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Mini-review

Immunotherapy in pancreatic cancer: New hope or mission impossible?

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ABSTRACT

Pancreatic cancer (PC), one of the most lethal diseases, remains a challenging problem. Novel cancer therapy targeting the immune system has been explored. Although immunotherapy has yielded a favorable response in pre-clinical models, no significant improvement has been confirmed in clinical trials for PC. This may be partly attributable to the unique immunosuppressive tumor microenvironment of PC. Studies focusing on combination therapy showed the ability to break the immunosuppressive tumor microenvironment and enhance the immune response, which can translate to clinical benefits. Moreover, the application of sequencing techniques and neoantigen vaccines has achieved promising results in clinical trials, which promote the development of personalized immunotherapy. However, lack of effective biomarkers is another challenge for the realization of personalized immune medicine. Biomarkers are urgently needed to identify subgroup of patients who would benefit from immunotherapy. In this review, we discuss advances in immunotherapy for pancreatic cancer, as well as the challenges and prospects for personalized immune medicine.

1. Introduction

Pancreatic cancer (PC) is the fourth leading cause of cancer death, and has a high mortality in the U.S. Every year, nearly 43,000 individuals diagnosed with PC will die of this disease in the U.S. [1]. Surgical resection is usually the only potentially curable option for PC patients. However, the majority of patients with PC are diagnosed in advanced stages and for these patients, surgery is not an option [2,3]. Even after a successful resection, cancer recurrence is inevitable in most patients; this results in a median survival of approximately 11–15 months [4]. Despite significant advances in chemotherapy and radiotherapy, death rates from PC have continued to increase slightly in men and have leveled off in women [1]. Meanwhile, the 5-year survival rate of patients with PC is less than 10% [5]. Therefore, new effective therapies for PC are urgently needed.

Recently, immunotherapy has been shown to be a promising treatment for various cancers [6–11]. Immunotherapy can target tumor-specific antigens, activate the immune system, and destroy tumor cells without damaging normal tissues [12]. In particular, inhibition of cytotoxic T lymphocyte antigen-4 (CTLA-4) was approved by the FDA for the treatment of advanced melanoma [13]. Other immunotherapies, including programmed-death-1 (PD-1) and programmed-death-Ligand 1 (PD-L1) blocking antibody, were demonstrated to induce objective responses in approximately 20–30% of patients with different types of cancer, including melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma [14–16]. In this review, we discuss advances in immunotherapy and existing challenges in personalized immunotherapy for PC.

2. Tumor microenvironment in PC

Compared with other cancers, PC has unique immunologic conditions with low mutational burden, a dense stromal environment, and less immunogenicity (Fig. 1) [17,18]. Indeed, most conventional and

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Abbreviations used

PC	pancreatic cancer
CTLA-4	cytotoxic T lymphocyte antigen-4
PD-1	programmed-death-1
PD-L1	programmed-death-Ligand 1
NSCLC	non-small cell lung cancer
ECM	extracellular matrix
TILs	tumor-infiltrating lymphocytes
Tregs	regulatory T lymphocyte
MDSCs	myeloid-derived suppressor cells
PEGPH20	PEGylated human recombinant hyaluronidase
SD	stable disease
MMR	mismatch-repair
GVAX	GM-CSF cell-based vaccines
GM-CSF	Granulocyte-macrophage colony-stimulating factor
PRRs	Pattern recognition receptors
HSV	herpes simplex virus
CAR	Chimeric antigen receptor
CARTmeso cells	CAR T-cells that target mesothelin
MAV	metabolic active volume
Ad-mTNFa-mIL2	adenovirus expressing IL-2 and TNF-α
FAK	focal adhesion kinase
IFNγ	interferon γ
CDK4/6	cyclin-dependent kinases 4 and 6
TAMs	tumor-associated macrophages
PR	partial response

