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Mechanical Insights into Immunosuppression in Pancreatic Ductal Adenocarcinoma

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Abstract: Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal malignancy, which is characterised by an immunosuppressive tumour microenvironment (TME) that leads to poor responses to immunotherapies. Here, we discuss recent advances in our understanding of the PDAC TME and provide a comprehensive overview of both tumour cell-intrinsic and extrinsic factors that contribute to immune evasion in PDAC. The roles of tumour intrinsic factors in remodelling the TME and promoting tumour progression will be discussed, which includes mutations in KRAS and activation of pathways such as IL-6/STAT3, Wnt/β-Catenin and NF-κB. Moreover, based on the pre-clinical and research evidence, we depict the immune landscape within the PDAC TME and highlight the dynamic reciprocal interaction between tumour cells and various immune cell populations. Also, we outline the impact of non-immune cells, particularly pancreatic stellate cells (PSCs), cancer-associated fibroblast (CAFs) and adipocytes in shaping an immunosuppressive TME. Finally, we explore how metabolic reprogramming and altered nutrient dynamics within the TME further enhance immunosuppression. Understanding these interconnected mechanisms offers promising avenues for novel therapeutic strategies that target the immunosuppressive landscape of PDAC.

Keywords: Pancreatic ductal adenocarcinoma, tumor microenvironment, immunosuppression.

1. Introduction

Pancreatic cancer is an aggressive disease with a 5-year relative survival rate of merely 10% in the US [1]. Despite the increased understanding of its genetic background, PDAC remains resistant to most current treatment options. The standard of care for most patients remains conventional chemotherapy, such as FOLFIRINOX [2] or a combination of gemcitabine and nab-paclitaxel [3]. Additionally, due to its low immunogenicity and immunosuppressive TME, PDAC has shown limited response to cancer immunotherapy [4-7], such as immune checkpoint inhibitors, though it has benefited patients with many other cancers.

Given the critical role of the immune system in cancer, characterising the immune components of the TME is essential for understanding the interaction between host immune cells and cancer cells. The PDAC TME is unique, characterised by its dense extracellular matrix (ECM), various fibroblast subpopulations, and localised hypoxia resulting from poor vascularisation [8, 9]. Fibroblasts represent a major component of the TME, which contribute significantly to ECM deposition [10]. In addition to fibroblasts, other key cellular constituents, such as myeloid-derived suppressor cells (MDSCs),

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dendritic cells (DCs), tumour-associated macrophages (TAMs), T cells, and pancreatic stellate cells (PSCs) collectively shape and give rise to the physiological properties of the TME.

Another major impediment to effective cancer treatment is immune evasion [11]. In general, cancer cells recruit immunosuppressive regulatory T cells (Tregs) into the TME by chemokines signalling [12], downregulate major histocompatibility complex (MHC) class I molecules and other key proteins involved in the antigen presentation pathway [13]; and fail to express surface costimulatory molecules [14]. Additionally, PDAC is considered as a "cold tumour" due to its low T cell infiltration and low tumour mutation burden [15].

This review provides a comprehensive summary of the intrinsic features of PDAC that drive immunosuppression in TME. It further explores the roles of both immune and non-immune cells in promoting immunosuppression and how the traits of metabolism mediate immunophenotype in PDAC. Finally, the potential therapeutic interventions and future perspectives for tackling the immunosuppressive TME in PDAC will be discussed. These efforts will benefit the development of therapeutic options to augment immune response in the TME of PDAC.

2. PDAC Intrinsic Factors-Driven Immunosuppression

The activating KRAS mutations are found in more than 95% of PDAC patient samples [16, 17] with different mutated sites, including G12, G13 and Q61. KRAS proto-oncogene encodes small GTPases, which transmit signals through canonical MAPK/ERK [18], PI3K/Akt, and the Ral guanine nucleotide exchange factor pathways [19, 20]. The roles of oncogenic KRAS in supporting PDAC cell initiation and survival have been well-studied, including promoting cell proliferation directly and shifting cancer cell metabolic preference to promote growth [21, 22]. In addition, it has become more evident that mutant KRAS can modulate autocrine effects and remodel TME through cell-extrinsic mechanisms [23].

KRAS mutations contribute to tumour-promoting inflammation by inducing the expression of interleukin-6 (IL-6), which is an inflammatory cytokine with a pleiotropic effect on inflammation and immune response in cancer [24]. The canonical IL-6 mediation is through the activation of Janus activated kinase 1 (JAK1) and followed by phosphorylation of the transcription factor signal transducer and activator of transcription 3 (STAT3) in myeloid cells [25] and hepatocytes [26], which promotes pro-tumorigenic inflammation and pre-metastatic niche formation. Additionally, IL-6 polarises macrophages towards an M2-like state in the TME, which in turn excludes CD8+ T cells and promotes Treg differentiation in the tumour, enhancing immune evasion and reducing responsiveness to immunotherapies [27]. Furthermore, elevated IL-6 levels can directly upregulate the transcription factor Indoleamine 2,3-dioxygenase 1 (IDO1) in tumour infiltrating lymphocytes (TILs) via NF-kB and STAT3 signalling [28]. This results in metabolic reprogramming with an increase in kynurenine production and tryptophan removal [29], which in turn leads to increased expression of programmed cell death protein 1 (PD-1) and exhaustion in CD8+ T cells [30].

