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Review

Dendritic cells in pancreatic cancer immunotherapy: Vaccines and combination immunotherapies

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ABSTRACT

Despite significant advances over the past decades of research, pancreatic cancer (PC) continues to have the worst 5-year survival of any malignancy. Dendritic cells (DCs) are the most potent professional antigen-presenting cells and are involved in the induction and regulation of antitumor immune responses. DC-based immunotherapy has been used in clinical trials for PC. Although safety, efficacy, and immune activation were reported in patients with PC, DC vaccines have not yet fulfilled their promise. Additional strategies for combinatorial approaches aimed to augment and sustain the antitumor specific immune response elicited by DC vaccines are currently being investigated. Here, we will discuss DC vaccination immunotherapies that are currently under preclinical and clinical investigation and potential combination approaches for treating and improving the survival of PC patients.

1. Introduction

By 2030, pancreatic cancer (PC) is predicted to become the second leading cause of cancer-related deaths in the United States [1]. Currently, the 5-year survival rate of patients with PC is less than 5% due to late diagnosis and early metastases [2]. Surgical resection is the only potentially curative option for PC. However, less than 20% of PC patients are eligible for surgery while up to 60% of patients who undergo surgical resection subsequently relapse with the first year [3,4]. For most patients present with advanced PC disease, the standard of care is systemic therapies which provide only short-term benefit. This highlights an urgent need to develop novel and effective therapeutic strategies for PC. Immunotherapy is superior over radiation and chemotherapy because it targets the induction or augmentation of antitumor immune response without damaging normal tissues [5,6]. In recent years, immunotherapy has revolutionized cancer treatment. As of February 2019, a total of 43 immunotherapies had been approved by the United States FDA, which cover almost every major cancer type [7]. Its therapeutic efficacy in treating patients with PC, however, is limited by the immunosuppressive microenvironment associated with this cancer [8]. Recently, much effort has focused on the *ex vivo* generation of dendritic cells (DCs) that can be used as therapeutic vaccines against PC. In this review, we highlight the emerging roles of DC-based immunotherapy in PC treatment and how a combination approach can be used.

2. Key biological features of DC for immunotherapy

DCs are the most potent professional antigen-presenting cells in the immune system [9]. As such, mediate the role of capturing antigens in the periphery, processing, and presenting them as antigenic peptides to the T cells of the immune system. Under normal circumstances, DCs are maintained in an immature and inactivated state, acting as the sentinels of the immune system. Upon exposure to optimal stimuli such as inflammatory cytokines, microbial factors, or endogenous alarmins, DCs undergo a complicated series of phenotypic and functional changes termed maturation [10]. Mature DCs have a series of phenotypic and functional characteristics, including i) acquisition of chemokine receptors (e.g., CCR7); ii) upregulation of adhesion molecules, T cell costimulatory molecules (CD80 and CD86), immunoproteasomes and peptide-MHC class I and II molecules; and iii) the ability to secrete different cytokines (e.g., IL-12), that are essential for migration of the cells to the lymphoid tissues and optimal activation of the immune responses [11–15]. They also have the capacity to activate naive and

