frontiers in Immunology

TYPE Review
PUBLISHED 07 July 2026
DOI 10.3389/fimmu.2026.1885999

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OPEN ACCESS

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RECEIVED 20 May 2026
REVISED 05 June 2026
ACCEPTED 09 June 2026
PUBLISHED 07 July 2026

CITATION
Wang J, Tan JSY, Shelat VG and Lim J (2026) IL-6 as a central driver of immune evasion in PDAC: from IDO-mediated tolerance to multi-pathway immunosuppression.
Front. Immunol. 17:1885999.
doi: 10.3389/fimmu.2026.1885999

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IL-6 as a central driver of immune evasion in PDAC: from IDO-mediated tolerance to multi-pathway immunosuppression

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Pancreatic ductal adenocarcinoma (PDAC) is among the most lethal cancers and is characterised by an immunologically "cold" microenvironment that limits responses to immunotherapy. This review focuses on interleukin-6 (IL-6), produced by stromal and immune cells as well as PDAC cells, as a central driver of immune evasion via JAK–STAT3 signalling. We outline how SOCS3 silencing in tumour cells inverts the IL-6–IDO relationship seen in dendritic cells, generating an autocrine IDO–Kyn–AhR–IL-6–STAT3 feedforward loop. We further describe IL-6–mediated stabilisation of PD-L1, sustained PD-1 expression on $CD8^+$ T cells, and ST6GAL1-driven hypersialylation that activates Siglec glyco-immune checkpoints. In addition, we examine the IL-6–Blimp-1–IL-10 axis and its reprogramming of dendritic cell and T cell compartments. Given the repeated failure of IL-6(R) blockade in clinical trials, we contrast these outcomes with the more encouraging signals from RAS-targeted strategies. We propose rational IL-6–integrated combinations with upstream oncogenic targeting may represent an unrealised frontier for this disease.

KEYWORDS
immune checkpoints, immune evasion, JAK-STAT-3 signalling, pancreatic ductal adenocarcinoma, regulatory T cells, targeted therapy, tumour microenvironment

1 Introduction

Approximately 95% of patients with pancreatic cancer still do not survive (1), and clinical outcomes have shown little improvement (2) over the last four decades. Key hallmarks of pancreatic ductal adenocarcinoma (PDAC, the most common form of pancreatic cancer) include a dense fibrotic stroma comprising over 80% of tumour mass (3) within a highly immunosuppressive microenvironment comprising immunomodulatory cancer-associated fibroblasts (CAFs) derived largely from activated pancreatic stellate cells (4), and myeloid cells including myeloid-derived suppressor cells (MDSCs) and tumour-associated macrophages (TAMs), which can produce high levels of IL-6 (5–9), and in some

settings further promote Tregs proliferation instead of mediating Tregs suppression in highly inflamed tissues (10, 11).

While several cytokines are traditionally known to be upregulated in pancreatic cancer including IL-6, IL-8, IL-10 and TNFα (12), high serum IL-6 level is strongly correlated with PDAC disease progression (13, 14). Presently, many IL-6 reviews cover its broad roles across cancers, inflammatory diseases or autoimmunity (15–17). Here, we provided a more mechanistic view of IL-6-STAT3 pathways in PDAC including how IL-6 has opposite effects on IDO depending on SOCS3 status, integration of glyco-immune checkpoints (ST6GAL1) that can shape a highly immunosuppressive tumour environment, multi-level PD-L1 regulation, the less common IL-6-Blimp-1-IL-10 axis, and highlight clinical lessons and emerging therapeutic strategies to improve PDAC patients' outcomes.

2 Methods

This review is a narrative mechanism-focused synthesis of the literature of IL-6 and its associated pathways in the settings of pancreatic ductal adenocarcinoma. It emphasizes key biological domains, including PDAC therapeutic resistance, IDO-dependent immune plasticity, cell-type specific inversion, control of PD-1 and PD-L1 expression and other broad co-inhibitory receptor programming.

