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Annals of Pancreatic Disorders and Treatment Open Access Journal

ISSN: 2692-4730 DOI: https://dx.doi.org/10.17352/apdt

Mini Review

Progress in the development of vaccines for pancreatic adenocarcinoma

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Received: 18 March, 2024
Accepted: 05 April, 2024
Published: 06 April, 2024

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Keywords: *Salmonella*-based vaccine; Vaccine design; Cancer vaccine; Pancreatic adenocarcinoma; Immunotherapy

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Abstract

Pancreatic cancer, which is regarded as the third deadliest cancer globally, poses a significant challenge because of its limited range of treatment options and high mortality rate. Currently, there is a focus on both the development of a novel concept in vaccine designing and the parallel study of the associated immune mechanisms. To further our understanding of the healthcare field, a variety of promising designs have been introduced for in-depth study. The designs were developed to include the mKRAS-specific amphiphile vaccine, which targets a specific mutation in the KRAS gene in addition to the multi-antigen targeted DNA vaccine, which aims to stimulate an immune response against multiple cancer antigens. Furthermore, later designs of vaccines were introduced based on the development of peptide-based cancer vaccines, mRNA-based vaccines, cell-based vaccines, and engineered bacterial vectors using an oral *Salmonella*-based vaccine. The study presents the concept on which the new vaccine is based and discusses the up-to-date immunological manifestations of these designed vaccines.

Introduction

Pancreatic cancer has a 5-year survival rate of 5% - 8% [1] and Pancreatic Ductal Adenocarcinoma (PDAC) accounts for ~90% of fatal cases [2]. Although PDAC is the ninth most prevalent cancer, it is the fourth leading cause of cancer-related death in Western countries [3]. Even with early detection, only ~20% of individuals are suitable for surgical resection [4]. Gemcitabine and 5-fluorouracil (5-FU) are the most often used treatments with little progress in outcomes [4]. The quest to develop a vaccine for PDAC has garnered significant attention in both pre-clinical and clinical trials for a long time [1]. Upon evaluation, it is found that the tumor site does not have tumor-specific lymphocytes, which could be attributed to the tumor's poor immunogenicity, steric hindrance of T-cell migration, and potential tolerance to the effect of the surrounding microenvironment [5,6]. An important field of study involves investigating the potential of vaccine-based treatments to promote the proliferation and stimulation of lymphocytes that specifically target pancreatic cancer. The potential failure of current cancer vaccines is disheartening, especially because of the inadequacy of antigen delivery or the activation of innate immunity [7]. Therefore, a need for a more specific neo-antigen, controlling the tumor microenvironment, and integration of innate and adaptive immune cells are the main pillars for addressing a novel and successful theory for vaccine design.

Current and future vaccine designs

mKRAS-specific amphiphile vaccine: KRAS is a gene that makes a protein called K-Ras that is part of the RAS/MAPK signaling pathway. The presence of mutations in the KRAS gene is a common characteristic (90-95%) observed in pancreatic adenocarcinomas. Among all the genes in PDAC, this one is the most mutated [8]. A clinical study was carried out to examine constitutive activation of KRAS, which usually represents more than 98% of all activating mutations, using amphiphile modification of G12D and G12R mutant KRAS (mKRAS) (Ki-

Citation: Singer M, Elsayed AM, Husseiny MI (2024) Progress in the development of vaccines for pancreatic adenocarcinoma. Ann Pancreat Disord Treatm 6(1): 001-005. DOI: https://dx.doi.org/10.17352/apdt.000011

ras2 Kirsten rat sarcoma viral oncogene homolog) peptides (Amph-Peptides-2P) in conjunction with CpG oligonucleotide adjuvant (Amph-CpG-7909) [9]. In his study, an essential focus is placed on the appearance of cross-reactive T-cells in non-immunizing mKRAS antigens. Furthermore, there is a notable absence of data regarding innate immunity.