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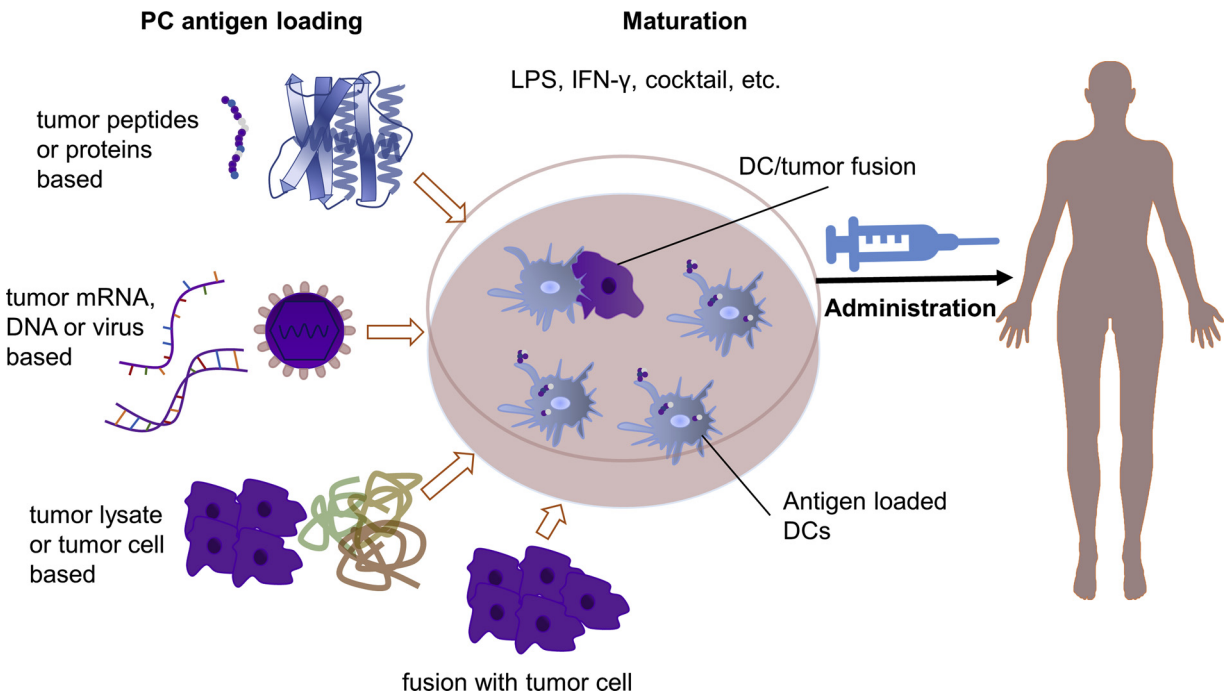

Fig. 1. The state of the art in DC vaccines designing for the patients with PC. The immature DCs were loaded with TAA which can take many forms, including peptides, proteins, DNA, RNA, virus, and cells. The Ag-pulsed DC are often matured with other cytokines, growth factors or LPS, and then prepared for administration.

memory B cells, natural killer (NK) cells, and natural killer T (NKT) cells [16–19]. Thus, DCs can conduct all components of the immune orchestra, and they are therefore key mediators in directing antitumor immunity. Importantly, DC biology can be impaired by tumors [20]. Multiple tumor-derived factors appear to collectively suppress DC function by inhibiting DC recruitment, activation and antigen presentation, which results in impaired antitumor activity of DC vaccines [21]. Therefore, DC-based immunotherapy will need to adapt treatments against these factors as a combination to augment their therapeutic potential and achieve tumor regression in PC treatment.

3. DC vaccines

Numerous studies have shown that DCs loaded with tumor associated antigens (TAAs) can induce therapeutic and protective antitumor immune responses [22,23]. To develop the optimal vaccine for PC, immune-relevant antigens that can be recognized by effector T cells must be identified. According to the sources of loading antigens, DC vaccines for PC currently can be categorized: 1) peptide/protein-based, 2) RNA, DNA or viruses-based, 3) whole tumor cell based, or 4) tumor cells fused (Fig. 1).

3.1. Peptide/protein-based DC vaccines

Pulsing DCs with peptides or protein fragments (called epitopes) is highly feasible. This approach also preserves tumor selectivity while minimizing the risks for adverse autoimmune-related effects. The ideal TAA target should not only be expressed at high levels on tumor cell but should also be minimally or not expressed in all normal cells. To date, different TAAs in PC have been identified and currently under an active state of investigation (Table 1).

Mucin 1 (MUC1) is a large membrane glycoprotein that is overexpressed in an incompletely glycosylated form in various human cancers, including PC [24,25]. A Phase I/II clinical trial evaluated the efficacy of MUC1 peptide pulsed autologous DC vaccines in 12 pancreatic and biliary cancer patients following resection of their primary tumors [26]. MUC-1 pulsed DC-vaccines were found to be tolerable and feasible, and 4 out of 12 vaccinated patients were alive for over four years after treatment. In comparison, median survival for PC patients is only 5 months after diagnosis. A similar phase I pilot trial involved administered with MUC1-peptide-pulsed DCs in 7 advanced PC patients, who showed significantly increased immune response characterized by high IFN-γ and granzyme B expression [27]. In another study, combination therapy using MUC1-pulsed DCs and MUC1-specific cytotoxic T lymphocytes (CTLs) was evaluated in 20 advanced PC patients. Mean survival time was 9.8 months. One patient with multiple lung metastases experienced a complete response while 5 patients had stable disease [28].