KRAS mutations in PDAC have also been associated with the upregulation of the PD-1 immunosuppressive axis [31], where the increased PD-1 expression in lymphoid cells exacerbates CD8+ T cells exhaustion, impairs macrophages and DCs function, and promotes pro-tumorigenic Th17 differentiation in the TME [30, 32]. Moreover, KRAS mutations in PDAC have been implicated in suppressing FAS-dependent apoptosis via facilitating DNA methylation of the FAS promotor in an EZH2-dependent manner [33, 34].

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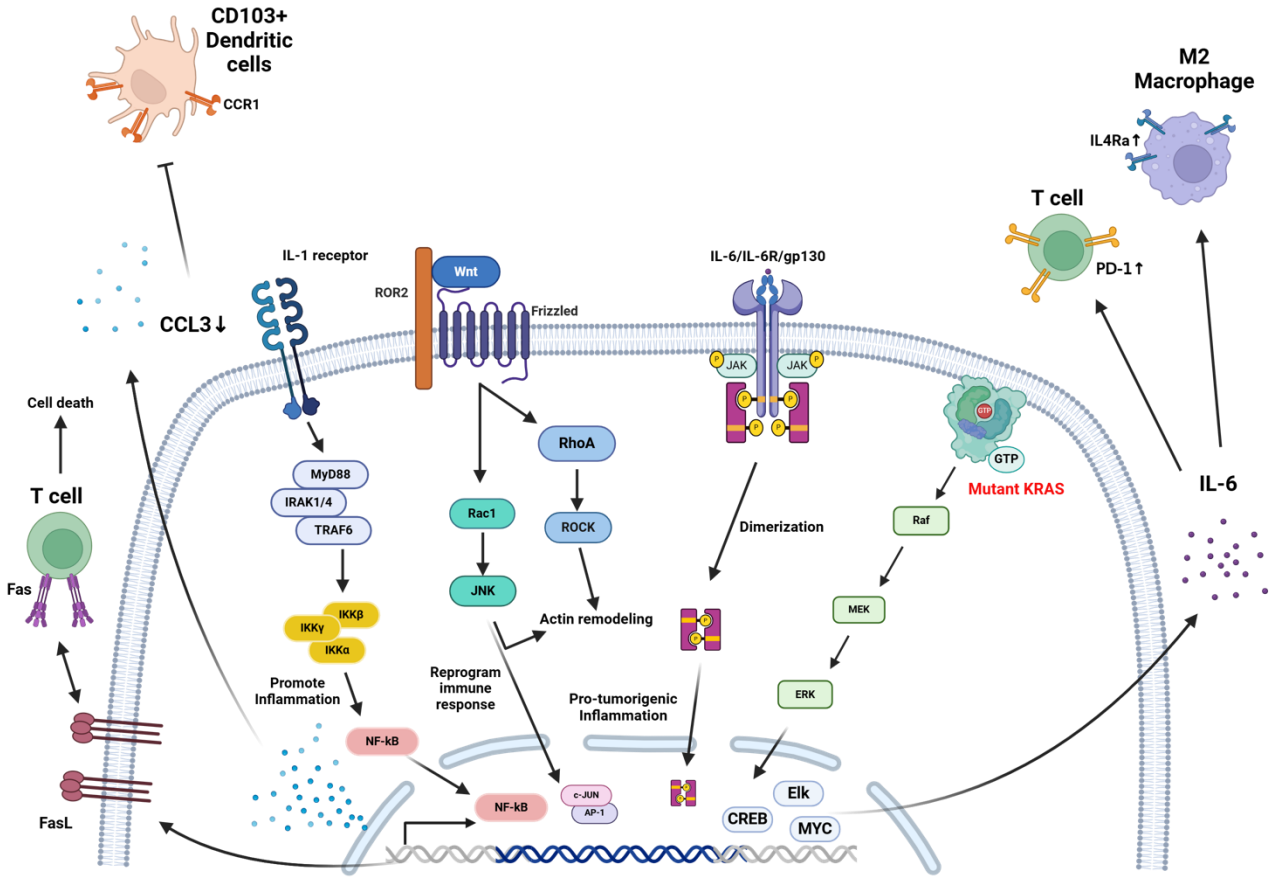

Figure 1: Immunosuppressive signalling pathways in KRAS-mutant PDAC. IL-1 receptor activation drives the NF-κB pathway which leads to inflammation and tumorigenesis. Activation of the Wnt/β-Catenin pathway promotes ECM remodelling and suppresses local immune response. Elevated IL-6 secretion from activated JAK/STAT pathway polarises macrophages towards an immunosuppressive M2 phenotype and causes T cell exhaustion. Mutant KRAS drives downstream signalling via the Raf/MEK/ERK pathway to facilitate PDAC cell proliferation and survival. Finally, Fas/FasL interaction between PDAC cells and T cells induces T cell apoptosis and thus immune evasion.