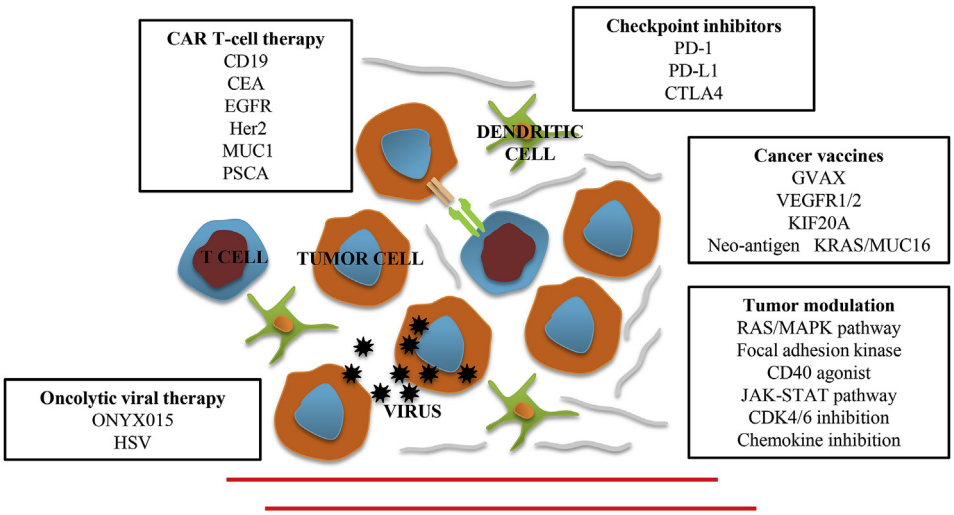

Fig. 1. Immunotherapy strategies for pancreatic cancer. Immunotherapy strategies include checkpoint inhibitors, cancer vaccines, CAR T-cell therapy, oncolytic viral therapy and tumor modulation.

immune therapies fail to provide substantial response rates in patients with PC. These failures are mainly attributable to the highly immunosuppressive tumor microenvironment [19], which consists of fibroblasts, immune cells, blood vessels, proteins produced by these cells, and extracellular matrix (ECM) [18].

Uncovering the underlying mechanisms of TME is challenging due to the heterogeneous nature of PC stroma that is infiltrated with multiple immune regulatory cells. Tumor-infiltrating lymphocytes (TILs) are functionally distinct immune cells interacting with the TME, in which the antitumor effectors $CD8^+$ T lymphocytes and $CD4^+$ helper T1 lymphocytes are associated with favorable outcomes, while $CD4^+$ helper T2 lymphocytes have an adverse effect on patient survival [20–23]. Regulatory T lymphocyte (Tregs) infiltration is also correlated with reduced survival in humans with cancer [24,25]. Enrichment of $FOXP3^+$ Tregs was identified in the "immune-escape" molecular subtype of PC, indicating the potential prognostic significance of Tregs [26,27].

Within this stromal reaction, macrophages and myeloid-derived suppressor cells (MDSCs) are another predominant population. Similar to T cells, macrophages contain cell types with different functions. For example, classically activated M1 macrophages are associated with longer survival, whereas alternatively activated M2 macrophages have permissive influences on tumor proliferation by recruiting Th2 and Treg cells [28]. MDSCs support immune evasion by EGFR/MAPK-dependent regulation of PD-L1 expression on tumor cells [29]. The TME also limits the interaction between T-cells and malignant cells. T-cells are unevenly distributed in tumor mass; these cells commonly infiltrate at the invasive front of the tumor or are trapped within peritumoral tissues [30,31].

PEGylated human recombinant hyaluronidase (PEGPH20) can sustain enzymatic depletion of hyaluronic acid (HA) in tissues, which may effectively break the immunosuppressive conditions of the TME and enhance the infiltration of T-cells into pancreatic tumors [32]. A preclinical study demonstrated that PEGPH20 in combination with gemcitabine can break down HA, inducing the re-expansion of PC blood vessels and improving the intratumoral delivery of chemotherapeutic agents [33]. Similar to the results of work with mouse models, a phase Ib study conducted in untreated stage IV PC showed a higher overall survival (OS) in "high"-HA patients (13.0 months) than in "low"-HA patients (5.7 months) when treated with PEGPH20 and gemcitabine [34]. These results support enzymatic remodeling of the tumor stroma with PEGPH20 to treat tumors characterized by the accumulation of HA. Drugstargeting the TME provide a promising strategy to overcome the barrier and improve the delivery efficacy of therapeutic agents.