The Wilms' tumor 1 (WT1) antigen is one of the most widely expressed TAA in various types of tumors, including PC [29]. Recently, several clinical trials of WT1-targeted DC vaccines for patients with PC have been performed [30–34]. These findings demonstrated that WT1-based DC vaccines immunotherapy are promising and can achieve better success when combining with chemotherapy. Yanagisawa et al. showed that seven out of 34 vaccinated patients had detectable specific antitumor response, and WT1 and human leukocyte antigen class I antigens were positive in all 34 cases [34]. Carcinoembryonic antigen (CEA) is another suitable antigen target for PC due to its overexpression in > 90% of PC but not in normal pancreas [35,36]. A phase I study evaluated the clinical efficacy of CEA-pulsed DCs in patients with metastatic malignancies, including PC [37]. These vaccines were found to induce *in vivo* antigen-specific immune responses. However, CEA is poorly immunogenic due to immune tolerance making it a less clinically relevant target for PC treatment. Mutated KRAS are frequently found in PC patients and are currently under investigation as an immunotherapy target [38,39]. Mesothelin [40] and epidermal growth factor receptor (HER/EGFR/ERBB) family proteins [41,42] are also overexpressed in PC patients making they as potential immunotherapeutic targets. DC vaccines targeting mesothelin and epidermal growth factor receptor (HER/EGFR/ERBB) family proteins for PC treatment are undergoing pre-clinical and clinical evaluation.

Table 1
A non-exhaustive list of tumor associate antigen targets for PC immunotherapies.

Target	Expression		Notes
	Normal Pancreas	Pancreatic Cancer	
MUC1 [43]	Expressed at low levels on ductal and glandular epithelial cells.	Aberrantly overexpressed and glycosylated in PC	Transmembrane glycoprotein that consists of multiple 20 amino acid repeats that are heavily O-glycosylated. However, cancer associate MUC1 is under-glycosylated and no longer restricted to cell surface.
WT1 [29,44]	Absent in normal pancreas	Overexpressed in PC	The *WT1* gene encodes a zinc finger transcription factor, WT1, which has been identified as a potent transcriptional regulator that correlates with cell development and progression in various cancer type.
CEA [35,36]	Absent in normal pancreas	overexpressed in over 90% of PC	CEA is a 180-kDa immunoglobulin-like molecule that is expressed on the cell surface and functions in cellular adhesion.
Mesothelin [45,46]	Limited expression in normal pancreatic tissues and in chronic pancreatitis	Highly overexpressed in almost all PC	Mesothelin is a 40-kD glycosyl phosphatidylinositol-linked cell surface glycoprotein that is present on normal mesothelial cells lining the pleura, peritoneum, and pericardium. Its function in humans is not clear at this time.
Mutated KRAS [38,39]	Mutated KRAS is a TSA	Mutated in up to 90% of PC	An intracellular GTPase important for cell growth and survival. Mutations in the KRAS oncogene are frequent and contribute to the formation and progression of many human cancers.
HER/EGFR/ERBB family proteins (e.g., HER1, HER2, HER3) [41,42]	Expressed at lower levels in normal pancreas	HER2/neu is overexpressed in approximately 50% and EGFR in approximately 70% of PC	Cell-surface receptors implicated in tumor growth.

