Cancer-Associated Fibroblasts and T Cells

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pancreatic ductal adenocarcinoma (PDAC) | cancer-associated fibroblasts (CAFs) | T cells | tumor microenvironment | immune checkpoint inhibitors | chemokines

1. Introduction

Pancreatic cancer is projected to be the second leading cause of cancer-related deaths in 2030 as a result of the lack of an effective treatment and the increasing incidence rate [1]. The only potential cure for pancreatic cancer is surgery, but due to its late detection only 15–20% of the diagnosed patients present with resectable tumors, and with surgery alone, less than 10% survive 5 years or more. Resection followed by chemotherapy increases the 5-year overall survival to only 16–20% [2][3]. The standard treatment for unresectable tumors is chemotherapy but the median overall survival is at best 16 months [4].

Although cancer immunotherapy has been shown to be effective against a variety of cancers during the last decade, there is very little progress in pancreatic cancer [5]. The majority of pancreatic tumors are defined as pancreatic ductal adenocarcinoma (PDAC), which is characterized by a dense stroma surrounding the cancer cells [6]. Release of extracellular matrix components by CAFs triggers fibrosis which obstructs the intra-tumoral vessels and prevents therapy delivery and infiltration of tumor-reactive immune cells. Therefore, it is likely that immunotherapy combined with other treatments targeting the stromal barrier could be promising for pancreatic cancer patients.

CAFs release a number of different factors, including chemokines, cytokines, and growth factors, that promote immunosuppression through recruitment of immunosuppressive cells such as T regulatory cells (Tregs) and myeloid cells, upregulation of immune checkpoint molecules on T cells, and regulation of T-cell migration. It is still not well understood which factors are involved in regulating T-cell exhaustion and migration. However, several recent studies and subsequent clinical trials support that reprogramming of the suppressive microenvironment by blocking certain chemokine/chemokine receptor axes can improve immunotherapy outcomes in pancreatic cancer patients.

2. Therapeutic Treatments to Target CAF-Derived Immunosuppressive Factors

Several clinical trials have evaluated the benefit of targeting immunosuppressive factors in pancreatic cancer patients measured by clinical outcomes. However, to our knowledge, there are no studies investigating the effects on the immune profile after therapy. **Table 1** includes a summary of the completed and active clinical trials targeting CAF-derived immunosuppressive factors in pancreatic cancer.

Table 1. Immunosuppressive targets in the pancreatic tumor microenvironment used in preclinical models and clinical trials with the reported observations on the effects on immune cells and the primary end point of the clinical trial.

Observations	CLINICAL TRIALS					
Targetin Preclinical Models [ref]	NCT	Treatment	Phase	Condition	Status	Primary Endpoint// Observations [ref]
IL-6						
	NCT00841191	Siltuximab	I/II	Unresectable	Completed	CBR// No benefit =inflammatory cytokines =Angiogenesis markers ↓pSTAT3 [67]
	NCT02767557	Tocilizumab Gemcitabine Nab-paclitaxel	II	Unresectable	Recruiting	OS
IL-6 + ICI						
↓Tumor growth ↑Survival ↑T-cell infiltration [68]	NCT04258150	Nivolumab Ipilimumab Tocilizumab SBRT	II	Unresectable	Active	ORR
	NCT04191421	Siltuximab Spartalizumab	I/II	Unresectable	Recruiting	Determine dose
COX-2						
	NCT00176813	Celecoxib Gemcitabine Cisplatin	II	Unresectable	Completed	OS// No benefit [69]
		Celecoxib Gemcitabine	II	Unresectable	Completed	DFS/OS/tolerability// No benefit ↓VEGF [70]

Observations Targetin Preclinical Models [ref]	CLINICAL TRIALS					
	NCT	Treatment	Phase	Condition	Status	Primary Endpoint// Observations [ref]
		Celecoxib Gemcitabine	II	Unresectable	Completed	Toxicity/ORR// ↑OS ↓CA19.9 [71]
		Celecoxib Gemcitabine Irinotecan	II	Unresectable	Completed	Toxicity/ORR// ↑OS ↓CA19.9 [72]
	NCT03838029	Etodolac Propranolol Placebo	II	Resectable	Recruiting	DFS/biomarkers in blood
	NCT03498326	Celecoxib Gemcitabine	II	Resectable	Recruiting	DFS
COX-2 + ICI						
↓Tumor growth ↑$CD8^+$ T-cell infiltration [73]	NCT03878524	Multiple drugs including Celecoxib Nivolumab	II	Unresectable	Recruiting	Find the best combination of drugs
TGF-β						
	NCT00844064	AP 12009	I	Unresectable	Completed	MTD// ↑OS
	NCT04624217	SHR-1701	I/II	Unresectable	Recruiting	RP2D/ORR
	NCT03666832	TEW-7197	I/II	Unresectable	Recruiting	DFS
	NCT03685591	PF-06952229 Enzalutamide	I	Unresectable	Recruiting	DLT
TGF-β + ICI						
↓Tumor growth ↑T-cell infiltration ↑$CD8^+$ T-cell cytotoxicity [74,75]	NCT02734160	Galunisertib Durvalumab	I	Unresectable	Completed	DLT// Limited effects [76]
	NCT04429542	BCA101 Pembrolizumab	I	Unresectable	Recruiting	Safety/tolerability/DLT
	NCT02947165	NIS793 PDR001	I	Unresectable	Active	DLT