Another oncogenic driver that causes immunoresistance in PDAC is the activation of the Wnt/β-Catenin signalling pathway. Under normal physiological conditions, β-Catenin signalling regulates critical cellular processes such as cell proliferation, migration, survival and maintenance of somatic stem cells [35, 36]. Dysregulation of this pathway is implicated in many human diseases, including cancers [37]. The canonical Wnt signalling pathway prevents the degradation of β-Catenin, thereby promoting the transcription of several genes, such as cyclin D1, cyclin E, matrix metalloproteinase 7 (MMP7), c-myc etc., all of which are involved in various hallmarks of cancer. From an immunological perspective, pan-cancer transcriptomic profiling has revealed that β-Catenin signalling is over-activated in half of the patients with poor T-cells infiltrating tumours [38]. PDAC is characterised by the frequent nuclear localisation of β-Catenin [39], which drives PDAC development and progression by enhancing invasion and malignancy [40]. Moreover, a recent study by Rui et al. [41] found that β-Catenin signalling is involved in inflammation-driven PDAC progression. This results from the downregulation of DC-inducing chemokine CCL3 (chemokine ligand 3) and the promotion of tumour immune escape. Lastly, the inhibition of β-Catenin signalling

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in PDAC TME reprogrammed the immune response [42], where the blockade of Porcupine, a key component of Wnt, recruited more cytotoxic CD8+ T cells and less Treg in PDAC TME.

NF-κB signalling pathway also contributes to PDAC pro-tumorigenic inflammation and immune escape. NF-κB is a family of transcription factor protein complexes that regulates the expression of genes involved in immune function, cell survival, stress responses and apoptosis [43]. In response to extracellular stimuli such as oxidative stress, cytokines and pathogenic agents, the IκBs (inhibitors of κB) are phosphorylated and degraded [44], which allows NF-κB heterodimers rapidly translocate into the nucleus and initiate the transcription of κB-dependent genes. Constitutive activation of NF-κB happens in 70% of PDAC patients and has been shown to increase IL-1α in a KRASG12D mutation-associated manner. This leads to ubiquitination of IκB and triggers the transcription of p62 as well as other NF-κB target genes, which eventually leads to sustained NF-κB activity. This activity promotes proinflammatory and antiapoptotic responses, resulting in PDAC progression [45].

3. Immune Cell-Mediated Immunosuppression

During the progression of PDAC, the intricate and dynamic interplay between tumour cells and immune cells within the TME plays a critical role in driving tumour pathogenesis [46]. The PDAC TME is predominantly populated by myeloid lineage cells, including macrophages, monocytes, granulocytes, and dendritic cells, which are pivotal mediators that induce local inflammation and facilitate immune evasion, ultimately contributing to poor clinical outcomes [47]. Pathologically, these myeloid cells are commonly referred to as MDSCs, which are characterised by several key features: 1) they undergo distinct transcriptional and epigenetic modifications that differentiate them from conventionally activated myeloid cells [48, 49]; 2) they secrete crucial cytokines and soluble mediators that promote tumorigenesis and metastasis [50, 51]; and 3) they exert potent immunosuppressive effects on various effector immune cells, including T cells, natural killer (NK) cells, and B cells [52] (Fig. 2).

3.1. Tumour-Associated Macrophages

Macrophages are abundant in the PDAC TME. Despite their inherent ability to phagocytose tumour cells, M2-like TAMs have been demonstrated in multiple studies to promote tumour progression, enhance cancer cell proliferation and survival, and attenuate local immune responses [53]. A primary mechanism by which TAMs exert their immune functions is through the secretion of cytokines, chemokines and growth factors. In PDAC, TAMs upregulate immunosuppressive cytokines such as CCL20, which bind to CCR6 receptors on the cancer cells, thereby facilitating tumour cell migration, growth and liver metastasis [54]. Additionally, TAMs have been demonstrated to drive acinar-to-ductal metaplasia (ADM) transdifferentiation through the secreted RANTES and tumour necrosis factor (TNF) [55]. TAMs originate from both tissue-resident macrophages and circulating monocytes. While monocyte-derived TAMs primarily participate in antigen presentation, embryonically derived TAMs remodel the ECM and promote fibrosis [56]. Moreover, monocyte-derived TAMs have been shown to limit CD8+ T cell infiltration [57] via efferocytosis-driven reprogramming and promote PDAC liver metastasis [58]. TAMs also facilitate the differentiation and maturation of Treg cells from CD4+ T lymphocytes, which impairs antitumor T cell immunity in the TME [59]. However, TAMs also possess the potential to initiate anti-tumour response. Tekin and colleagues reported that newly tumour-infiltrated naïve M0 macrophages exert anti-tumour activities via TNF-α secretion, although such cytotoxic ability is rapidly diminished as macrophages differentiate into polarised subsets [60]. One recent study further elucidated the differentiation of TAM subpopulations from monocytes via an intermediate TAM stage, by which subsequent polarisation is driven by local hypoxia and nutrient deprivation [61].

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3.2. Neutrophils

Neutrophils are essential infiltrating immune cells in the PDAC microenvironment and are frequently associated with poor prognoses [62]. Their recruitment is driven by several CXC families of chemokines, including CXCL1, CXCL2, CXCL5 and CXCL8 [63, 64]. Elevated secretion of these chemokines from tumour cells is positively correlated with increased neutrophil infiltration in PDAC compared to normal pancreatic tissue [63-65]. Notably, CXCL1, a potent chemoattractant of neutrophils via the CXCR2 receptor, is overexpressed due to the loss of SETD2 in *KRAS*-mutated PDCA [66]. This drives the recruitment and immunosuppressive phenotype of neutrophils, and subsequently restricts CD8+ T cell infiltration via neutrophil-derived TNF [67]. At a cellular level, studies have found that depleting neutrophils from the PDAC TME could inhibit tumour growth and metastasis. By utilising anti-Ly6G antibodies in KPC mice, researchers observed higher tumour epithelial apoptosis [68], reduced metastasis [64] and delayed tumour growth [69]. Additionally, Zhang et al. showed that IL-17 secreted by CD4+ T cells is involved in neutrophil recruitment, which in turn reduces total number and activated CD8+ T cells [69]. However, neutrophils can also be polarised towards an "antitumour" phenotype with low doses of interferon-β [70, 71]. It is reported in colorectal cancer that antitumour neutrophils can increase cytotoxicity and reduce immunosuppression by the production of TNF-α, reactive oxygen species (ROS) and CD95 [72].

