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Commentary

Symphony in chaos: Immune orchestra during pancreatic cancer progression

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Pancreatic cancer (PDAC) continues to be a dreadful disease with 5-year overall survival surpassing single digits recently [1]. With the lack of early diagnosis and continued failure of treatment options in PDAC, it is imperative that we comprehensively understand its evolving immune landscape, as our immune system is the only defence that is as heterogeneous as this cancer itself. Although immunotherapy has not worked in PDAC, a better understanding of the mechanism(s) of resistance [2,3] may be able to change this. The adage 'PDAC is an immunologically cold tumour' is deceptive as both precursor lesions PanINs (Pancreatic Intraepithelial Neoplasia) and IPMNs (Intraductal Papillary Mucinous Neoplasms) are heavily immune infiltrated and immune architecture changes towards immunosuppressive phenotype during progression. Furthermore, it has been shown that long-term survivors of PDAC (median survival 6 yrs) had a significantly greater number of activated, tumour−specific cytolytic $CD8^+$ cells compared to those with poorer outcomes [4]. Thus, at least in a subset of PDAC patients, the immune system maintains the capacity to keep cancer cells at bay, rather than being protumourigenic. This again emphasizes the need for understanding the complex interactions between tumour, its stroma and immune system to improve therapeutic outcomes.

PDAC arises from two precursor lesions - PanINs and IPMNs. IPMNs contribute to about 10% of precursor lesions that result in PDAC [5]. While some progress has been made in our understanding of the pathogenesis of IPMN, the immune landscape and the factors influencing it during its progression to PDAC are not very well understood. A study by Roth et al. published in *EBioMedicine* focuses on this important aspect and characterizes the spatial organization of different immune cell types during the progression of IPMN from precursor to the invasive stage [6]. The authors note that critical change in immune composition occurs at the step of tissue invasion when the immune surveillance is overcome and the immune microenvironment in peritumoural and juxta-tumoural location transitions to an immunosuppressive phenotype. They also identify the presence of Th9 and Th22 T-cell subtypes in the tumour milieu, the functional significance of which is yet to be discovered. Along the similar lines, Barco et al. using single-cell RNA-seq demonstrated the presence of activated CD4+, CD8+ *T*-cells and unique DC2 type dendritic cells and the absence of MDSCs in both low-grade and high-grade IPMN and a shift towards immunosuppressive cell types in invasive stage [7]. This contrasts with PanIN lesions (which contribute to 90% PDAC) wherein even the lowest grade pre-invasive lesions harbour immunosuppressive moieties like MDSCs, tumour-associated macrophages and T regs. Taken together with the fact that IPMNs are easily identifiable through imaging, this suggests a window of opportunity for immunotherapy or vaccine trials for chemoprevention.

Recently, the lessons learnt from the failure of checkpoint blockade therapy in PDAC have resulted in an increased focus on the interactions between the major stakeholders in the microenvironment- briefly, cancer, stromal, immune cells and extracellular matrix. This has resulted in a few striking breakthroughs in PDAC immunotherapy like CD40 stimulation on CD8+ *T* cells, CSF1R inhibition on TAMs and MDSCs and CXCL12/CXCR4 signalling axis inhibition in stroma-driven immunosuppression [8]. Even though we have enhanced our knowledge of the immune landscape of PDAC over the last few decades, such clinically significant breakthroughs remain few and far between. The need of the hour is to undertake investigations to completely unravel this molecular symphony being played in the tumour microenvironment. Our understanding of the regulatory switches, which allow transition from an immunocompetent to an immunosuppressive environment, remains limited. Stromal heterogeneity in PDAC, wherein CAFs can assume an inflammatory/myofibroblastic/antigen-presenting phenotype has added a layer of complexity [9]. The gut microbiome has also recently announced itself to be a major player in tumour progression via the microbiome-immune-cancer axis where microbes undermine cancer immune surveillance and indirectly promote oncogenesis [10]. Studies have shown that modulation of gut microbiota can augment the anti-cancer immune response and can enable successful immunotherapy [2]. Just like their microbial counterparts, emerging host immunocytes like Th9, Th22, $\gamma\delta$ T cells, type 2 dendritic cells need to be scrutinized through a stronger lens to determine their exact role in the PDAC landscape. Techniques like RNA and protein-based in situ methods, laser capture microdissection or imaging mass cytometry that provide gene

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expression profiles in a spatial context might provide us with a better idea about the complex tumour-stroma-immune cell crosstalk.

The inherent challenges in exploring this crosstalk include but are not limited to accurately capturing sparsely expressed immune cell markers, heterogeneous and redundant signalling pathways, cost-intensive techniques like single-cell RNA sequencing and microbial metagenomics/metabolomics and acquiring early stage human samples for a disease that most of the time has a late presentation. Nonetheless, identifying targets to reprogram the immune machinery into the robust anti-tumour immune response is important to achieve better clinical outcomes in PDAC. Collaborative research efforts are needed to fully comprehend the underlying notes in this fluctuating symphony of immune cells and identify the conductor.

Declaration of Competing Interest

All authors declare no competing financial interests.

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