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Mini-review

Prevailing over T cell exhaustion: New developments in the immunotherapy of pancreatic cancer

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ABSTRACT

Pancreatic cancer is one of the most aggressive malignancies and has been considered poorly immunogenic for decades. However, this characterization might be over-simplistic. A more sophisticated approach is needed in order to develop new treatment strategies. In this review, we will focus on T cell exhaustion as a phenomenon of immune failure that is a useful paradigm to characterize immunosuppressive effects. Cancer creates an environment of constant antigen exposure and inflammation. In this setting, T cells transform into a differentiation state that has been termed T cell exhaustion, which is characterized by upregulation of inhibitory receptors, resulting in loss of effector function. The discovery of receptor-mediated immune checkpoints, which prevent uncontrolled T cell reactions, led to the development of a new class of antibodies termed checkpoint inhibitors. Unprecedented results in patients with metastatic melanoma and lung cancer have renewed interest in the immunotherapy of other solid tumor entities, including pancreatic cancer. Data on the efficacy of checkpoint inhibitors in pancreatic cancer are still sparse and indicate limited efficacy as single agents. Combination of checkpoint inhibitors with other immune-activating strategies or cytotoxic drugs might be a way to overcome therapy resistance in the treatment of pancreatic cancer.

Pancreatic cancer: a continuing challenge

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer death in the western world and remains one of the deadliest malignancies [1]. Even patients that qualify for surgical resection have a 5-year survival rate of not more than 20%. Reasons for the dismal prognosis are aggressive tumor biology with extensive local tumor infiltration, early metastasis, late diagnosis and limited efficiency of current therapies [2].

For decades, gemcitabine has been the standard treatment for patients with advanced PDAC despite its modest effect on patient survival [3,4]. Recently, advances have been achieved by combination with new drugs, such as erlotinib or nab-paclitaxel [5]. A more aggressive regime consisting of oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) has shown superior efficacy; however, this therapy is limited to patients with very good performance status. A major problem of pancreatic cancer therapy appears to be the strong desmoplastic reaction limiting accessibility of cytotoxic drugs to cancer cells. The stromal depletion hypothesis suggested that inhibition of pro-stromal signaling cascades might increase the efficacy of chemotherapeutic drugs and/or irradiation by increasing drug and oxygen delivery [6]. However, clinical trials have failed to reproduce treatment results obtained in genetically engineered mouse models [7]. Moreover, reduced stromal content in a murine model of PDAC increased tumor aggressiveness, indicative of a more complex role of the stromal compartment

Abbreviations: ACT, adoptive cell transfer; AP-1, activator protein-1; APC, antigen-presenting cells; CAR, chimeric antigen receptor; CTL, cytotoxic T cells; CTLA-4, cytotoxic T lymphocyte antigen 4; FDA, US Food and Drug Administration; IL-7, interleukin-7; IDO, indoleamine 2, 3-dioxygenase; IFN, interferon; IPMN, intraductal papillary mucinous neoplasms; LCMV, lymphocytic choriomeningitis virus; mAb, monoclonal antibodies; MDSC, myeloid-derived suppressor cells; NFAT, nuclear factor of activated T cells; PI3K, phosphoinositide 3-kinase; PDAC, pancreatic ductal adenocarcinoma; PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein-1; Treg, regulatory T cells; RIG-I, retinoic acid-inducible gene; SPRY2, sprouty homologue 2; TIM3, T cell immunoglobulin domain and mucin domain 3; TIGIT, T cell immunoreceptor with Ig and ITIM domains; TCR, T cell receptor (); TGF-β, transforming growth factor-beta; TAM, tumor associated macrophages; TIL, tumor-infiltrating T lymphocytes.

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[8]. Clinical trials exploring a plethora of drugs that showed efficacy in other solid tumors were disappointing in PDAC. Thus, novel therapeutic approaches are urgently needed.

The interplay of innate and adaptive immune cells within tumors plays a pivotal role in directing cell-based immunity against malignancies. $CD8^+$ cytotoxic T cells (CTL) are the most prominent cytotoxic cell fraction. An immunosuppressive tumor milieu, however, drives regulatory stimuli, hampering tumor eradication by putting a brake on efficient CTL responses. The Science magazine celebrated cancer immunotherapy as "Breakthrough of the Year 2013", mainly due to unprecedented results in patients with metastatic melanoma and lung cancer using antibodies that released the brake on the immune system, so called checkpoint inhibitors [9,10]. These studies renewed interest in T cell-based approaches to target other solid malignancies, including PDAC [11]. The discovery of immune checkpoints that had evolved to prevent uncontrolled immune reactions, made it possible to develop a whole new class of antibodies termed checkpoint inhibitors. Data on the efficacy of checkpoint inhibitors in PDAC are sparse and indicate limited efficacy as single agents [12,13]. More clinical trials are on the way to explore this strategy (NCT00836407, NCT00112580). Preclinical data reveal that checkpoint inhibitors are more effective when combined with other immune-activating strategies or cytotoxic drugs to induce relevant immune responses in PDAC [14,15], prompting a wave of new clinical trials (Table 1).

To understand why PDAC reacts so poorly to most therapies, including immunotherapy, and how this therapy resistance can be overcome, it is necessary to dissect the cellular and molecular components of anti-tumor immune responses. In this review, we will focus on T cell exhaustion as a phenomenon of immune failure that has proven to be a useful paradigm to characterize immunosuppressive effects of various cellular players and molecular pathways.