3.2. RNA, DNA or viruses-based DC vaccines

Gene modified DCs has emerged as an alternative therapeutic approach for a variety of human cancers, including advanced PC. A phase I/II clinical trial evaluated the efficacy of MUC1 cDNA transfected DCs in 10 patients with malignancies, including advanced PC [47]. This study demonstrated the feasibility and safety of immunotherapy with autologous gene transfected DCs, and that immune responses could be induced in patients. Miyazawa et al. showed that stimulation of PBMCs with DCs transduced with the full-length mesothelin gene elicited a potent MSLN-specific cytotoxic activity against PC cells *in vitro* [48]. Schmidt et al. vaccinated murine pancreatic tumor model with tumor RNA-pulsed DCs and observed a specific antitumor effect which showed as generation of tumor-specific CTLs and inhibition of tumor growth [49]. Additionally, Kalady and colleagues demonstrated that DCs transfected with autologous total tumor RNA generated an effective antitumor T-cell response in PC patients [50]. A similar study also demonstrated that DCs transfected with amplified MUC1 mRNA stimulate cytotoxic T lymphocyte responses against PC *in vitro* [51]. Recently, MUC1-mRNA-transfected DCs have also been used as adjuvant therapy for patients with unresectable or recurrent PC [52]. Another study showed that DCs co-transfected with two TAA mRNAs (MUC4 and survivin) can induce effective CTL responses against PC target cells *in vitro* [53]. Baculovirus (BV) can infect a range of mammalian cells but not replicate in them, which suggests its function as a potential tool for gene therapy when recombinants virus with a mammalian expression promoter [54,55]. It was demonstrated that BV infected bone marrow-derived DCs can induced antitumor effect against human pancreatic carcinoma in a nude mouse model [56].

3.3. Whole tumor cell pulsed-DC vaccines

Whole tumor cell based-DC vaccines deliver a wide range of tumor antigens without the need for specific knowledge of the relevant target. Preclinical and clinical trials have shown that specific T-cell responses against pancreatic tumor as well as tumor regression can be achieved when DCs are pulsed with whole PC cell lysates [57–62]. Previously, a study conducted where twenty malignant patients (including pancreatic carcinoma cases) with stage IV disease were vaccinated with tumor lysate pulsed DC vaccines. Seven out of twenty patients showed objective changes in measurable lesions or tumor markers [63]. Another clinical trial was conducted in which tumor cell pulsed DCs were vaccinated in seventeen PC patients. This study suggested that immunotherapy with DC vaccination may prolong the survival of patients with refractory PC [64].

3.4. Tumor cells fused DC vaccines

DC-tumor cell fusion hybrids can induce antitumor immune response by presentation of multiple tumor antigens in complex with MHC class I and II molecules and in the context of co-stimulatory signals [65,66]. To date, several studies using these fusion hybrids have been reported in experimental setting of PC [67,68]. Ziske and colleagues demonstrated that DC-tumor hybrids were a promising approach to increase the efficiency of antitumoral response in murine pancreatic tumor model [67]. However, Chen et al. showed that DCs pulsed with whole tumor RNA are superior to those fused with tumor cells in priming anti-PC CTL responses [68]. Additionally, Andoh et al. demonstrated that the cytotoxicity induced by DCs fused with pancreatic cancer cell lines was different between each cell line [69]. These results taken together suggested that the safety, feasibility, and efficacy of tumor cells fused DC vaccines should be further evaluated.

4. Breaking immunosuppression within the tumor microenvironment

The pancreatic tumor microenvironment (TME) is particularly immunosuppressive, suppressing effective antitumor immune responses [70,71]. Substantial evidence demonstrated that pancreatic TME consists of cancer cells as well as various other types of cells in the tumor stroma, including fibroblasts, endothelial cells, immune cells, and the extracellular matrix attributes to tumor progression [72–74]. Thus, overcoming this immunosuppression TME is essential for improving DC vaccines in the PC treatments. DC vaccination might be more efficient in combination with therapies that break the suppressive TME. Yamamoto et al. demonstrated that regulatory T cells (Tregs) depletion combined with DC-tumor fusion hybrid vaccine enhanced the efficacy of immunotherapy in PC by activating CTLs and NK cells [75]. Suppressive cytokines such as TGF-β and IL-10, are produced by the pro-inflammatory infiltrate of PC lesions and can stimulate tumor growth. A recent study showed that mice with the therapy of DC vaccine combined with TGF-β antibodies may possibly cure tumors in a murine PC model [76]. Marvel and Finn demonstrated that transient inhibition of IL-10 prior to vaccination could improve responses to cancer vaccines