Multi-antigen targeted DNA vaccine: The hypothesis of using multi-antigen is mainly based on targeting the melanoma-associated antigen type-I protein (MAGE-type I) which is well-conserved, associated with cancer, and exhibits strong immunogenicity [10]. MAGE plays a role in regulating tumor-stromal crosstalk in PDAC and is found to be overexpressed in a chemo-resistant patient. Vaccination against multiple MAGE antigens robust a favorable immune response against the growth of gemcitabine-resistant tumors [11]. Due to the current lack of understanding of the exact mechanism of MAGE and its safety in overcoming cancer chemoresistance and progression, it is too early to plan for clinical treatment.

Peptide-based cancer vaccines: Targeting the immunosuppressive and fibrotic tumor microenvironment has recently attracted attention in the immunotherapy for PDAC by using different key molecules such as transforming growth factor-β (TGFβ) derived peptides, anti-PD-1 antibodies, anti-CSF-1R antibodies and Anti-VEGF receptor 2 [12]. The concept is originally initiated by targeting viral peptides [13]. Until now, no single immune-inhibitory checkpoint has been proven to be an effective therapy or vaccine *in vivo*, and none have shown long-term protection against disease recurrence. Therefore, many clinical trials are currently running with different therapeutic modalities, including immune checkpoint inhibitors, to improve clinical outcomes.

mRNA-based vaccines: The new approach of using mRNA vaccines has improved the maturity of personalized neoantigen vaccines. mRNA can be captured by antigen-presenting cells and presented via major histocompatibility complex (MHC) molecules, which leads to clonogenic immune activation and expansion [14,15]. Although the early clinical trials show promising results, several challenges, like the identification of suitable antigens and immune evasion by tumors, still need to be addressed.

Cell-based vaccines: The fusion of tumor cells and dendritic cells (DCs) triggers the activation of a diverse antitumor immune system. Vaccination with DC/tumor fusions also resulted in the proliferation of lymphocytes specific to tumor antigens and infiltrated the tumor site [7]. DC-based vaccines are very promising in establishing a personalized effective therapy because of the tumor microenvironment. However, recent clinical trials using DCs combined with immune checkpoint inhibitors are under investigation. Another method employed in cell-based research involves the use of human PDAC cell lines that have undergone genetic modification. This modification allows the cells to express αGal via retroviral transfer of the murine αGT gene. This approach is commercially referred to as Algenpantucel-L [16]. The study showed an effective result when combined with gemcitabine chemotherapy in advanced HCC.

Engineering bacterial vectors: *Oral Salmonella-based vaccine.* Engineering bacterial vectors to deliver tumor antigens provides an efficient way of better stimulating immune cell attack of tumor cells or suppressing the immune cells to control immune reactions [17]. Such bacterial-based therapies are in development and hold promise for hard-headed neoplasms. Bacteria have advantages, including the expression of anti-tumor proteins and the transfer of expression vectors into cancer cells. In addition, bacteria are highly mobile and actively move away from the vasculature, penetrate deeply, and accumulate in tumor tissue [18]. Other cancer treatments may not penetrate the cancer well [19]. The oral vaccine model for cancer is designed from the type III secretion system (T3SS) of *Salmonella* and exploited for expression of tumor antigen into the cytosol of antigen-presenting cells (APCs) to generate tumor-specific cytotoxic lymphocytes (CTLs) [20]. Afterward, APCs process and present antigens to the immune cells [21-23]. This technology is being used for the development of a vaccine for cancers [24]. The *Salmonella* Pathogenicity Island 2 (SPI2) system of *Salmonella* has been used to construct a cancer vaccine [23-25]. Herein, surviving has been used, which is known as a tumor antigen overexpressed by 70-80% of cancers and a target for cancer immunotherapy [26]. This vaccine-induced CD8 T-cell-mediated antitumor activity in overexpressed survivin mice tumor models [24,25]. Similarly, the *Salmonella*-based vaccine could enhance NKT activation through CD1d and TLR-mediated-DCs and induce subsequent effector responses by NKT, NK, and T-cells in colon and glioblastoma cancers [23]. Similarly to the *Salmonella*-based vaccine, others have used the GVAX pancreas vaccine containing *Listeria monocytogenes* expressing mesothelin [19]. As a superior model, Oral *Salmonella* could improve long-term antigen presentation with higher penetration and favorably invade tumors [27]. Engineered *Salmonella* was tested in pre- and clinical cancers [28-30] and in pancreatic cancer [31] and was found to be safe with no risk of lung [32] or liver damage [33].