3.3. Dendritic Cells

DCs play a vital role in inducing and maintaining antitumor immunity by activating cytotoxic T lymphocytes. However, DCs are sparse in the TME of PDAC and primarily localise to the periphery [73]. PDAC patients exhibit reduced levels of circulating DCs [74], and higher levels of both circulating DCs [74, 75] and infiltrating DCs [76] are associated with better clinical outcome and survival rate. DCs possess an extraordinary capacity to cross-present antigens and induce effective CD8+ cytotoxic T cell responses. Upon activation, DCs can produce IL-12 and polarise naïve CD4+ T cells into Th1 cells, which promotes NK cell cytokine production and cytotoxicity [77]. Despite their association with favourable prognosis, tumour-infiltrating conventional DCs (cDCs) are rare and often functionally impaired [78]. Furthermore, Tregs in TME promote a tolerogenic phenotype of PDAC-associated DCs, resulting in poor activation of CD8+ T cells [79] and leading to an immunosuppressive TME.

3.4. B Cells

B cells are highly prevalent in the PDAC TME, where they normally function as antigen-presenting cells to regulate T cell activation and produce antibodies. In PDAC, B cell functions are not uniformly stimulatory or inhibitory in the TME. *In vivo* studies have demonstrated that the injection of mutant *KRAS* KPC-derived cell lines into wild-type mice pancreas led to accumulation of B-lymphocytes due to secretion of CXCL13 by stromal cells in the growing neoplasia. In the absence of B cell recruitment at early stages, tumour growth was hampered, which suggests potential pro-tumorigenic roles of infiltrating B cells [80]. Moreover, regulatory B cells are suspected to influence the TME towards an immunosuppressive phenotype by secreting inflammatory cytokines such as IL10, TGFβ and IL-15 [80-82]. These cytokines attenuate the anti-tumour immune response via inhibition of CD8+ effector T cells [83] and recruitment of Treg [84]. The secreted cytokines also polarise macrophages towards an M2-like phenotype, further impairing cytotoxic responses and supporting tumour growth.

Regarding the potential anti-tumorigenic roles of B cells, although the underlying mechanisms are not well-defined, some clinical studies have reported that increased B cell densities are associated with better survival [85]. Also, Castino and colleagues showed that B cells in the tumour-associated

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tertiary lymphoid structures serve as a positive prognostic factor [86]. While animal models predominantly indicate a tumour-promoting and immunosuppressive role of B cells in the TME, clinical studies present conflicting evidence, which underscores the need for further studies to clarify the roles of B cells in PDAC.

3.5. T Cells

T cells are the primary effectors of adaptive immunity and encompass various subpopulations such as CD4+ helper T cells, CD8+ cytotoxic T cells and γδ T cells. One unique feature of the PDAC TME is the low infiltration of T cells, especially by CD8+ T cells, that hinders antigen-specific immune responses [15, 87, 88]. The PDAC TME leverages different mechanisms to hinder CD8+ T cell infiltration. One well-established mechanism involves the production of excessive ECM by PSCs, which results in a highly fibrotic stroma that entraps and physically excludes infiltrating T cells from engaging with tumour cells [89, 90]. Moreover, PDAC cells upregulate focal adhesion kinase (FAK) that further drives fibrosis to dampen cytotoxic CD8+ T cell infiltration [91]. Lastly, CAFs also play a key role in expressing high levels of direct immune regulating factors such as CXCL12, which excludes T cell infiltration via fugetaxis [92, 93].

In one study, researchers evaluated PDAC samples from surgeries by quantifying CD8+ T cells in the tumour core and periphery. Their funding indicated that a higher infiltration of CD8+ T cells, and consequently a higher immunoscore, correlated with better overall survival in PDAC [94]. Additionally, other studies showed T cells tend to aggregate in tertiary lymphoid structures or tumour periphery, rather than within the central tumour mass [95]. Moreover, most infiltrated CD8+ T cells may not be fully functional, thus unable to exert their cytotoxic functions [89, 96].

Other T cell populations have been predominantly associated with pro-tumorigenic roles in PDAC, such as Tregs, CD4+ helper T cells and γδ T cells. Elevated Treg level is associated with reduced CD8+ T cell activation, impeding immunotherapy and thus leading to poor prognosis [79, 97]. Ablation of these immune-tolerant CD4+ T cells enables CD8-mediated regression of PDAC tumours in mice [79]. However, the depletion of Tregs accelerates tumorigenesis due to a loss of tumour-restraining myCAFs and higher infiltration of immunosuppressive MDSCs [98]. Moreover, the recruitment of Th17 and Th22 cells drives tumour initiation and progression via feeding tumour cells with pro-growth signals [99, 100]. Additionally, infiltrating γδ T cells constitute approximately 70% of the total T cell population within PDAC and are characterised by a high expression of PD-L1. The ablation of intra-pancreatic γδ T cells significantly attenuates tumorigenesis in vivo and leads to a pronounced influx of immunogenic Th1 cells and CD8+ T cells into the TME [101].