3. Immune checkpoint inhibitors

Immune checkpoint inhibitors, including CTLA-4, PD-1, and PD-L1 blocking antibodies, have considerable utility in cancer treatment, especially in renal cell carcinoma, melanoma, and non-small cell lung cancer [13–16,35]. Permanent tumor regression with a 6-to-17% objective response rate and long-term stabilization of disease were reached in the aforementioned cancers in a multicenter phase I trial of PD-L1 [14]. Unfortunately, attempts at immune checkpoint inhibitors

to treat PC have achieved limited clinical benefits when applied as single agents (Table 1), which may be attributed in part to the unique immunosuppressive tumor microenvironment [14,36,37].

Another important factor may be the expression of PD-1/PD-L1. The reported PD-1 expression level is inconsistent, ranging from 12 to 90%. This inconsistency may explain the unresponsiveness of PC to checkpoint blockade therapy [38–41]. Predictive biomarkers for checkpoint inhibitors are needed to improve the therapeutic benefits; combined biomarkers such as mismatch-repair (MMR), oncogene mutations and neoantigens burden may provide a new strategy [42]. Thus, the expression of PD-1/PD-L1 should be tested and seriously considered before the application of checkpoint inhibitors for patients with pancreatic cancer.

The combination of checkpoint inhibitor with chemotherapy has not shown significant improvements in clinical trials [43,44]. In a phase Ib trial, patients taking tremelimumab plus gemcitabine reached 7.4 months median OS; two of 28 patients achieved partial response at the end of treatment [43]. The best response to pembrolizumab combined with gemcitabine was stable disease (SD), reported in a phase Ib study [44]. Thus, the efficacy of checkpoint inhibitors combined with chemotherapy requires further validation.

Checkpoint inhibitors combined with another immunotherapy achieved encouraging results in PC. Granulocyte-macrophage colony-stimulating factor (GM-CSF) cell-based vaccines (GVAX), when administered as a single agent or in combination with low-dose cyclophosphamide, have been confirmed to deplete Tregs and form intratumoral tertiary lymphoid aggregates to alter the TME. This finding provides the first example of immunotherapy converting a “non-immunogenic” cancer into an “immunogenic” cancer, and suggests that vaccine-primed patients with PC may be better candidates for immune checkpoint therapies [39]. In a phase Ib study, the combined treatment of GM-CSF cell-based vaccines with ipilimumab yielded a longer OS than that observed with ipilimumab alone in patients with advanced metastatic PC. Interestingly, an expansion in mesothelin-specific T-cell repertoires was found in patients who received combined therapy, suggesting that GVAX can induce T-cell immunity and enhance the efficacy of CTLA-4 antibody [45]. This combination provides a novel method that may facilitate clinical translation.

Recent studies have demonstrated that the differential composition of patients' microbiomes may be another variable affecting the inter-patient heterogeneity to checkpoint inhibitors. Preclinical mouse models with fecal material from responding melanoma patients showed better tumor control and greater efficacy than these treated with anti-PD-L1 therapy alone [46–48]. In the pancreas, intestinal bacteria can directly influence the tumor environment by migration. Compared with normal tissues, markedly more bacteria were detected in both mouse and human PC. Bacterial ablation was related to immunogenic reprogramming of the PC tumor microenvironment, and also improved the efficacy of checkpoint inhibitors by upregulating PD-1 expression. Therefore, gut microbiota play a critical role in mediating the response to immunotherapy [49].

Taken together, the literature indicates that checkpoint blockade in combination with another immunotherapy has the potential for clinical benefit superior to that of the inhibitor alone or that observed in combination with chemotherapy. Further study should be undertaken to determine the best strategy.

