is more applicable to female breast cancer [5].

4. Personalized cancer vaccines in veterinary oncology

Tumors exhibit distinct genetic characteristics and a diversity of protein expressions among different patients, leading to a high degree of heterogeneity in the disease. Taking the example of programmed cell death-1 (PD-1) and its ligand PD-L1 blockade therapy, its efficacy is closely associated with the pre-infiltration of T cells in the tumor microenvironment. In patients with high microsatellite instability (MSI-H) pancreatic ductal adenocarcinoma (PDAC), less than 1% exhibit tumor-infiltrating T cell responses specific to neoantigens [6]. However, personalized vaccines can overcome tumor heterogeneity by encoding individualized proteins based on the tumor's gene expression profile, suggesting that personalized vaccines have the potential to serve as effective treatments for canine and feline cancers. Personalized cancer vaccines represent an approach in precision medicine aimed at eliciting targeted immune responses by presenting tumor-specific antigens to the immune system. For instance, neoantigen-based vaccines can identify tumor-specific mutations and generate synthetic peptides or RNA sequences to initiate CTL responses.

4.1. Vaccine platforms

DCs, as the principal APCs, identify external warning signs through pattern recognition receptors, which trigger their activation. Following activation, they process and present antigens to T cells while secreting cytokines that orchestrate TH1, TH2, or Tc1 immune responses. Given their enhanced ability in antigen cross-presentation, DCs have been utilized in developing dendritic cell vaccines as a form of personalized immunotherapy. This strategy involves the ex vivo isolation of autologous DCs, subsequent loading with TAs, and reinfusion to provoke a robust T cell-mediated immune response. Early clinical trials in canine oncology have confirmed both the feasibility and immunogenicity of dendritic cell vaccines. Nevertheless, the therapeutic efficacy of these vaccines is currently limited by several factors, including diminished tumor antigen expression, the inhibitory effects of immune checkpoints (e.g., CTLA-4 and PD-1/PD-L1), as well as abnormalities in the abundance and functional capacity of various DC subsets [7]. Nucleic acid vaccines (NAV), including DNA and RNA vaccines, are gradually emerging as multifunctional platforms. The genetic information of TAs can be encoded by DNA and RNA vaccines and delivered to host cells, enabling the host to recognize and induce immune responses against cancer cells expressing these TAs. Overall, these research outcomes on personalized vaccines could be further applied in veterinary medicine to aid in the treatment of canine and feline cancers.

4.2. Application performance

In the context of canine cancers, recent preclinical studies and early clinical trials have demonstrated encouraging results. For example, a canine EGFR/HER2 polyvalent antibody cancer vaccine developed by a team at Yale University showed that in over 300 cancer-afflicted dogs, the 12-month survival rate for osteosarcoma increased from 35% with conventional treatment to 60% [8]. The vaccine, administered through a series of injections, elicited a robust immune response, targeting malignant cells with precision. In certain cases (e.g., in a Golden Retriever named Hunter), no recurrence was observed within two years following amputation, chemotherapy, and vaccine treatment. Additionally, approximately 30% of the dogs exhibited significant tumor reduction, with some cases showing nearly a tenfold decrease in tumor volume. The tumors, once palpable lumps

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causing discomfort, visibly shrank, allowing many dogs to regain mobility and comfort. Follow-up X-rays confirmed the disappearance of metastatic lesions in vaccinated dogs, revealing clear lung fields and bone structures free from cancerous spread. This breakthrough offers hope for extending the lives of beloved pets and improving their quality of life during their remaining time (Figure 1).

Figure 1: A chest X-ray image of an individual dog diagnosed with OSA lung metastasis, obtained at approximately three months [8].

Genomic analyses across various canine cancers have provided targets for the design of personalized vaccines, supporting future vaccine development. In one study involving genomic sequencing of 828 tumor samples from 53 types of canine cancers, 7,856 mutations (including SNVs and CNVs) were identified, with nearly 90% of cases presenting actionable biomarkers (such as TP53 and PIK3CA mutations). For instance, a vaccine targeting KIT mutations combined with targeted drugs prolonged the median survival time to 18 months in dogs with mast cell tumors [9].

Although studies on feline oncology are relatively fewer compared to canines, personalized vaccine therapy still offers new directions for feline cancer treatment. A recent study demonstrated the feasibility of a novel tumor-specific mRNA vaccine for personalized treatment in cats with spontaneous oral cancer [10]. The experimental data revealed no evidence of toxicity or adverse reactions from the vaccine. Additionally, significant activation of both CD4+ and CD8+ T cells was observed in the bloodstream within four hours post-administration. The survival rate in the treatment group showed a clear advantage: while none of the cats in the control group survived, 3 out of 4 cats in the treatment group achieved stable disease or reached undetectable levels [10]. These experimental results indicate a positive effect of personalized vaccines in preclinical models of feline oral cancer.

Due to individual patient differences and the complexity of the TME, each personalized vaccine must undergo rigorous quality control and individualized design. Although some experimental data support the clinical application of personalized cancer vaccines in dogs and cats, ethical concerns regarding the use of experimental treatments in companion animals, as well as high production costs, remain major obstacles to their clinical promotion. The ethical considerations involve ensuring that the welfare of pets is prioritized, avoiding unnecessary suffering, and obtaining informed consent from pet owners. High production costs arise from the need for sophisticated manufacturing processes, specialized equipment, and extensive testing to ensure safety and efficacy. Stakeholders must address these issues cautiously, ensuring that clinical trials adhere to high ethical standards while fostering innovation in individualized therapies. This involves balancing the potential benefits of groundbreaking treatments with the imperative to protect animal welfare and manage financial constraints responsibly.

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5. Conclusion

Recent advancements in immunology, nanotechnology and personalized immunotherapy have collectively redefined the landscape of veterinary oncology. Therapeutic vaccines, by enhancing antigen delivery, robustly activating T-cell responses, and strategically modulating the TME, offer considerable promise in treating cancers in dogs and cats. Clinical trials employing nanoparticle-based vaccine platforms have demonstrated significant tumor regression, prolonged progression-free survival, and impressive safety profiles. Furthermore, personalized vaccines that designed to encode individualized proteins based on tumor gene expression profiles underscore the potential of tailored immunotherapeutic strategies to overcome the inherent heterogeneity of cancers in companion animals. Preclinical and early clinical studies reveal that these vaccines can substantially reduce tumor volumes and metastatic lesions, thereby extending overall survival.

Looking forward, personalized vaccines are poised to become a pivotal strategy in veterinary oncology. Nonetheless, the translation of these innovative therapies into standard clinical practice remains challenged by the need for standardized production protocols, large-scale randomized clinical trials, and comprehensive ethical and regulatory frameworks. In addition, further research is essential to refine antigen selection and optimize delivery mechanisms in order to maximize therapeutic efficacy while minimizing adverse effects. Addressing these challenges will require robust interdisciplinary collaboration among veterinarians, immunologists, nanotechnologists, and bioengineers.

Overall, sustained research and continuous innovation in cancer vaccine technology are anticipated to significantly improve treatment outcomes and enhance the quality of life for canine and feline patients, thereby advancing animal welfare. These advancements herald a transformative era in veterinary medicine, offering renewed hope for the effective management of cancer in companion animals and paving the way for future breakthroughs.

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