Relevant studies were identified through systematic searches of major biomedical databases including PubMed, Web of Science and ClinicalTrials. The search strategy combined terms describing IL-6 (R) primary and secondary roles in PDAC with terms related to inflammatory and metabolic mechanisms, such as immunometabolism, cell exhaustion, immunosuppression, Indoleamine 2,3-dioxygenase (IDO), PD-1/PD-L1 and Siglecs. Relevant peer-reviewed articles, clinical trials, and foundational papers relating to PDAC were retrieved from year 2004 to 2026 but with greater emphasis for papers published within the last five years. Older studies were included selectively when considered to be foundational or highly relevant to the topic. Reference lists of selected articles were also screened to identify additional relevant publications.

3 Pancreatic ductal adenocarcinoma

Pancreatic cancer can originate in either the endocrine or exocrine region, but most commonly arises from the exocrine compartment (18, 19). PDAC accounts for more than 85% of all pancreatic malignancies (20). Due to the lack of symptoms at the early stage of cancer development, PDAC are often diagnosed at a late stage (21), when the cancers would have metastasized to the liver or lymph nodes (22).

PDACs arise from precursor lesions – specifically pancreatic intraepithelial neoplasias (PanINs found in small ductal) and intraductal papillary mucinous neoplasms (IPMNs found in main ductal or its branches) – which are characterized by their precancerous nature and high likelihood of progressing into cancer (23, 24). This progression is commonly associated with stepwise accumulation of tumour-associated genetic mutations (25, 26). KRAS mutations are said to drive PanINs and IPMNs initiation (27), whereas additional mutations in genes such as cyclin-dependent kinase inhibitor 2A (*CDKN2A*) and tumour protein p53 (*TP53*) are crucial for its progression from low-grade to high-grade dysplasia (27).

4 The extracellular matrix-IL-6 axis in PDAC therapeutic resistance

A major contributor to therapeutic resistance in PDAC is the dense desmoplastic extracellular matrix, which serves not only as a physical barrier but also as a biochemical modulator of tumour-stroma communication (Figure 1). This fibrotic network restricts chemotherapeutic penetration and impedes immune cell infiltration by limiting T-cell migration and activation (28, 29). Within this complex tumour microenvironment, the major IL-6 producing cells – cancer-associated fibroblasts and tumour-activated myeloid cells – play central and dynamic roles in shaping immunosuppression and therapeutic resistance.

Activated pancreatic stellate cells (PSCs) secrete IL-6 alongside TGF-β and structural extracellular matrix components such as collagen and hyaluronan (30), perpetuating both inflammation and fibrosis. CAFs, which arise from PSC activation and other mesenchymal lineages, represent the major stroma reservoir of IL-6 in PDAC (Table 1) (6). Through persistent IL-6 release, these fibroblastic populations stimulate JAK/STAT3 and NF-κB signalling in both tumour and immune cells, fostering chemoresistance to gemcitabine (5, 6, 31). Simultaneously, CAF-driven deposition of collagens, proteoglycans, and hyaluronic acid increases extracellular matrix stiffness and interstitial pressure (4), establishing a feedback loop where mechano-transduction sustains IL-6 production and stroma activation (32).

The tumour microenvironment profoundly shapes the biology of IL-6 producing cells through hypoxia, nutrient deprivation and immune polarization (Table 1). In PDAC, extracellular matrix-driven hypovascularization increases interstitial pressure and exacerbates intratumoural hypoxia, thereby activating hypoxia-inducible factor-1-α (HIF-1α)-dependent transcriptional programmes that sustain IL-6 expression (50). At the same time, these conditions promote the accumulation of immunosuppressive $CD206^{hi}$ and fibrotic TAM states, previously grouped under the broad M2-like category (51, 52). These TAM subsets secrete IL-10 and TGF-β (53), reinforcing cytotoxic immune suppression and consolidating the immunologically cold phenotype of PDAC (54).