4. Cancer vaccines

The use of cancer vaccines has been evaluated in clinical settings and has demonstrated an antitumor immune response in PC. GVAX, which is composed of GM-CSF secreted by two irradiated allogeneic PC cell lines, is the most extensively evaluated vaccine [50]. GVAX induced T-cell immunity to cancer antigens and offered favorable prognosis when used in combined therapy [39,45]. In a phase II study, 60 patients with resected pancreatic cancer treated with chemotherapy in combination with GVAX showed 17.3 months DFS and 24.8 months OS. In addition, mesothelin-specific $CD8^+$ T cells were correlated with disease-free survival [51]. The application of GVAX before checkpoint inhibitors was confirmed to change the immunosuppression of the TME and induce T-cell immunity, which profoundly improved clinical responses and survival rates in patients with PC [39,45]. In brief, the combination therapy of GVAX and checkpoint inhibitors showed a promising prognosis in patients with PC. However, more studies with well-designed and robust validation clinical trials are needed to provide evidence to support personalized immune medicine.

Another promising vaccine targets to the neo-antigen, which is derived from somatic variations unique in the tumor. Unfortunately, research into neo-antigens has remained stagnant for decades due to technical restrictions. The recent development of sequencing techniques makes it possible for researchers to identify individualized tumor mutations and perform computational prediction of neo-antigens, for use in the design and manufacturing of a vaccine unique for each patient. Different from other immunotherapy, specific neo-antigen antibodies could simultaneously target various antigens and thus achieve several-fold efficacies in patients with cancer. Although neo-antigen vaccine has showed favorable result in PC, most trials were individual cases. More evidences are needed to translate neo-antigen vaccine into clinical application.

The first application of neo-antigen vaccine was in melanoma. After vaccination, four of six enrolled patients achieved no recurrence at 25 months; two with recurrent disease were subsequently treated with anti-PD-1 therapy and had complete tumor regression [52]. A patient with PC received six cycles of gemcitabine after resection, and metastasis in the liver was diagnosed without resection. Then, 19 cycles of FOLFIRINOX were administered. The patient achieved a second complete remission (CR). Subsequently, this patient was treated with five tumor-specific peptide vaccinations combined with GM-CSF, while FOLFIRINOX chemotherapy continued in parallel for another seven cycles. Six years after cancer diagnosis, this patient still alive and has been in CR for more than 4 years. This case demonstrated that specific neo-antigen vaccines can lead to a long-lasting and diverse immune response against these targets, and was related to prolonged clinical remission [53]. The signature mutations identified in PC include KRAS, TP53, SMAD4, and ROBO2; KRAS mutations were observed in > 90% of cases [54,55]. A Phase I/II clinical trial enrolled 23 patients who were treated with a mutant RAS vaccine. The results showed that 20% of patients experienced 10-year survival (4 patients out of 20 evaluable)

Table 1
Checkpoint inhibitor therapy trials in pancreatic cancer.

Phase	Setting	*N*	Intervention	Response rate	Reference
I	Advanced or metastatic	5	Anti-PD-L1 TGF β	1/5	[107]
I	Advanced	1	Atezolizumab	0	[108]
Ib	Metastatic	19 evaluable	Tremelimumab Gemcitabine	2/19	[40]
I	Advanced or metastatic	14	Anti-PD-L1	0	[10]
II	Locally advanced/metastatic	7/20	Ipilimumab	0	[33]
Ib	Advanced or metastatic	11	Pembrolizumab Chemotherapy	2	[41]
I	Advanced	1	Pembrolizumab	0	[109]

and long-term immunological T-cell reactivity [56]. Another study identified both high neo-antigen number and abundant $CD8^+$ T-cell infiltrates in long-term survivors of PC, in whom a large amount of MUC16 neo-antigen was also detected [19]. MUC16 (also known as CA125) is a tumor-specific antigen that is overexpressed in PC [57]. Investigation of MUC16 and Tregs revealed that MUC16 promoted Foxp3 expression and Tregs enrichment in tumor lesions through the JAK2/STAT3 pathway, which was activated by tumor-secreted IL-6 [58]. Thus, MUC16 may be a biomarker to predict the overall survival and a potential treatment target for PC.

Other cancer vaccines have yielded little success in clinical trials. Adding telomerase vaccination to chemotherapy made no significant difference in median OS in a randomized phase III trial performed with patients with advanced PC [59]. A multicenter, single-armed, phase II trial combining gemcitabine with VEGFR1, VEGFR2, or KIF20A in locally advanced and metastatic PC showed that a better survival rate seems to occur in patients who exhibit peptide-specific T-cell induction [60]. In a phase II study, peptide cocktail vaccine OCV-C01, containing epitope peptides derived from KIF20A, VEGFR1, and VEGFR2, was combined with gemcitabine in an adjuvant treatment for patients with resected PC. However, no significant improvement of median DFS was demonstrated [61]. Despite the unsatisfactory results of the above cancer vaccines, however, most vaccines were found to be immunogenic and increased vaccine-specific T-cell responses.