Discussion

Recently, there has been promising efficacy for PDAC with individualized neoantigen cancer vaccines. The main target for all the recent therapeutic vaccines is to generate a well-developed immune response to eradicate pancreatic adenocarcinoma. However, the immune mechanisms behind this treatment are not fully established, and no vaccine has successfully eradicated PDAC [37]. Several clinical trials with different vaccine approaches have been wrought in the hope of controlling and recovering pancreatic cancer (Table 1) [5,6,8,10]. While aiming to target cancer T-cells specifically, the effectiveness in achieving the desired goal is not fully efficient [26,30] by modulating various immune subsets, a re-formulator equation can be induced, resulting in better-enhanced tumor necrosis. Several trials were pursued to inhibit the cancer-promoting role of neutrophils [38,39]. Some studies were more developed to rationalize the neutrophil-to-lymphocyte impact on tumor progression and modulate this ratio to induce better clinical outcomes, as lower ratio value and elevated lymphocyte frequency improved the response for immunotherapy designing [40-42].

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Table 1: Clinical trials for pancreatic cancer vaccine therapy.

Clinical trial	Identifier	Vaccine approach	Cohort (n)	Ref.
Pant, et al. 2024	NCT04853017	mKRAS	25	[9]
Chen, et al. 2021	NCT03645148	peptide	7	[34]
Hardacre, et al. 2013	NCT00569387 NCT01072981	Algenpantucel Cell-based	73	[35]
Kang, et al. 2023	NCT04161755	mRNA neoantigen	16	[14]
Bassani-Sternberg, et al. 2019	CHUV-DO-0017_PC-PEPDC_2017	DC vaccine	3	[36]

The cross-talk between fibroblast and macrophages in the tumor microenvironment is enhanced when the expression of oncoprotein p21 is elevated in tumor-associated macrophages (TAM) because of stromal interaction or chemotherapy treatment. Modulating or blocking p21 expression levels in TAMs was found to be an effective strategy in suppressing tumor progression [38]. This cross-talk is also believed to involve efferocytosis-associated genes, which have been implicated in promoting tumor metastasis [39]. It is worthy to mention that NK cells are acquiring a greater understanding of their role in combinatorial immunotherapy using gemcitabine and NK immunotherapy [43], or combinatorial using NK cells and chemotherapy [44]. The interaction between NK cells and the conditions of the tumor microenvironment controls the fate of the therapy in pancreatic cancers [45]. When considering this perspective, it becomes clear that the immune profiling surrounding the tumor and the combination formula play a crucial role in determining tumor regression or progression.

Conclusion

Developing novel therapies for pancreatic adenocarcinoma poses a significant challenge due to the various approaches required. There is a high demand for a vaccine that can serve as a prophylactic, protective, and therapeutic measure. By delving into the intricate workings of the immune system and exploring the potential of combining different vaccine components, we can pave the way for the development of a highly efficacious, long-lasting vaccine.

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Citation: Singer M, Elsayed AM, Husseiny MI (2024) Progress in the development of vaccines for pancreatic adenocarcinoma. Ann Pancreat Disord Treatm 6(1): 001-005. DOI: https://dx.doi.org/10.17352/apdt.000011

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Citation: Singer M, Elsayed AM, Husseiny MI (2024) Progress in the development of vaccines for pancreatic adenocarcinoma. Ann Pancreat Disord Treatm 6(1): 001-005. DOI: https://dx.doi.org/10.17352/apdt.000011