ref, reference; ICI, immune checkpoint inhibitor; NCT, clincialtrials.gov identifier; CBR, clinical benefit response; OS, overall survival; ORR, objective response rate; DSF, disease-free survival; MTD, maximum tolerated dose;

RPD2, recommended phase 2 dose; DLT, dose-limiting toxicities; CA19.9, carbohydrate antigen; =, no changes; ↓, decrease; ↑, increase; //, separation between primary endpoint and observations.

A phase I/II clinical trial (NCT00841191) assessing the safety and efficacy of anti-IL-6, siltuximab, administered as a monotherapy to patients with pancreatic cancer, showed a good tolerance, but did not detect any clinical benefit [7]. The efficacy of anti-IL-6 combined with immune checkpoint inhibitors or with chemotherapy is currently being studied in several clinical trials (NCT04258150, NCT04191421).

The benefits of the COX-2 inhibitor, celecoxib, administered in combination with standard chemotherapy treatment, have been studied in several phase II clinical trials [8][9][10][11]. The treatment was well tolerated by the patients in all the studies but with varying clinical effects. Another study showed a 4-fold increase in one-year overall survival for patients treated with combination therapy compared to chemotherapy alone [11]. The benefits of COX-2 inhibitors are being further investigated in several clinical trials (NCT03838029, NCT03498326, NCT03878524).

A phase I clinical trial (NCT02734160) evaluating anti-TGF-β-R1 combined with anti-PD-L1 in metastatic pancreatic cancer patients showed limited clinical effects with an objective response rate of only 3% and a median overall survival of 5 months [12]. The synergistic effect of anti-TGF-β and immune checkpoint inhibitors is being evaluated in different ongoing clinical trials (NCT04624217, NCT04429542, NCT02947165). Furthermore, a phase I/II clinical trial (NCT00844064) with advanced pancreatic cancer patients who received the TGF-β2 anti-sense oligonucleotide, OT-101, followed by subsequent chemotherapy, showed an improved overall survival [13]. Further clinical trials with anti-TGF-β are ongoing (NCT03666832, NCT03685591).

3. Therapeutic Treatments to Target Chemokines

T-cell infiltration into the tumor nest is crucial for a good prognosis in pancreatic cancer patients. As described above, many antagonists have been tested in preclinical animal models. However, only a few are currently being evaluated in clinical trials to treat pancreatic cancer patients. These include blocking of CCR2, CCR5, CXCR2, and CXCR4.**Table 2** includes a summary of the completed and active clinical trials targeting chemokine receptors in pancreatic cancer.

Table 2. Inhibitors of chemokines used in preclinical models and clinical trials with the reported observations on the effects on immune cells and the primary endpoint of the clinical trials.

Observations Targetin Preclinical Models [ref]	CLINICAL TRIALS					
	NCT	Treatment	Phase	Condition	Status	Primary Endpoint// Observations [ref]
CCR2						
+ CXCR2 target: ↓ MDSC	NCT01413022	PF-04136309 Folfirinox	Ib	Unresectable	Completed	Optimal dose and toxicity// ↓TAMs