Hannifin S et al. has previously shown that hypoxic TAMs are strongly linked to elevated IL-6-STAT3 pathway activity and immunosuppression in both human and mouse PDAC (34). Metabolic constraint further amplifies IL-6-STAT3 activation exacerbated by the desmoplastic barrier and extensively rewires tumour cell metabolism *via* stabilization of HIF-1α (55, 56). HIF-1α upregulates the transcriptional expression of numerous glycolytic enzymes by binding to the hypoxia response element (HRE) consensus sequence (56), resulting in an inefficient but highly glucose-consumptive glycolysis

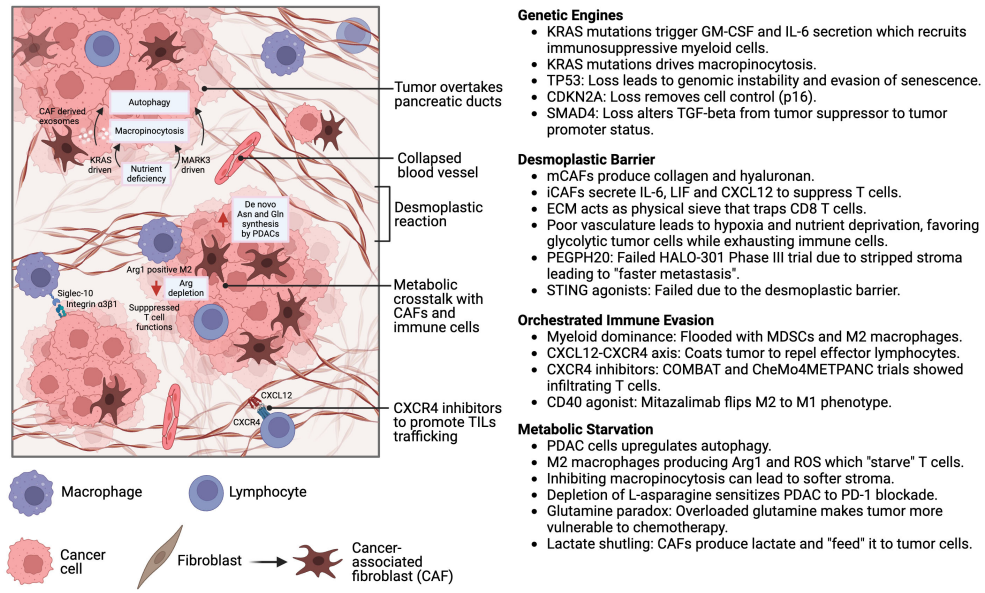


FIGURE 1
Immune-cold pancreatic ductal adenocarcinoma (PDAC): stromal, metabolic and immune mechanisms driving immune evasion. PDAC is characterized by oncogenic KRAS-driven metabolic rewiring, a dense desmoplastic stroma, and profound immune suppression. cancer-associated fibroblasts (CAFs) deposit collagen and hyaluronan, secrete immunomodulatory cytokines, and create a physical barrier that limits vascular perfusion and T cell infiltration. In parallel, tumour-associated myeloid cells, including macrophages and MDSCs, promote T cell suppression, arginine depletion and immune exclusion, These features collectively generate a hypoxia, nutrient deprived, and immune-cold tumour microenvironment that limits antitumour immunity and contributes to resistance to therapy.

TABLE 1 **Major mechanistic pathways of IL-6-STAT3 influence across multiple cell types in PDAC.**