5. Oncolytic viral therapy

Oncolytic viral therapy is a novel treatment that utilizes replication-competent viruses, which selectively infect, replicate in, and lyse tumor cells, while leaving normal cells unharmed [62]. The amplification and spread of viruses were limited by innate immunity, while the re-infection of viruses was defended by adaptive immunity. Pattern recognition receptors (PRRs) can detect different evolutionarily conserved structures on viruses, constituting the first line of innate immunity. PRRs also cause intracellular signaling cascades and subsequently activate adaptive immunity against re-infection of viruses [63]. Adenovirus-based oncolytic viruses are the most extensively evaluated approaches to oncolytic viral therapy. Initially, an E1B 55 kDa region-deleted adenovirus ONYX015 was evaluated in PC, which selectively replicates in and lyses TP53-deficient cancer cells [64]. ONXY-15 was found to be effective in nude mouse-human tumor xenografts, demonstrating antitumor efficacy and increased survival [65]. However, in a phase I dose escalation trial of ONYX-015, no objective responses and viral replication were detected in patients with unresectable PC [66]. In another phase I/II trial, ONYX015 in combination with gemcitabine was a feasible and well-tolerated therapy in patients with PC [64]. Among the 21 patients included in this trial, only two achieved partial responses.

The herpes simplex virus (HSV) is a large enveloped virus with double-stranded DNA, consisting of HSV1 and HSV2, which could mediate T-cell reactivity and indirectly induce an immune response to cancer [67]. In a phase I clinical trial, among six patients treated with HF10, three were stable, one was in regression, and two were in progression [68].

In conclusion, work using preclinical animal models of PC has provided promising results when animals were treated with different oncolytic viruses. However, the results from the current published clinical trials remain frustrating (Table 2). The higher level of Tregs in oncolytic virotherapy may be a key factor limiting the efficacy in patients with metastatic PC [69]. More clinical trials are urgently needed to improve the efficacy of oncolytic viral therapy in the treatment of PC.

6. Adoptive T-cell therapy

Chimeric antigen receptor (CAR) T-cell therapy is an adoptive T-cell therapy that has shown favorable results in the treatment of patients with acute lymphoblastic leukemia positive for CD19 antigen, and it is the first CAR T-cell therapy approved by the FDA [70–72]. Recently, Fraietta et al. described an unusual chronic lymphocytic leukemia case treated with CD19 CAR T-cell therapy. There was no response until the fiftieth day after therapy. Subsequently, researchers found that 94% of CAR T-cells originated from a single clone in which lentiviral vector-mediated insertion of the CAR transgene disrupted the methylcytosine dioxygenase TET2 gene. The mutant CAR T-cell produced a non-curative response into a deep molecular remission in this patient, suggesting that TET2 modification may be useful for improving immunotherapies [73].

Despite promising outcomes in clinical trials of hematological malignancies, this is still a new approach for targeting solid tumors, such as PC [74]. Preclinical studies of PC have achieved satisfactory prognosis using genetically engineered T-cells, which express specific tumor-associated antigens, including mesothelin, CEA, EGFR, Her2, MUC1, and PSCA [75–79]. Mesothelin is an antigen that is expressed in almost 80% of the pancreatic cancer surface and is correlated with unfavorable prognosis [79]. A study of mRNA CAR T-cells that target mesothelin (CARTmeso cells) provided evidence for inducing epitope spread and mediating antitumor activity in patients with advanced PC [80]. Another phase I clinical trial has evaluated the safety and efficacy of CARTmeso cells in six patients with chemotherapy-refractory metastatic PC. The tumor metabolic active volume (MAV) remained stable in three patients and decreased in one patient expressing mesothelin. Meanwhile, all liver nodules had a complete reduction at 1 month compared with baseline in the patient expressing mesothelin [81].