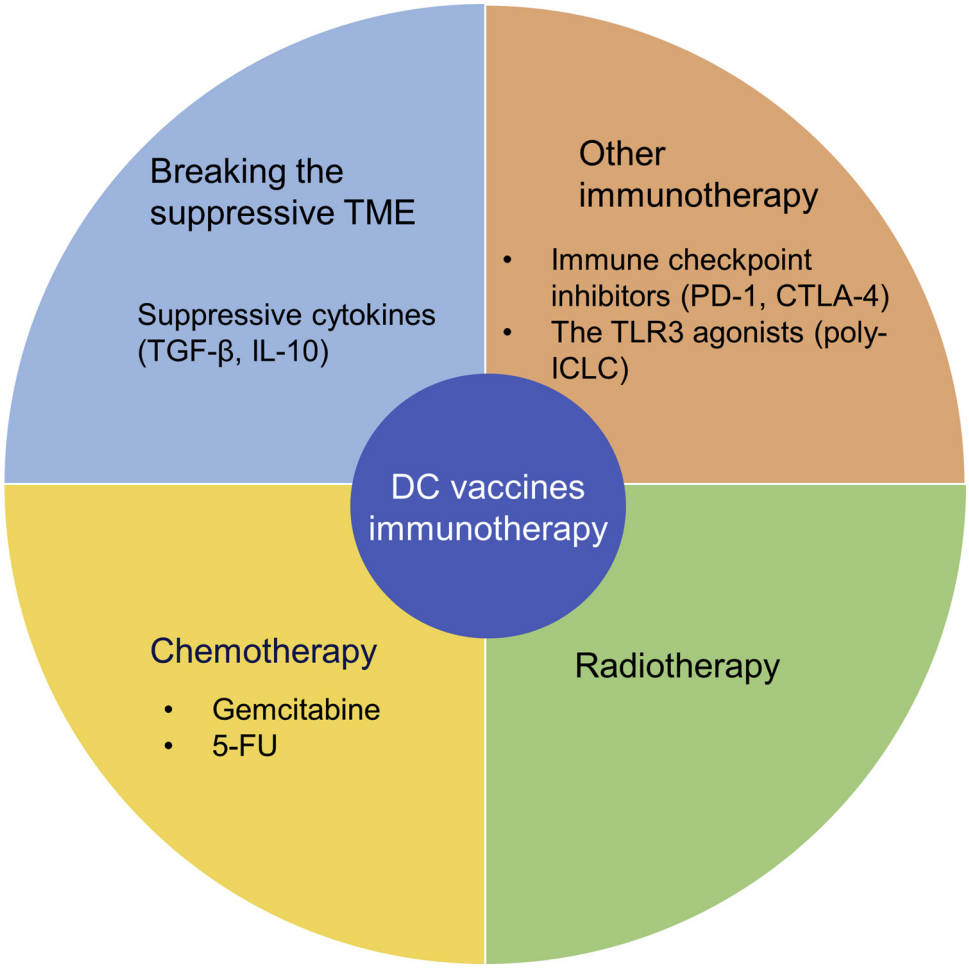

Fig. 2. Potential therapeutic combinations with DC vaccines immunotherapy. DC vaccination combined with various strategies such as targeting immunosuppressive factors, other immunotherapy, chemotherapy, and radiotherapy, which may yield synergistic or promising clinical outcomes.

that utilize self-tumor antigens in MUC1 transgenic mice [77]. Additionally, indoleamine 2,3-dioxygenase (IDO) exerts its immunoregulatory functions by regulating the function of DCs, inducing CTL apoptosis and increasing the number of Tregs [78–81]. The combination of 1-MT (an IDO inhibitor) and DC vaccination has been tested in murine PC model and has proven to augment the antitumor efficacy [61].

5. Combination with other immunotherapies

Recent discoveries have revealed that monoclonal antibodies targeting inhibitory signals, also called immune checkpoint inhibitors, such as CTLA4 and PD-1/PD-L1, can induce effective antitumor immunity in PC [82–84]. A recent study demonstrated that vaccination with DC-targeted tumor antigen plus anti-CTLA-4 antibodies triggered an increased infiltration of $CD4^+$ T effector cells in a mouse PC model [85]. Nesselhut and colleagues reported that systemic anti-PD-1 therapy for patients with PC can be effective even at lower dose when combined with DC vaccines therapy [86]. Collectively, these studies indicated that combination immune checkpoint inhibition with DC vaccine may be a promising therapeutic approach in PC treatment.