Cell type	Key pathway(s)	Level of evidence	Potential intervention strategy
PDAC tumour cells and TAMS	• Activated STAT3 stabilizes HIF-1α which drives immunosuppressive TAMs. • SOCS3 methylation inhibits IDO degradation despite presence of IL-6. • Activated STAT3 leads to upregulation of PD-L1. • Activated STAT3 leads to upregulation of ST6GAL1, resulting in glycan-immune inhibition. • KRAS mutation upregulates IL-6 (33), activating STAT3 and promoting PanIN progression.	• PDAC tumour and murine samples (34) • PDAC cell lines and PDAC tumour vs healthy tissue (35) • PDAC cell lines and PDAC tumour vs adjacent tissue (36) • PDAC chemo-resistant and metastatic cell lines (37) • PDAC primary and metastatic tumour patient-derived cell lines and murine models (38, 39)	• STAT3 inhibitors • IL-6/6(R) inhibitors • KRAS inhibitors
CAFs	• Mutations in KRAS and activated STAT3 result in cancer-derived lactate, a signalling molecule which drives IL-6 production.	• PDAC tumour samples (40)	• STAT3 inhibitors • IL-6/6(R) inhibitors • KRAS inhibitors
TAMs and Bregs	• IL-10 from TAMs and Bregs upregulate CTLA-4, TIGIT and 2B4 on T cells. • TGF-β from TAMs and Bregs promotes Treg accumulation.	• PDAC tumour and blood samples (41, 42) • Healthy patients (43)	• STAT3 inhibitors • Immune checkpoint inhibitors
MDSCs	• Activated STAT3 in MDSCs promotes ROS generation, upregulating Arg1 and IDO expression, contributing to T cell anergy (44).	• PDAC spleen samples (44, 45)	• STAT3 inhibitors
Activated PSCs	• TGF-β– NF-κB-IL-6 amplification loop.	• PDAC tumour samples (46)	• STAT3 inhibitors • IL-6/6(R) inhibitors
Immune cells	• STAT3 propagates Rorc activation in Tregs, facilitating Th17-like Tregs conversion. • SOCS3 promotes IDO degradation, generating IDO- immunogenic DCs. • SOCS3 promotes IDO degradation, prevents Kyn production that is needed to activate AhR. • IL-10 from TAMs and Bregs upregulates TIM-3, propagates STAT3 upregulation and increases IL-10 production in cDC2.	• PDAC tumour samples (47) • PDAC spleen samples (45) • PDAC cell lines and murine model (48) • PDAC metastatic cell line conditioned medium effect on DCs (49)	• STAT3 inhibitors • IL-6/6(R) inhibitors • Immune checkpoint inhibitors

(57, 58). Thus, elevated glycolysis is a metabolic feature and results in reduced glucose availability in PDAC, approximately 50% lower than in benign pancreatic tissue (59). Under oxidative and metabolic stress, particularly in the presence of granulocytic myeloid derived suppressor cells (G-MDSCs), CAFs undergo metabolic rewiring that preserves IL-6 production even under glucose-limited conditions (40, 58, 60). The resulting accumulation of lactate acidifies the PDAC tumour microenvironment, suppressing T-cell and NK-cell effector function while favouring regulatory T-cell (Treg) persistence, as previously reviewed by Gao F et al (61). Together, these metabolic adaptations maintain sustained IL-6 output and reinforce an immune-evasive niche.

Collectively, IL-6 producing CAFs and myeloid cells function as metabolic and inflammatory gatekeepers within the PDAC tumour microenvironment. By integrating cytokine signalling, extracellular matrix remodelling, and metabolic adaption, they sustain an immunosuppressive and therapy-resistant ecosystem that continues to impede treatment responses. Therapeutic stromal remodelling has therefore yield mixed results: in the HALO-301 trial, hyaluronidase-mediated extracellular matrix depletion with pegvorhyaluronidase alfa did not improve outcome and raised concerns that excessive matrix removal may facilitate invasion and metastasis (62). These findings highlight the dual role of the extracellular matrix-IL-6 axis, in which matrix stiffness promotes therapeutic resistance, whereas complete stromal ablation may inadvertently remove constraints on tumour spreading.

Taken together, evidence supporting an extracellular matrix-IL-6 axis in PDAC therapeutic resistance is substantial with direct PDAC data demonstrating CAF- and PSC-derived IL-6 production (40), HIF-1α-dependent upregulation and gemcitabine resistance (direct PDAC evidence shown in *in-vitro*, murine PDAC models and patient-derived) (56, 63). The role of metabolic co-option by granulocytic-MDSCs preserving IL-6 output under glucose deprivation is supported by indirect murine data and requires direct confirmation in PDAC (40). The primary therapeutic implication is that targeting the extracellular matrix alone is insufficient and must be combined with multi-modal IL-6 pathway(s) inhibition to achieve immunological reprogramming. A key unresolved question is whether the sequence of stromal depletion versus IL-6 blockade determines outcome, given the contrasting lessons from HALO-301.