Mechanisms of immunosuppression in PDAC

Cytotoxic $CD8^+$ effector T cells mark the centerpiece of a successful tumor immune response, and tumor infiltration with $CD8^+$ T cells is associated with better prognosis of PDAC patients [16–18]. However, in most patients (and in murine models of pancreatic cancer) $CD8^+$ T cells are rather scarce and show decreased signs of activation suggesting an impaired infiltration and/or inhibited activation of tumor-reactive T cells [19,20]. It has been demonstrated that tumor-specific T cell infiltration is mandatory for beneficial efficacy: Survival was significantly longer in patients with tumor-associated antigen-specific CTL responses than in patients without [21]. In contrast to effector T cells, M2 tumor-associated macrophages (TAM) and myeloid derived suppressor cells (MDSC) are immunosuppressive, and a higher ratio of suppressive cells to $CD4^+$ and $CD8^+$ T cells has been associated with poor survival [22]. Genetically engineered models of PDAC cancer exhibit tumor T cell infiltration, as demonstrated by immunohistochemical staining, but most T cells sequester preferentially at the tumor margin, very similar to the pattern of T cell infiltration found in pancreatic cancer patients (Fig. 1). Thus, these tumors models appear to be suitable to investigate immunotherapeutic approaches [23]. Importantly, however, the sheer presence of $CD8^+$ T cells in a tumor is necessary, but not sufficient for successful antitumor immune responses [24]. Dysfunctionality of intratumoral T cells bears close resemblance to T cell exhaustion, and mechanisms of exhaustion play an important role in PDAC immuno-resistance. In a recent study the

Table 1
Selected ongoing clinical trials evaluating checkpoint blockade in pancreatic cancer.

Immune modifier	class	Target	Co-treatment	n	Phase	Est. primary completion date	Clinical trials.gov Identifier
Ipilimumab	ant-mAb	CTLA-4	Gemcitabine	28	Ib	Apr. 2016	NCT01473940
Ipilimumab	ant-mAb	CTLA-4	Tyrosine kinase inhibitor (Imatinib)	96*	I	Feb. 2017	NCT01738139
Ipilimumab	ant-mAb	CTLA-4	FOLFIRINOX + GVAX	92	II	Nov. 2017	NCT01896869
Nivolumab	ant-mAb	PD-1	Nab-Paclitaxel +/– gemcitabine	138*	I	Apr. 2018	NCT02309177
Nivolumab	ant-mAb	PD-1	Temsirolimus Irinotecan Irinotecan + capecitabine	49*	I/II	Apr. 2016	NCT02423954
Nivolumab	ant-mAb	PD-1	Anti-KIR mAb (Irilumab)	162*	I	Sep. 2017	NCT01714739
Nivolumab	ant-mAb	PD-1	GVAX	50	I/II	Aug. 2017	NCT02451982
Nivolumab	ant-mAb	PD-1	GVAX + CRS-207	94	II	Jan. 2019	NCT02243371
Nivolumab	ant-mAb	PD-1	–	1100*	I/II	Aug. 2017	NCT01928394
+/– Ipilimumab	ant-mAb	CTLA-4					
BMS-986016	ant-mAb	LAG-3	–	540*	I	Sep. 2016	NCT01968109
+/– Nivolumab	ant-mAb	PD-1					
Pembrolizumab	ant-mAb	PD-1	–	440*	I	Apr. 2016	NCT02054806
Pembrolizumab	ant-mAb	PD-1	Radiation + capecitabine	56	I/II	Jun. 2017	NCT02305186
Pembrolizumab	ant-mAb	PD-1	Bruton Tyrosine kinase inhibitor (ACP-196)	76*	II	May 2017	NCT02362048
Pembrolizumab	ant-mAb	PD-1	mFOLFOX6	128*	I/IIa	Jan. 2020	NCT02268825
Pembrolizumab	ant-mAb	PD-1	Tyrosine kinase inhibitor (Pexidartinib)	400*	I/II	May 2019	NCT02452424
Pembrolizumab	ant-mAb	PD-1	MVA-p53 Vaccine	12	I	Oct. 2016	NCT02432963
Pidilizumab	ant-mAb	PD-1	Gemcitabine	29	II	Feb. 2016	NCT01313416
MPDL3280A	ant-mAb	PD-L1	–	344*	I	Apr. 2014	NCT01375842
MEDI4736	ant-mAb	PD-L1	–	918*	I/II	Dec. 2016	NCT01693562
MEDI4736	ant-mAb	PD-L1	–	130	II	Mar. 2019	NCT02558894
+/–Tremelimumab	ant-mAb	CTLA-4					
+/– MEDI4736	ant-mAb	PD-L1	–	96*	II	Apr. 2018	NCT02527434
+/– Tremelimumab	ant-mAb	CTLA-4					
MEDI4736	ant-mAb	PD-L1	Radiation	60	I	Oct. 2017	NCT02311361
Tremelimumab	ant-mAb	CTLA-4					
MEDI4736	ant-mAb	PD-L1	Anti-CCR4 mAb (Mogamulizumab)	108*	I	Jun. 2016	NCT02301130
Tremelimumab	ant-mAb	CTLA-4					
PF-05082566	ago-mAb	CD137	Anti-CD20 mAb (Rituximab)	161*	I	Dec. 2016	NCT01307267
Urelumab	ago-mAb	CD137	–	122*	I	Mar. 2019	NCT01471210
Indoximod	small molecule	IDO	Gemcitabine + nab-Paclitaxel	98	I/II	Dec. 2015	NCT02077881

* Including several solid tumor entities, ant-mAb – antagonistic monoclonal antibody, ago-mAb – agnonistic monoclonal antibody.

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