Preclinical and clinical studies have demonstrated that CAR T-cell therapy is a promising treatment for pancreatic cancer. Compared with hematological malignancies, the main obstacles to CAR T-cell therapy in solid tumors include inefficient T-cell trafficking, antigen recognition specificity, antitumor activity, and safety control. In contrast to other solid tumors, PC has an immunosuppressive tumor microenvironment that plays an important role in its immune response [82]. Novel treatment combining CARTmeso cells with an oncolytic adenovirus expressing IL-2 and TNF-α (Ad-mTNFa-mIL2) demonstrated an enhancement of antitumor efficacy and a robust increase in TILs in human-xenograft mice. Ad-mTNFa-mIL2 enhanced CAR T-cell and host T-cell infiltration in tumor, changed tumor immune status through M1 polarization of macrophages, and increased dendritic cell maturation [83]. This combined therapy provides a promising approach to overcome the immunosuppressive TME to treat PC.

In brief, further investigation should be performed. Combination therapy may become an effective approach to overcome the hurdles currently limiting the application of CAR T-cell in solid tumor treatment.

7. Targeted therapies to amplify T-cell-mediated immunity

7.1. RAS/MAPK pathway inhibition

Although more than 90% of pancreatic cancer is accompanied by KRAS mutation, treatments that directly target KRAS mutation have not produced the expected effect [55]. Drugs targeting the downstream

Table 2
Oncolytic viral therapy trials in pancreatic cancer.

Phase	Setting	*N*	Intervention	Response rate	Reference
I	Locally advanced	9 evaluable	HF10 Erlotinib Gemcitabine	3/9	[110]
II	Metastatic	34	Pelareorep	1/34	[111]
II	Metastatic	7	ParvOryx	NR	[112]
II	Metastatic	36	Pelareorep Chemotherapy	7/36	[24]
I	Advanced	3	HF10	1/3	[65]
I	Advanced	23	ONYX-015	6/23	[63]

molecular markers, such as MAPK, have attracted attention. Tumor-infiltrating $CD8^+$ T cells can escape from death and MHC class I molecules on tumor cells can up regulate by MAPK inhibition [84]. Currently, MAPK inhibition is being tested in combination with another immunotherapy that targets focal adhesion kinase (FAK) (NCT02428270).

7.2. Focal adhesion kinase

FAK is a protein tyrosine kinase localized to focal adhesions, which are contact points between a cell and its ECM. FAK is also involved in multiple cellular functions, including cell proliferation, survival, and invasion [85]. A recent study identified that FAK inhibition can sensitize genetically engineered mouse models of PC to the anti-tumor effects of immune checkpoint inhibitors [86]. This work demonstrated synergistic activity based on the reprogramming of the fibrotic and immune-suppressive pancreatic TME in response to the FAK kinase inhibitor. In brief, FAK kinase inhibitor shows potential for combined treatment with immunotherapy in pancreatic cancer.

7.3. CD40 agonist

CD40, a member of the tumor necrosis factor α receptor superfamily, is expressed on immune cells, including macrophages, B cells, and dendritic cells. CD40 agonist antibodies promote APC maturation, activate macrophages rapidly to infiltrate tumors, facilitate the depletion of tumor stroma, alter the immunosuppression of the TME, and promote clinical responses in patients with advanced solid tumors [87,88]. Interferon γ (IFNγ) was reported to halt the antitumor functions of CD40 ligand-stimulated macrophages more efficiently than do IL-4 and IL-13 [89]. In A phase I study, out of 21 evaluable patients with PC treated with CD40 agonists (CP-870,893) combined with gemcitabine, four had a partial response (PR) and eleven had SD [90]. In summary, CD 40 agonist therapy can reverse immune suppression and promote antitumor T-cell responses by activating macrophages, which may increase the efficacy of other immunotherapy, such as checkpoint inhibitors [88].

7.4. JAK-STAT pathway inhibition

The JAK/STAT signaling pathways are associated with tumor proliferation and survival, and play an important role in regulating stromal cells, including immune cells recruited in the TME. The application of JAK-STAT inhibitor ruxolitinib in a mouse model of PC inhibited stromal inflammation and facilitated cytotoxic T lymphocyte infiltration, which may result in enhanced efficacy of α-PD1 therapy [91]. In a phase II study, patients with metastatic PC treated with JAK inhibitor ruxolitinib combined with capecitabine showed significantly longer OS than did those patients treated with capecitabine alone [92].

