

New revolution in immunology: PDAC model.

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Abstract

Several diseases undergo diagnosis difficulty due to complex pathology and the problem is aggravated due to patients developing resistance to current methods of treatment. Therefore, the need of the hour is the discovery of alternative diagnosis and treatment modules and immunoprofiling holds great promise in this respect. This issue has been discussed in this review with PDAC (Pancreatic Ductal Adenocarcinoma) as a complex disease model with common recurrence and diagnosis and treatment obstacles.

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a lethal disorder and one of the most common cancer subtypes today, especially in the developed world. It is an aggressive solid malignancy characterized by painless expansion, rapid progression through metastasis and absence of distinct symptoms. These clinical features lead to delayed diagnosis, mostly, at a late metastatic stage. Only 20% of patients with PDAC can be treated [1]. The existing treatment regime includes surgical removal (resection) of the tumor along with chemotherapy. Resistance to chemotherapy and radiation therapy is a major problem seen. This arises due to the complex tumour microenvironment (TME) which is characterized by epithelial-to-mesenchymal transition (EMT), desmoplasia of the stroma and evasion of tumour surveillance leading to a multistage interaction between the neoplastic and stromal cells [1-3]. Pancreatic stellate cells are the major orchestrators of desmoplasia in PDAC. The contribution of PSCs to the development of the tumor microenvironment is manifold. The PSCs differentiate into cancer-associated fibroblasts (CAFs) which produce desmoplastic stroma and two sub-populations of CAFs exist. One sub-population expresses elevated levels of α -smooth muscle actin (α SMA) while the other one distantly situated from neoplastic cells express low levels of α SMA and produce IL-6 which promotes cancer progression and immune suppression. Activated PSCs express cytokines, chemokines and adhesion molecules that regulate T-cell migration that are involved in immune-surveillance. CXCL12 secreted by activated PSCs serve as a chemoattractant for CD8+ T cells which show pronounced chemotaxis towards the activated PSCs [4]. Biomarkers and signaling pathways useful in PDAC for immunoprofiling.

The major problem of delayed diagnosis in PDAC due to the unavailability of suitable biomarkers can be overcome by the clinical application of immunoprofiling. Discovery of novel biomarkers with prognostic value include various immune molecules and stroma derived proteins. For example, in pancreatic cancer patients higher levels of endostatin and endostatin processing MMPs (matrix metallo-proteases) like MMP-3, MMP-9, MMP-13 have been shown to circulate and these can be used as markers to determine the stage of PDAC. Cytokines like IL-1 β , which is a key mediator of inflammation, IL-

7, which plays a crucial role in the development of lymphocytes, and G-CSF (granulocyte-colony stimulating factor) are found to be lowly expressed compared to autoimmune pancreatitis (AIP) while higher expression of IL-8 and TNF- α were also reported by a recent study [5]. TNF- α induces pancreatic cell proliferation and promotes invasiveness of human pancreatic cancer cells, tumour growth and metastasis in mice. These can serve as discriminatory markers for diagnosis. Infiltration of PDAC tissue by macrophages, especially, CD33+ CD163+ +M2 macrophages and CD4+ T cells that concomitantly express PD-1 (programmed cell death-1) takes place. Concentration of IL-6, IL-7, IL-15, monocyte chemoattractant protein-1, interferon- γ -inducible protein-1 have been found to be upregulated in PDAC sera [6]. CD15+ neutrophils, CD20+ B cells and CD206+ tumour associated macrophages (TAMs) are frequently present in tumour and correlate with reduced survival in PDAC patients (7). CD4+ T helper cells, CD8+ cytotoxic T lymphocytes and CD117+ mast cells in PDAC patients are associated with favourable prognosis. Three intra-tumoral infiltrating immune markers, namely, CD15+, CD206+ and CD117+ and a MAD4 mutation can be used to predict recurrence and survival in postoperative patients [7]. Biomarkers, recently found to have diagnostic and prognostic value include THBS2 (thrombospondin-2 [8]; SYCN and REG1B combined with CA19-9 for pancreatic cancer diagnosis [9]; TIMP-1 and LRG-1 along with CA19-9 (carbohydrate antigen 19-9) are useful for distinguishing between healthy subjects and early-stage pancreatic cancer [10]. Signaling pathways play a crucial role in cell growth, proliferation and secretion of cytokines. Therefore, they are pivotal instruments modulating the progression of disease. These are being maneuvered and are highly promising for the treatment of PDAC. The Important signalling pathways which have the potential of being exploited for the treatment of PDAC are TGF- β signaling that regulates G-CSF secretion in the pancreatic epithelium with its role in tumorigenesis through angiogenesis and immune suppression [11]. STAT3/Nrf2 signaling pathway is significantly involved in PDAC metastasis and progression. The PSCs secrete IL-6 which stimulates PDAC cell proliferation via nuclear factor erythroid 2 (Nrf2)-mediated metabolic reprogramming [12]. The EGFR/p38-MAPK signaling pathway is involved in angiogenesis in PDAC and functions through overexpression of COX2 (cyclooxygenase-2) and SP1 (specificity protein-1) [13]. The PANCALYZE trial is

a multi-center study based on the application and assessment of the efficacy of four biomarkers CXCR4, SMAD4, SOX9 and IFIT3 after resection in PDAC patients [14].

Conclusion

The recent discovery of novel biomarkers and their application in the prognosis of pancreatic cancer has been a stupendous development in the PDAC treatment regime. The major strategies maneuvered here include exploiting the key signaling pathways to impede tumor progression. The availability of biomarkers can help in routine diagnosis and prognosis of PDAC and many of these biomarkers are already hitting clinical trials. The complex TME of PDAC, the biggest obstacle to chemo-radiation therapies can now be looked upon as a less aggressive enemy due to availability of combination therapy like a combination of gemcitabine and Nab-paclitaxel(Nab-P) or the application of another drug FOLFIRINOX [15].

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