Observations Targetin Preclinical Models [ref]	CLINICAL TRIALS					
	NCT	Treatment	Phase	Condition	Status	Primary Endpoint// Observations [ref]
infiltration [113]						↑$CD8^+$ and $CD4^+$ T-cell infiltration [114]
	NCT02732938	PF-04136309 Gemcitabine Nab-paclitaxel	Ib/II	Unresectable	Completed	DLT// No benefit Pulmonary toxicity [115]
CCR5 + ICI						
	NCT04721301	Maraviroc Nivolumab Ipilimumab	I	Unresectable	Active	Safety and tolerability
CCR2 + CCR5 + ICI						
	NCT03184870	Multiple drugs including BMS813160 Nivolumab	I/II	Unresectable	Active	Toxicity/Tregs numbers/ORR/PFS
CXCR1/2 + ICI						
↑ $CD4^+$ and $CD8^+$ T-cell infiltration [116,117] ↑ $CD4^+$ and $CD8^+$ T-cell cytotoxicity [116] ↓Neutrophils [116] ↓Metastasis ↓Tregs [117]	NCT04477343	SX-682 Nivolumab	I	Unresectable	Recruiting	MTD
CXCL12/CXCR4 axis						
	NCT02179970	AMD3100	I	Unresectable	Completed	Safety// ↑ T-cell, NK-cell infiltration and activation ↑ B-cell activation ↓CXCL8 [118]

Observations Targetin Preclinical Models [ref]	CLINICAL TRIALS					
	NCT	Treatment	Phase	Condition	Status	Primary Endpoint// Observations [ref]
CXCL12/CXCR4 axis + ICI						
↑$CD8^+$ T-cell infiltration and cytotoxicity [51]	NCT03168139	NOX-A12 Pembrolizumab	I/II	Unresectable	Completed	Safety// Stable disease ↑Th1 cytokines [119]
	NCT02826486	BL-0840 Pembrolizumab	IIa	Unresectable	Completed	ORR// ↑OS ↑$CD8^+$ T-cell infiltration ↓MDSC ↓Tregs [120]
	NCT04177810	AMD3100 Cemiplimab	II	Unresectable	Recruiting	ORR
	NCT02907099	BL-0840 Pembrolizumab	II	Unresectable	Active	ORR
	NCT04543071	BL-0840 Cemiplimab Gemcitabine Nab-paclitaxel	II	Unresectable	Recruiting	ORR

ref, reference; NCT, clinicaltrials.gov identifier; ↓, decrease; ↑, increase; MDSC, myeloid-derived suppressor cells; TAM, tumor-associated macrophages; ICI, immune checkpoint inhibitor; NK, natural killer cells; Th1, T helper type 1 cells; OS, overall survival; DLT, dose-limiting toxicities; ORR, objective response rate; PFS, progression-free survival; MTD, maximum tolerated dose; // separation between primary endpoint and observations.

The safety and the efficacy of CCR2 blockade with PF-04136309, in combination with chemotherapy (folfirinox), has been shown in a phase Ib clinical trial in pancreatic cancer patients with advanced or borderline resectable tumors [14]. Blockade of the CCL2/CCR2 chemokine axis was well tolerated by the patients, which also showed a partial response. Combination treatment with chemotherapy resulted in a reduction in tumor-associated macrophages and an increased number of CD8+and CD4+T cells in the primary tumor compared to chemotherapy alone [14]. However, another safety and pharmacokinetics/pharmacodynamics phase Ib study which combined PF-04136309 and chemotherapy (gemcitabine/nab-paclitaxel) in patients with metastatic PDAC showed no significant improvement compared to chemotherapy alone but showed possible toxic effects in the lungs [15].

Preclinical models in pancreatic cancer have shown that inhibition of the CCL5/CCR5 axis with maraviroc leads to tumor cell apoptosis and growth arrest [16]. Clinical trials in colorectal cancer with this drug (NCT01736813, NCT03274804) have shown promising results [17][18], with reduced proliferation of tumor cells and a shift towards

M1 macrophages in one of the trials [17]. After these encouraging results, clinical trials with maraviroc combined with immune checkpoint inhibitors are currently ongoing for metastatic pancreatic cancer (NCT04721301). To boost the specific and encouraging effects of CCR2 and CCR5 antagonists, a phase Ib/II clinical trial with dual blockade of CCR2 and CCR5 with BMS 813160 as a monotherapy or in combination with chemotherapy or immunotherapy is currently ongoing for advanced pancreatic cancer patients (NCT03184870)

Another chemokine antagonist that has been shown to alter the tumor immune environment is the CXCR1/2 antagonist SX-682. The main function of CXCR2 is to regulate the recruitment and migration of neutrophils and MDSCs. SX-682 has been shown to enhance Th1 immune response in several animal models including melanoma, breast, lung, and prostate cancer [19][20][21]. This inhibitor is currently undergoing a safety evaluation in a phase I clinical trial for pancreatic cancer patients in combination with anti-PD-1 treatment (NCT04477343).