7.5. Cyclin-dependent kinases 4 and 6 (CDK4/6) inhibition

Cyclin-dependent kinase-4 and 6 are hallmarks of the cancer cell cycle. Specific inhibitors that target CDK4 and CDK6 have been used to treat a variety of tumors [93,94]. Palbociclib was the first CDK4/6 inhibitor to illustrate clinical efficacy in ER-positive, HER2-negative advanced breast cancer [95]. CDK4/6 inhibitors depend on the mitotic cell cycle in the phosphorylation and inactivation of the retinoblastoma tumor-suppressor protein Rb to arrest the cell cycle [96]. However, the regulation of Rb frequently loses efficacy in tumor cells due to the absence of the CDKN2A locus [97]. Approximately 80% of PC has mutations in p16INK4A, an inhibitor of CDK4 and CDK6, which is encoded by CDKN2A [98]. In a study of patient-derived xenografts of PC, tumor proliferation was completely suppressed by CDK4/6 inhibitors [99]. In addition to tumor cell cycle arrest, CDK4/6 inhibitors promote anti-tumor immunity by enhancing tumor antigen presentation and suppressing the proliferation of Tregs in breast cancer [100]. Thus, CDK4/6 inhibitors should be evaluated in combination with other immunotherapy in multiple solid tumors, including PC.

7.6. Chemokine pathway inhibition

Chemokines play an important role in immunotherapy. The CXCL12/CXCR4 axis is a predominant chemokine moderator of the TME, and high levels of CXCR4 expression are associated with poor prognosis in PC [101,102]. When combined with α-PD-L1, the number of proliferating tumor cells is greatly reduced [18]. The chemokine CC-chemokine ligand 2 (CCL2) is responsible for the recruitment of CC-chemokine receptor type 2^+ (CCR2) inflammatory monocytes to pancreatic tumors, where the monocytes become immunosuppressive tumor-associated macrophages (TAMs) [103]. In a phase Ib clinical trial, CCR2 inhibitor (PF-04136309) in combination with chemotherapy (FOLFIRINOX) was administered to patients with borderline resectable or locally advanced pancreatic cancer, demonstrating 97% (32 out of 39) local tumor control and greater safety and tolerance with the combined therapy [104]. Another study reported that CCR2 blockade combined with CXCR2 inhibitor reduced total tumor-infiltrating myeloids, promoting a greater antitumor immune response in PC mouse models when compared with either therapy alone [105].

8. Conclusion

Pancreatic cancer is a lethal disease with a complex molecular landscape that hinders both research advances and treatment efficiency. Indeed, the unique immunologic conditions of PC, especially the highly immunosuppressive tumor microenvironment, may be the main reason for unsuccessful treatment [106]. Due to the low immunogenic characteristics of PC, most immunotherapies have not reached the expected efficacy observed in other cancers, such as melanoma. In particular, checkpoint inhibitors as single agents have failed in clinical trials.

With the rapid development of immunogenomics, more effective and personalized immunotherapy for PC should be proposed and verified in clinical trials. The key to improving immune therapy efficacy in PC is to break the immunosuppressive TME and then convert a “non-immunogenic” cancer into an “immunogenic” cancer. Therefore, great effort should be made to overcome the barriers from the immunosuppressive microenvironment.

Various combinations of immunotherapy provide a promising strategy to break the immunosuppressive microenvironment, and enhance safety and efficacy in PC treatment. Moreover, neoantigens/neoepitopes for personalized vaccines have shown the ability to target multiple mutations and stimulate relevant immune cells. Most studies for immunotherapy were phase I/II trials; thus, more multicenter, phase III clinical trials are urgently needed. Nevertheless, emerging genomics and biomarker data provide an unprecedented opportunity to identify new targets, investigate novel strategies, and establish a personalized, precision medicine. There exist prospects for as well as challenges to personalized immune medicine for PC treatment.

Conflicts of interest

The authors have no conflict of interest to disclose.

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