Despite a an initially diverse T cell repertoire, pre-existing cytotoxic CD8+ T cells are progressively supplanted by immunosuppressive and tumour-promoting Treg cells as pre-malignant IPMN lesions progress to invasive cancer [102]. Given thatCD8+ T cells use the Fas-FasL and perforin-granzyme pathways to exert cytotoxic effect against tumour cells, the loss of Fas expression in tumour cells as a result of *KRAS* mutation leads to PDAC immune evasion [33, 34]. Treg-mediated suppression of effector response includes cytotoxic T-lymphocyte associated protein 4 (CTLA-4) expression and cytokine secretion such as TGF-β and IL-10 [103]. They also compete with CD8+ T cells for IL-2 and access to antigen-presenting DCs [104]. CD8+ T cells present in the tumour centres, invasive front and metastatic lymph nodes exhibit signs of exhaustion and senescence, downregulating key cytotoxic effectors such as granzyme B and are irresponsive to chemotherapies [105].

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3.6. NK Cells

NK cells represent another major cytotoxic cell population in TME, which perform nonspecific cytotoxic effects on tumour cells through interactions with cytotoxic receptors CD16, NKG2D, DNAM-1 etc [106]. However, they are numerically and functionally impaired in PDAC [96]. Single-cell sequencing reveals a strong correlation between NK cell markers and positive prognosis of PDAC patients [107]. Previous studies have found the reduction of NKG20 and DNAM-1 levels in pancreatic cancer patients compared with healthy controls, which was correlated to dampened cytotoxicity of the NK cells [108, 109]. Circulating NK cells from PDAC patients also exhibit reduced IFN-γ production and increased IL-10 secretion, which potentially suppresses immune responses and promotes immune evasion. This dysregulation of NKG20 and IFN- γ has been attributed to MMP9 and IDO signalling cascades. Additionally, tumour-infiltrating NK cells display reduced CD16 and CD57 expression, further suggesting poor activation and cytotoxic effect [109].