5 Multimodal IL-6-gp130 signalling drives STAT3-dependent immune suppression

IL-6 and its receptor components are expressed across multiple immune cell subsets and are markedly upregulated in human PDAC (25), where their expression correlates with reduced overall survival (64). IL-6 signalling is initiated by the formation of a hexameric receptor complex composed of two IL-6 molecules, two ligand binding α-subunits (IL-6R), and two signal-transducing β-subunits (glycoprotein 130, gp130). This complex mediates three mechanistically distinct signalling modes: classic-, trans- and cluster signalling (Figure 2).

In classic signalling, IL-6 engages membrane-bound IL-6R (mIL-6R) on a restricted set of cells, promoting gp130 recruitment and homodimerization. These confine signalling to IL-6R expressing cell populations such as hepatocytes and select leukocyte subsets (25, 65). In contrast, trans-signalling occurs when IL-6 binds soluble IL-6R (sIL-6R), generating a complex capable of activating gp130 on virtually all cells, as gp130 is ubiquitously expressed. This mechanism substantially expands the spectrum of IL-6 responsive cells in PDAC, enabling modulation of stroma, endothelial, and immune compartments that lack mIL-6R. Soluble IL-6R is primarily generated through proteolytic shedding of mIL-6R by the metalloproteases ADAM10 and ADAM17, with a lesser contribution from alternatively spliced IL-6R mRNA (65).

A third mode, termed cluster signalling, involves the presentation of membrane-bound IL-6-IL-6R complexes on "transmitter" cells, such as SIRPα$^+$ DCs, to gp130 on neighbouring "receiver" T cells during cognate interaction (66). This configuration promotes spatially restricted gp130 clustering at the immune synapse, facilitating localized IL-6 signalling that directly couples a dendritic cell bound IL-6Rα to T-cell, leading to differentiation of Th17 subset (66).

Activation of gp130 triggers downstream signalling via associated JAK kinases, leading to phosphorylation and dimerization of STAT transcription factors, alongside activation of MAPK and P13K pathways. Persistent IL-6-gp130 signalling – particularly through STAT3, MAPK, and PI3K axes - drives transcriptional programmes that promote inflammation, tumour cell survival, invasion, and immune suppression, thereby contributing to PDAC progression (25).

Negative regulation of this pathway is mediated in part by suppressor of cytokine signalling 3 (SOCS3), a STAT3-inducible proteins that binds phosphorylated gp130 to promote ubiquitin-dependent receptor degradation. SOCS3 can also directly inhibit JAK1/2, thereby attenuating downstream STAT activation (67).

6 IL-6- and the TGF-β control of Treg/Th17-like Treg balance in PDAC

IL-6 sits at the centre of a reinforcing inflammatory circuit in PDAC, integrating cues from non-canonical TGF-β signalling, Th17 biology and stromal activation. Non-canonical TGF-β signalling, particularly via NF-κB–dependent pathways, can promote pro-inflammatory cytokine production, including IL-6 by macrophages and monocytes; consistent with this, the IL-6 promoter contains putative NF-κB binding sites (68, 69). In activated human PSCs, neutralization of either IL-6 or TGF-β attenuates the corresponding downstream signalling pathway, supporting the existence of a reciprocal autocrine TGF-β–IL-6 loop (70).

IL-6 largely influences CD4$^+$ T cell fate (Figure 3). Naïve CD4$^+$ T cells can differentiate into either Foxp3$^+$ regulatory T cells (Tregs), which restrain immune responses, Th17 cells, that are pro-inflammatory and driven by RORγt. TGF-β alone favours Treg differentiation, whereas TGF-β together with IL-6 classical signalling promotes Th17 polarization (66, 71). In this context, IL-6 receptor (IL-6R) signalling shifts the balance away from immune regulation and towards inflammation, thereby shaping the tumour microenvironment (66).