The Toll-like receptor (TLR) 3 agonists such as polyinosinic-polycytidylic acid (poly-ICLC) are potent activators of DC maturation which would be important for induction of antitumor immune responses [87]. In a phase I clinical trial, co-administration of peptide-pulsed DCs and poly-ICLC appeared safe and induced a measurable tumor specific T cell population in patients with advanced PC [88]. IL-12 is a potent immunostimulatory cytokine, produced exclusively by DCs, and has shown to be necessary for DC efficacy. Intratumoral injection of DCs engineered to express IL-12 has been used in PC patients. After treatment, a partial response was observed in one out of three patients [89]. DC vaccines engineered to express IL-23 was found to enhance specific Th1-type and CTL responses against PC cells and induce not only autoimmune ability but also preventive immunity against PC inoculated in mice [90,91]. DCs engineered to express IL-18 were evaluated in murine PC model and showed that the combination therapy can induce a specific and effective immune response against pancreatic carcinoma [92]. Additionally, Adoptive immunotherapy with MUC1-DCs and MUC1-lymphocytes plus gemcitabine resulted in a 1-year survival rate of greater than 50% in patients with unresectable or recurrent pancreatic invasive ductal carcinoma [52].

6. Combination with chemotherapy

Immunotherapy and chemotherapy often seem counterintuitive to each other. However, increasing evidence suggest that the antitumor effects of some chemotherapeutic agents were related to immune responses for PC treatment.

Gemcitabine-based chemotherapy is the standard care for PC and was shown to increase tumor antigen availability as well as transiently decrease immunosuppressive Tregs and myeloid-derived suppressor cells (MDSC) in the PC TME [93–95]. Therefore, combination gemcitabine with DC vaccination is being tested in multiple trials for PC treatment. Previous studies have demonstrated that DC-based

vaccination can be combined with gemcitabine to increase survival in a mouse model of PC [60,96]. Moreover, recent several studies conducted in patients with advanced PC showed that DC vaccine-based immunotherapy combined with gemcitabine chemotherapy have proven to be safe, feasible, and effective [30,34,97,98].

S-1 is an oral 5-fluorouracil (5-FU) prodrug that has been shown to be superior to adjuvant chemotherapy with gemcitabine in prolonging overall survival in patients with PC [99,100]. Furthermore, a clinical trial which evaluates the safety and efficacy of DC vaccine combination with S-1 for patients with advanced PC refractory to standard chemotherapy is ongoing in Japan [101]. Combination therapy with tumor-lysate pulsed DCs and antiangiogenic inhibitor TNP-470 induced regression of tumor in mouse PC [58].

Other combination approaches including radiotherapy is actively being tested in patients with PC (Clinical trial NCT00843830). In this study, patients with metastatic pancreatic carcinoma will receive tumoral irradiation and dendritic cell vaccination. A summary of the combination therapy involving DC vaccine in PC is presented in Fig. 2.

7. Conclusion

In conclusion, DC vaccination has reported to be feasible, safe, and effective in PC treatment. Recently, significant improvements in the area of DC-based immunotherapy have been made and DC vaccines are continuously being optimized. However, the favorable responses including improvement of overall survival seen in preclinical studies unfortunately, have yet to be fully realized in clinical practice. The following problems should be considered. For one, the poorly immunogenic nature of PC suggests crucial limiting challenges ahead for evolvement of DC vaccination in PC treatment. Specific TAAs for PC should be identified as soon as possible, not only for immunotherapy but also for early diagnosis of these tumors. Moreover, PC presents extremely immunosuppressive TME due to rigid tumor matrix architecture, suggesting DC-based cancer immunotherapy may have limitations as a monotherapy. Therefore, combinatorial approaches involving DC vaccine, immunomodulating agents, and conventional treatment modalities may synergistically and significantly improve clinical benefits in PC patients. Further investigation is needed to optimize the therapeutic doses, sequence, and timing of combined therapy to make it a clinically promising modality in the PC treatment.

Declaration of Competing Interest

No potential conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.prp.2019.152691.

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