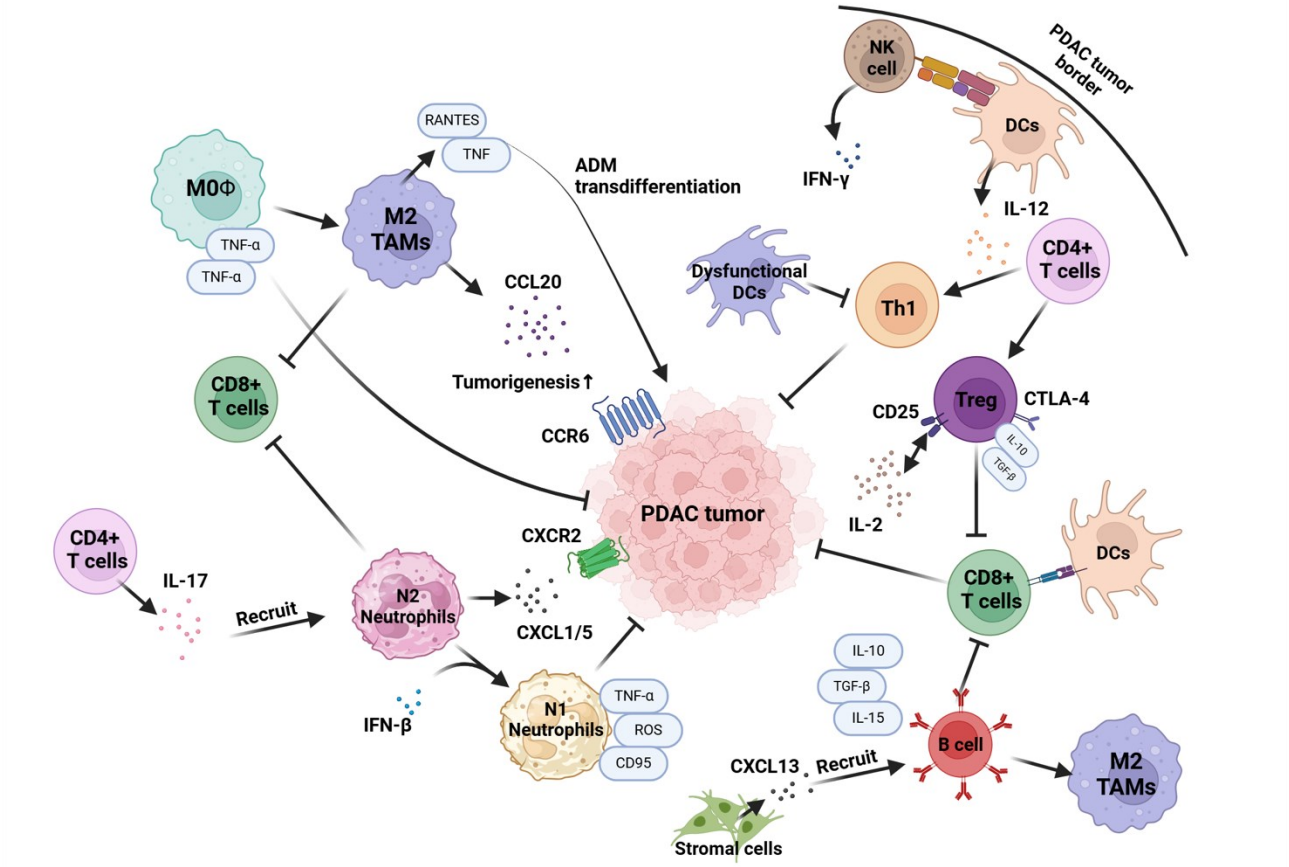

Figure 2: Paracrine effects of immune cells on promoting an immunosuppressive TME. M2 TAMs secrete CCL20, which binds to CCR6 on tumour cells and promotes tumorigenesis. Released RANTES and TNF-α from TAMs also promote inflammation and ADM transdifferentiation. TAMs are the major myeloid cells that hinder the infiltration and cytotoxicity of CD8+ T cells. Neutrophils exhibit dual roles: N2 neutrophils, recruited by CD4+ T-derived IL-17, secrete CXCL1/5 to promote tumour progression; while N1 neutrophils secrete IFN-β, TNF-α, and ROS that cause tumour cell death. B cells are recruited by CXCL13 from stromal cells and mainly contribute to immunosuppression. Tregs suppress immune responses through IL-10, TGF-β, and CTLA-4, while competing with effector CD8+ T cells for IL-2, inhibiting their anti-tumour activity. DCs are limited in numbers and are mostly dysfunctional to activate T cells.

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4. Non-Immune Cell-Mediated Immunosuppression

4.1. Pancreatic Stellate Cells

Significant efforts have been invested to understanding the roles of non-immune cell stromal populations that make up the TME. Neoplastic cells represent only a small fraction of the tumour, while the majority are made up of non-cancerous cells which give rise to the immune resistance and TME heterogeneity (Fig. 3). PSCs, a subset of fibroblasts present in normal pancreas. They are characterised by the expression of nestin and the presence of vitamin A-rich lipid droplets [110]. Under normal physiological conditions, PSCs remain quiescent. They can be activated during tissue repair or tumorigenesis, as they transit to a myofibroblastic state marked by increased secretion of ECM proteins and upregulation of α-smooth muscle actin (αSMA) [110]. The transition between quiescence and activation is regulated by the vitamin D receptor [111]. PSCs have been found to promote the aggressiveness of PDAC. Some studies depleted PSCs and found a reduction of tumour growth and improvement of chemotherapy responses potentially through the removal of the physical barrier that entraps the therapeutic chemicals [10, 112]. Also, activated PSCs were reported to release factors, such as periostin and stromal-derived factor-1 (SDF-1), to enhance the chemoresistance ability of PDAC cells via tumour cell intrinsic ERK1/2 and FAK/AKT pathways [113, 114]. Moreover, PSCs have been demonstrated to promote epithelial-mesenchymal transition (EMT) and metastasis via the production of secreting factors such as MMP3, SDF-1, VEGF and TGF- β [115]. In addition to the pro-tumorigenic effects, PSCs play an immunosuppressive role. One canonical pathway involves activation by MDSCs through the IL-6/STAT-3 signalling axis, which promotes the formation of TME resistant to immunotherapy [116]. Furthermore, PSCs polarise immunosuppressive Th2 phenotype via galectin-1 secretion [117] and improve Tregs recruitment via CXCL10 [118].

4.2. Cancer-Associated Fibroblasts

In normal development, fibroblasts are the major producers of connective tissue ECM and become activated in response to tissue injury [119]. Once activated, fibroblasts differentiate into “myofibroblasts”, with abilities to influence adjacent epithelial stem cell behaviours [120], produce TGF-β and express αSMA [121].

Due to the limited knowledge of specific fibroblast markers, it has been a challenge to trace the origin of CAFs. In many cases, fibroblast expansion occurs before the onset of malignancy and they are often localised at the periphery of early or premalignant lesions [122, 123]. Initially, these fibroblasts appear to exert tumour-suppressive properties by enriching and restricting tumour growth [124, 125], but they subsequently generate more protumorigenic fibroblast populations. Researchers have attempted to employ the Cre recombinase in mice to induce stable expression of reporter genes. However, identifying an ideal promotor for specific CAF expression remains a challenge.

CAFs are recognised as a heterogenous population, which can be broadly classified into two phenotypically distinct subpopulations: myofibroblastic CAFs with elevated expression of αSMA are located in close proximity to neoplastic cells; and inflammatory CAFs, that lack elevated αSMA expression but with increased proinflammatory cytokines secretion such as IL-6, are located further away from neoplastic cells [126]. The same group subsequently identified a new subpopulation of CAFs, characterised by the expression of MHCII and CD74. These antigen-presenting CAFs (apCAFs) are able to present to CD4+ T cells ex vivo but fail to induce T cell proliferation due to the absence of costimulatory molecules [127]. This evidence suggests apCAFs may exert an immunosuppressive effect by polarising CD4+ T cells into Treg and hindering CD8+ T cell infiltration. Given the different CAFs can interconvert [126, 127], the definitions of these populations

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could be arbitrary and highly plastic, which presents therapeutic opportunities to manipulate CAFs toward a more antitumorigenic state.

