The Tumor Microenvironment of Pancreatic Cancer

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Pancreatic ductal adenocarcinoma (PDAC) has a dismal prognosis along with rising incidence rates and will be responsible for many cancer deaths in the future [1,2]. Most patients present with metastatic and/or locally advanced, non-resectable disease and can only be treated with palliative chemotherapy [1–3]. PDAC patients with (borderline) resectable disease can profit from an oncologic resection [4,5]; however, a significant number of these patients will eventually develop recurrent disease a few months after resection [6]. The use of neoadjuvant chemoradiation (with or without systemic chemotherapy), which can improve the resectability of PDAC, as well as the administration of postoperative adjuvant chemotherapy with more modern regimens such as FOLFIRINOX (combination of Fluoruracil, Folinsäure (Leucovorin), Irinotecan and Oxaliplatin) and gemcitabine/nabpaclitaxel, have contributed to further, modest improvements in survival [7–10]. However, in order to substantially improve the survival rates of PDAC patients, we need new, more individualized clinical management strategies, including a more accurate prognostic/predictive patient classification.

Recently, genomic and transcriptomic profiling has allowed the characterization of distinct molecular PDAC subtypes with unique genetic signatures, deepening our knowledge of the intrinsic mechanisms of PDAC progression [11–14]. However, the translation of these findings into clinical practice has so far been very limited. One of the reasons for this is the relative lack of actionable targets as well as the widespread intra-tumoral heterogeneity (ITH) present in many solid tumors including PDAC and known to correlate with tumor progression and poor outcomes [15–19]. In this context, the evolutionary diversity within the tumor is driving the emergence of aggressive subclones, especially under pressure from therapeutic agents.

During PDAC evolution, the complexity and the dynamic interactions between tumor and immune cells within the tumor microenvironment (TME) play important roles in the pathogenesis and progression of the disease [20]. On the one hand, the tumor cells often display oncogenic mutations that help them evade anti-tumor immunity, while on the other hand, the TME of PDAC can also influence the local immune response [20–23]. Thus, the immunocomplex characteristics of the TME interact and cooperate with the tumor cells in a dynamic way to affect tumor progression. Therefore, when it comes to PDAC, analysis of the TME has to be taken into account as well.

The TME is a very complex ecosystem in which several factors, such as immune cells of the innate and adaptive immunity, cytokines and other immunoregulatory molecules, extracellular matrix as well as stromal fibroblasts, are involved, contributing to the development of a frequently immunosuppressive, highly hypoxic and desmoplastic tumor, resistant to all kinds of therapy, including chemotherapy, targeted therapy and immunotherapy [20]. For example, PDAC is known to be associated with a rich, strongly desmoplastic stroma comprising cancer-associated fibroblasts (CAFs), pancreatic stellate cells and extracellular matrix, resulting in a tumor that is highly hypoxic and hypovascular [24]. Moreover, the TME of PDAC is frequently characterized by a low number of tumor infiltrating lymphocytes (TILs) and a high number of T regulatory cells (Tregs) and myeloid-derived suppressor cells (MDSCs), which serve to decrease the tumor-specific immune response [25]. This immunosuppressive and desmoplastic TME is thought to help tumor cells evade anti-tumor immune response by impeding the access of T cells and precluding immune cells from the tumor cells, a phenomenon known as
immune privilege [26]. It is therefore important for TME factors to also be considered in the view of overcoming therapy resistance [12]. Some encouraging evidence comes, however, from studies on long-term survivors of PDAC. These recent studies have shown that the neoantigen quality (rather than quantity) can modulate immunogenicity in PDAC and have reported that both a high neoantigen number and an abundant CD8+ T-cell infiltrate was present in the tumors of long-term survivors, implying that the neoantigenic repertoire has been evolutionary selected in this cohort [27]. This underlines the importance of understanding and expanding our knowledge of the spectrum of tumor-immune interactions.

This is especially important regarding immunotherapy. Early clinical trials with checkpoint inhibitors, including monotherapy with monoclonal antibodies that block PD-L1 from binding its ligand, have yielded rather disappointing results in pancreatic cancer, apart from a few cases with microsatellite instability [28,29]. Thus, studies to detect further potential predictive biomarkers correlated to immunotherapy outcomes are necessary. Based on immunopathology and gene expression approaches, the TME of most cancers can be broadly characterized as either T cell inflamed (“hot”) or non-T cell inflamed (“cold”), depending on the frequency, composition and spatial organization of tumor-infiltrating lymphocytes (TILs) and immunomodulatory molecules [30,31] (Figure 1A,B). Generally, T cell inflamed tumors exhibit improved responses to immunotherapies [31]. Moreover, histopathologic examination of the TME can also reveal critical tumor-intrinsic characteristics. For example, biologically aggressive PDACs display increased numbers of dissociative growing tumor cells exhibiting partial epithelial–mesenchymal transition (EMT)-features, termed tumor buds. Tumor budding is an independent adverse prognostic factor in PDAC and is associated with an immunosuppressive TME [32,33].

Thus, insights into the different landscapes of PDAC would promote our understanding of the biology behind the tumor-immune interactions and would support a more accurate prognostic and predictive stratification of patients for more efficient clinical management. Moreover, integrative approaches, which take into account intrinsic tumor features, such as morphology and genetic changes in the tumor cells as well as extrinsic features such as the immune landscape of the TME, would provide a more efficient tool to tackle this recalcitrant disease, towards a more individualized clinical management of PDAC patients. As newer treatment regimens become available, both in the adjuvant and in the neoadjuvant settings, including immunotherapy [30,34], these approaches would help selecting patient subsets for appropriate treatment modalities.

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