The CXCL12/CXCR4 axis excludes effector T cells from the tumor nests, impacting the efficacy of immune checkpoint inhibitors. The administration of the CXCR4 antagonist AMD3100 induced CD8+T cells infiltration and promoted a rapid activation and response of intratumoral T cells, natural killer cells, and B cells in a phase I clinical trial for metastatic PDAC [22]. The safety and clinical benefit of AMD3100 combined with anti-PD-1 treatment is being assessed in a phase II clinical trial (NCT04177810). A phase

4. Conclusions

Pancreatic CAFs have emerged as important regulators of the tumor microenvironment, both as restrainers of tumor growth but also as suppressors of tumor-reactive immunity. The recent discoveries about the diverse functions of different CAF subpopulations have significantly increased our understanding of the complex pancreatic stroma, but many questions still remain. The low mutational burden and the suppressive milieu in pancreatic cancer have been suggested to contribute to the lack of response to immune checkpoint inhibitors, but a key issue may be to assist T cells to efficiently come within close proximity of the malignant cells. Several lines of evidence suggest that chemokines and their cognate ligands play an important role in promoting T-cell exclusion from the tumor and further preclinical and clinical studies evaluating the role of chemokines are necessary to take full advantage of immune checkpoint therapeutics.

References

1. Rahib, L.; Smith, B.D.; Aizenberg, R.; Rosenzweig, A.B.; Fleshman, J.M.; Matrisian, L.M. Projecting cancer incidence and deaths to 2030: The unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 2014, 74, 2913–2921.
2. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer statistics, 2020. CA Cancer J. Clin. 2020, 70, 7–30.
3. Neoptolemos, J.P.; Palmer, D.H.; Ghaneh, P.; Psarelli, E.E.; Valle, J.W.; Halloran, C.M.; Faluyi, O.; O'Reilly, D.A.; Cunningham, D.; Wadsley, J.; et al. Comparison of adjuvant gemcitabine and

capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): A multicentre, open-label, randomised, phase 3 trial. Lancet 2017, 389, 1011–1024.

4. Furuse, J.; Shibahara, J.; Sugiyama, M. Development of chemotherapy and significance of conversion surgery after chemotherapy in unresectable pancreatic cancer. J. Hepato Biliary Pancreat. Sci. 2018, 25, 261–268.
5. Wu, J.; Cai, J. Dilemma and Challenge of Immunotherapy for Pancreatic Cancer. Dig. Dis. Sci. 2021, 66, 359–368.
6. Erkan, M.; Michalski, C.W.; Rieder, S.; Reiser–Erkan, C.; Abiatari, I.; Kolb, A.; Giese, N.A.; Esposito, I.; Freiss, H.; Kleeff, J. The activated stroma index is a novel and independent prognostic marker in pancreatic ductal adenocarcinoma. Clin. Gastroenterol. Hepatol. 2008, 6, 1155–1161.
7. Angevin, E.E.; Tabernero, J.; Elez, E.; Cohen, S.J.; Bahleda, R.R.; Van Laethem, J.-L.; Ottensmeier, C.C.; Lopez-Martin, J.J.; Clive, S.S.; Joly, F.F.; et al. A Phase I/II, Multiple-Dose, Dose-Escalation Study of Siltuximab, an Anti-Interleukin-6 Monoclonal Antibody, in Patients with Advanced Solid Tumors. Clin. Cancer Res. 2014, 20, 2192–2204.
8. El-Rayes, B.F.; Zalupski, M.M.; Shields, A.F.; Ferris, A.M.; Vaishampayan, U.; Heilbrun, L.K.; Venkatramanamoorthy, R.; Adsay, V.; Philip, P.A. A Phase II study of celecoxib, gemcitabine, and cisplatin in advanced pancreatic cancer. Investig. N. Drugs 2005, 23, 583–590.
9. Dragovich, T.; Burris, H.; Loehrer, P.; Von Hoff, D.D.; Chow, S.; Stratton, S.; Green, S.; Obregon, Y.; Alvarez, I.; Gordon, M. Gemcitabine Plus Celecoxib in Patients With Advanced or Metastatic Pancreatic Adenocarcinoma. Am. J. Clin. Oncol. 2008, 31, 157–162.
10. Ferrari, V.; Valcamonico, F.; Amoroso, V.; Simoncini, E.; Vassalli, L.; Marpicati, P.; Rangoni, G.; Grisanti, S.; Tiberio, G.A.M.; Nodari, F.; et al. Gemcitabine plus celecoxib (GECO) in advanced pancreatic cancer: A phase II trial. Cancer Chemother. Pharmacol. 2005, 57, 185–190.
11. Lipton, A.; Campbell-Baird, C.; Witters, L.; Harvey, H.; Ali, S. Phase II Trial of Gemcitabine, Irinotecan, and Celecoxib in Patients With Advanced Pancreatic Cancer. J. Clin. Gastroenterol. 2010, 44, 286–288.
12. Melisi, D.; Oh, D.-Y.; Hollebecque, A.; Calvo, E.; Varghese, A.; Borazanci, E.; Macarulla, T.; Merz, V.; Zecchetto, C.; Zhao, Y.; et al. Safety and activity of the TGFβ receptor I kinase inhibitor galunisertib plus the anti-PD-L1 antibody durvalumab in metastatic pancreatic cancer. J. Immunother. Cancer 2021, 9, e002068.
13. Hwang, L.; Ng, K.; Wang, W.; Trieu, V.N. OT-101: An anti-TGF-beta-2 antisense- primed tumors to subsequent chemotherapies. J. Clin. Oncol. 2016, 34, e15727.
14. Nywening, T.M.; Wang-Gillam, A.; Sanford, D.E.; Belt, B.A.; Panni, R.Z.; Cusworth, B.M.; Toriola, A.T.; Nieman, R.K.; Worley, L.A.; Yano, M.; et al. Phase 1b study targeting tumour associated