4.3. Adipocytes

The pancreas is embedded within adipose tissue, a loose connective tissue predominantly composed of adipocytes. This adipose tissue is further integrated into a complex ECM and interspersed with various cell types, including fibroblasts, endothelial cells and both innate and adaptive immune cells [128]. In breast cancer, peritumoral adipocytes have been shown to exhibit lower lipid content, potentially fuelling surrounding tumour cells [129]. Also, they engage in crosstalk with tumour cells, acquire fibroblast-like morphology and promote tumour invasion [130]. Similarly, in PDAC, adipocytes are able to dedifferentiate to cancer-associated adipocytes (CAAs)[131] and promote pro-tumorigenic inflammation via pro-inflammatory cytokines release, ECM remodelling and fibrosis [132-134]. Walsh *et al.* recently found that PDAC cell-derived CXCL5 secretion was triggered by adipokines TNF and IL-1β, thus impeding PD-1 inhibitor therapy [135]. Moreover, through feeding inducible KPC mice with a high-fat diet, Inicio *et al.* illustrated that adipocyte-derived IL-1β recruited tumour-associated neutrophils and Treg, which led to an immunosuppressive TME [136]. Furthermore, other pro-inflammatory cytokines have been demonstrated to be secreted by adipocytes and promote pancreatic tumorigenesis in various ways, such as TNF-α [137], IL-6 [138] and IL-1 [139]. However, by leveraging RNA-sequencing data from the TCGA-PAAD cohort, Liu et al. recently identified a strong association between high adipocyte infiltration in PDAC TME and a significantly reduced tumour mutational burden, alongside improved overall survival. This finding was further correlated with an enhanced anti-tumour immune signature, which suggested an unexpected link between adipocytes and favourable immune-mediated outcomes [140].

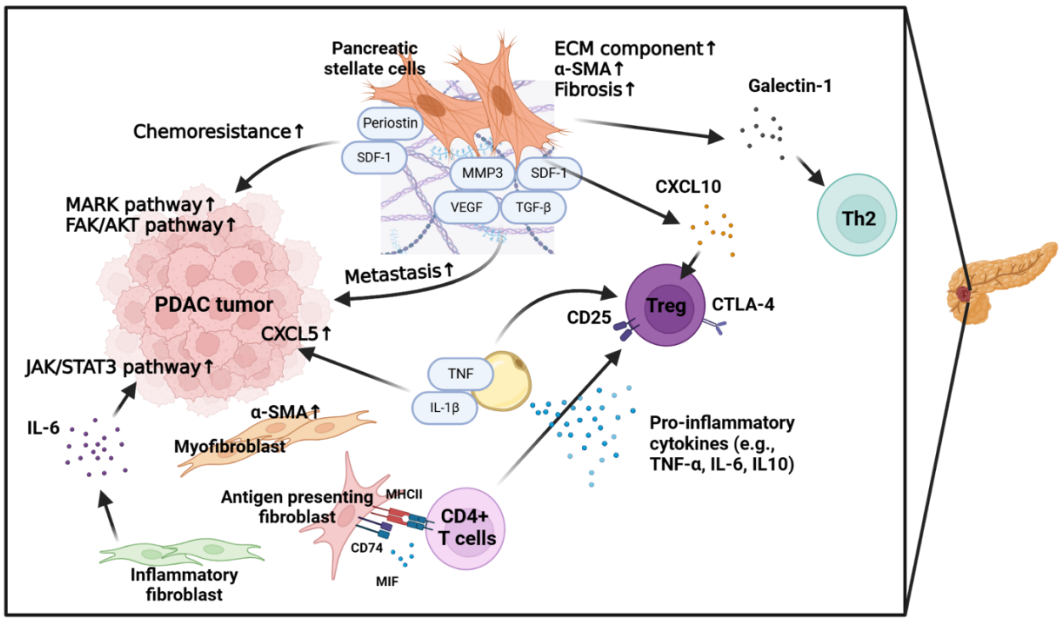

Figure 3: Non-immune stromal components contribute to immunosuppression. PSCs secrete matrix modelling factors and growth factors to enhance ECM production, leading to fibrosis, promote metastasis and chemoresistance. Released galectin-1 by PSCs favours Th2 polarisation, leading to immunosuppression. PSC-derived CXCL10 and adipocyte-derived IL-1β recruit immunotolerant Tregs. Proinflammatory cytokines from adipocytes further promote PDAC tumorigenesis. Fibroblasts contribute to ECM deposition, CD4+ T cell recruitment and IL-6 production, stimulating tumour progression.

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5. Metabolism Effects

Due to the dense desmoplastic stromal component which makes up to 90% of tumour mass [141], delivery of blood-derived nutrients and oxygen is limited, leading to disequilibrium in nutrients and localised hypoxia. Thus, PDAC cells evolve and adapt in many ways to thrive in the nutrient-deprived TME. To meet the high energy demands for proliferation and survival, PDAC cells harness glucose, amino acids and lipids in the TME, reshape intracellular metabolic reprogramming and the relevant interaction with other neighbouring cells.