macrophages with CCR2 inhibition plus FOLFIRINOX in locally advanced and borderline resectable pancreatic cancer. Lancet Oncol. 2016, 17, 651.

15. Noel, M.; O'Reilly, E.M.; Wolpin, B.M.; Ryan, D.P.; Bullock, A.J.; Britten, C.D.; Linehan, D.C.; Belt, B.A.; Gamelin, E.C.; Ganguly, B.; et al. Phase 1b study of a small molecule antagonist of human chemokine (CC motif) receptor 2 (PF-04136309) in combination with nab-paclitaxel/gemcitabine in first-line treatment of metastatic pancreatic ductal adenocarcinoma. Investig. N. Drugs 2019, 38, 800–811.
16. Huang, H.; Zepp, M.; Georges, R.B.; Jarahian, M.; Kazemi, M.; Eyol, E.; Berger, M.R. The CCR5 antagonist maraviroc causes remission of pancreatic cancer liver metastasis in nude rats based on cell cycle inhibition and apoptosis induction. Cancer Lett. 2020, 474, 82–93.
17. Halama, N.; Zoernig, I.; Berthel, A.; Kahlert, C.; Klupp, F.; Suarez-Carmona, M.; Suetterlin, T.; Brand, K.; Krauss, J.; Lasitschka, F.; et al. Tumoral Immune Cell Exploitation in Colorectal Cancer Metastases Can Be Targeted Effectively by Anti-CCR5 Therapy in Cancer Patients. Cancer Cell 2016, 29, 587–601.
18. Haag, G.M.; Halama, N.; Springfeld, C.; Grün, B.; Apostolidis, L.; Zschaebitz, S.; Dietrich, M.; Berger, A.; Weber, T.F.; Zoernig, I.; et al. Combined PD-1 inhibition (Pembrolizumab) and CCR5 inhibition (Maraviroc) for the treatment of refractory microsatellite stable (MSS) metastatic colorectal cancer (mCRC): First results of the PICCASSO phase I trial. J. Clin. Oncol. 2020, 38, 3010.
19. Yang, J.; Yan, C.; Vilgelm, A.E.; Chen, S.-C.; Ayers, G.D.; Johnson, C.A.; Richmond, A. Targeted Deletion of CXCR2 in Myeloid Cells Alters the Tumor Immune Environment to Improve Antitumor Immunity. Cancer Immunol. Res. 2021, 9, 200–213.
20. Kargl, J.; Zhu, X.; Zhang, H.; Yang, G.H.Y.; Friesen, T.J.; Shipley, M.; Maeda, D.Y.; Zebala, J.A.; McKay-Fleisch, J.; Meredith, G.; et al. Neutrophil content predicts lymphocyte depletion and anti-PD1 treatment failure in NSCLC. JCI Insight 2020, 4.
21. Lu, X.; Horner, J.W.; Paul, E.; Shang, X.; Troncoso, P.; Deng, P.; Jiang, S.; Chang, Q.; Spring, D.J.; Sharma, P.; et al. Effective combinatorial immunotherapy for castration-resistant prostate cancer. Nature 2017, 543, 728–732.
22. Biasci, D.; Smoragiewicz, M.; Connell, C.M.; Wang, Z.; Gao, Y.; Thaventhiran, J.E.D.; Basu, B.; Magiera, L.; Johnson, T.I.; Bax, L.; et al. CXCR4 inhibition in human pancreatic and colorectal cancers induces an integrated immune response. Proc. Natl. Acad. Sci. USA 2020, 117, 28960–28970.

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