PDAC cells exhibit pathways known as the Warburg effect, where glucose update is enhanced and lactate is produced as a by-product of anaerobic glycolysis [142]. This reprogramming is driven by KRAS mutation [143] and HIF-1α signalling [144]. This leads to increased expression of glucose transporter GLUT1, which has been linked to disease progression in clinical studies [145, 146]. Lactate accumulation within the TME results in acidification, which inhibits the activation of CD4+ T cells [147] and CD8+ T cells [148], leading to an immunosuppressive phenotype. Additionally, CD36, a scavenger receptor involved in lipid uptake from the extracellular environment, has been associated with PDAC metastasis, chemoresistance and lower overall survival [149]. Metabolomic studies further highlighted the importance of amino acids, particularly glutamine, in PDAC development [150]. Glutamine is converted into glutamate, which is subsequently transformed into aspartate and oxaloacetate and fuels the production of pyruvate and malate. This alternative glutaminolysis generates extra NADPH (Nicotinamide adenine dinucleotide phosphate) to support cellular respiration and tumour cell growth [151].

In addition to metabolic reprogramming, PDAC cells optimise and recycle internal resources via autophagy, a process by which damaged organelles and unnecessary proteins are degraded to generate macromolecules for biogenesis. Autophagy is crucial for tumour cell growth and tumorigenesis in PDAC, as demonstrated in mouse models where inhibition of autophagy-related proteins leads to tumour regression [152, 153]. Moreover, the downregulation of MHCI molecules on the tumour cell surface, coupled with their sequestration within autophagosomes and lysosomes, facilitates PDAC cells' immune evasion [154].

Metabolic interactions between PDAC cells and surrounding stromal cells also reshape the TME. PSCs have been demonstrated to selectively release alanine obtained from autophagy, which is subsequently utilised by PDAC cells [155]. Moreover, TAMs contribute to the metabolic support of PDAC by releasing pyrimidines derivatives, such as deoxycytidine, which impairs the efficacy of chemotherapy treatment [156]. Lastly, adipocytes adjacent to PDAC cells exhibit reduced lipid content and supply fatty acids and glutamine to fuel tumour growth [157]. Further research is needed to elucidate the specific pathways by which various stromal cell types provide nutrients to PDAC cells.

6. Current Therapeutic Options and Future Perspectives

The dense desmoplastic stroma is a hallmark of PDAC, which plays a critical role in tumour cell growth, invasion, and impaired chemotherapy delivery and efficacy. As the primary producers of ECM, CAFs exhibit high plasticity, which enables them to transition between subtypes. Thus, redirecting CAFs toward an anti-tumorigenic phenotype could effectively inhibit tumour expansion and reduce MDSC polarisation. By diminishing the ECM physical barrier, therapeutic chemicals and CD8+ T cells would have enhanced access to the TME. Furthermore, adipocytes serve as a source of essential metabolites for the PDAC cells. Targeting serum amyloid 1 (SAA1), a protein upregulated by peritumoral adipocytes that promote cell invasion and chemoresistance [131], could disrupt metabolic pathways that sustain PDAC progression.

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Currently, adaptive T cell therapy and cancer vaccines represent two promising immunotherapeutic approaches under exploration. Chimeric antigen receptor-T (CAR-T) therapy has gained significant attention in recent years, particularly for its remarkable efficacy in hematologic malignancies, which has led to multiple FDA approval. However, its effectiveness in solid tumours including PDAC remains limited, primarily due to poor T cell trafficking into the tumour. Mesothelin (MSLN) is overexpressed on PDAC cells and was targeted in two phase I studies using anti-MSLN CAR-T therapy, where the late-stage patients showed progression-free survival, though with limited success [158, 159]. Additional trials targeting MSLN (NCT03054298 [160], NCT03323944 [161]) are ongoing. Other CAR-T studies have explored alternative targets such as CD133 [162], epidermal growth factor receptor (EGFR) [163] and human epidermal growth receptor 2 (HER2) [164], but outcomes have been modest, with stable disease or partial remission achieved and no significant tumour regression.

Cancer vaccines aim to induce immunogenic response by training the immune system to recognise tumour antigens. In a recent phase I clinical trial, Balachandran and colleagues produced personalised vaccine, autogene cevumeran, based on neoantigens from resected tumours [165]. Responders exhibited sustained antigen-specific CD8+ T cell responses and recurrence-free survival (RFS) at three years. Another group developed an amphiphile vaccine incorporating mutant KRAS (mKRAS) peptides and immunostimulatory DNA fragments [166], which shows mKRAS-specific T cells expansion and a correlation between RFS and initial lymphocyte availability. Ongoing trials involving advanced vaccine platforms and novel CAR constructs hold promise for enhancing therapeutic efficacy and achieving clinical success in PDAC [167, 168].

Due to the poor fitness of patient-derived T cells and multiple exclusionary factors within the TME, small molecules have a greater ability to penetrate the PDAC stroma. To tackle the immunosuppressive activity of myeloid cells in the TME, CD11b agonists were tested in xenograft models and successfully polarised TAMs toward an antitumor phenotype [169]. Another strategy uses CD40 agonists to modulate TAMs, and while clinical trial outcomes have been modest, increased CD8+ T cell infiltration was reported [170, 171]. Further investigation is required to identify novel therapeutic targets with exclusive and selective expression on PDAC cells to enhance treatment efficacy.

Researchers have successfully reprogrammed melanoma tumour cells to express a cDC1-like phenotype via enforcing the expression of cDC1-specific transcription factors, both in vitro and in vivo [172]. Recently, the same group managed to reprogram tumour cells in vivo by adenoviral vector transfection. As a result, the tumour-cDC1 cells can present antigens, activate CD8+ T cells and induce melanoma tumour regression in mouse models [173]. This approach provides potential for in vivo cell reprogramming and may address the paucity of DCs in PDAC TME.

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