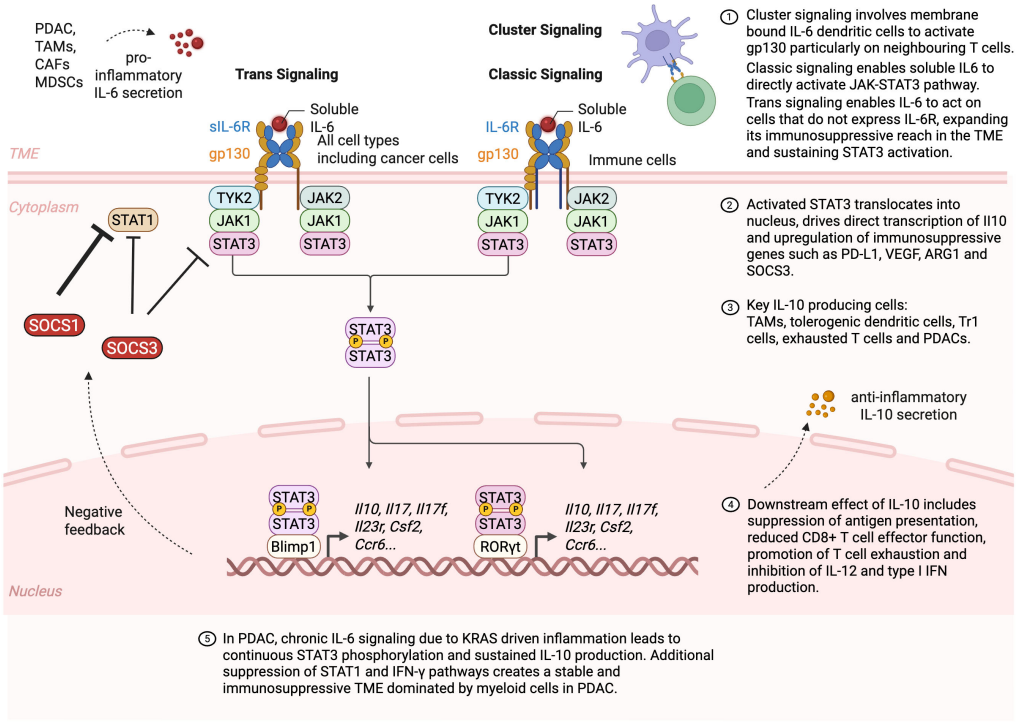


FIGURE 2
IL-6 signalling pathways shaping immune suppression in PDAC. IL-6 produced by PDAC cells and tumour-associated stromal and myeloid cells signals through classic, trans and cluster modes to activate JAK1/JAK2/TYR2-STAT3 pathways in immune and cancer cells. In classic and trans signalling, IL-6 binding to membrane-bound IL-6R or soluble IL-6R, together with gp130, drives STAT3 phosphorylation, nuclear translocation and transcription of immunosuppressive genes, including IL10, VEGF, ARG1 and SOCS3. Cluster signalling further amplifies local immune activation through membrane-bound Il-6 on dendritic cells and neighbouring T cells. Sustained IL-6-STAT3 signalling promotes IL-10 production by TAMs, tolerogenic dendritic cells, Tr1 cells, exhausted T cells and PDAC cells, while negative feedback via SOCS1 and SOCS3 modulates pathway intensity. Collectively, chronic IL-6 signalling reinforces an immunosuppressive, STAT3-dominant tumour microenvironment that supports PDAC progression and immune evasion.

At the transcriptional level, IL-6 dependent STAT3 signalling and IL-2 dependent STAT5 signalling exert opposing effects on the Foxp3-RORγt axis. STAT3 activates Rorc transcription and promotes RORγt expression, whereas STAT5 supports Foxp3 expression through binding to the Foxp3 conserved non-coding sequence 2 (CNS2) and enhances IL-10 production. Although Foxp3 normally suppresses RORγt-mediated IL-17 transcription, sustained STAT3 activity can weaken this restraint and permit the emergence of hybrid Foxp3$^+$RORγt$^+$IL-17$^+$ Tregs (Th17-like Tregs). These cells retain Treg lineage identity yet acquire inflammatory function, reflecting the plasticity of the Treg compartment under persistent IL-6 driven signalling (72, 73).

This balance has relevance in PDAC, where hybridized RORγt+ Tregs are increased and Foxp3-only Tregs are reduced relative to healthy donors (73). Such hybrid Tregs are immunologically ambivalent: they suppress anti-tumour T cell responses while also supporting protumour inflammation (47). More broadly, IL-17 produced by the hybrid Th17-like Tregs, conventional Th17 and γδT17 cells contributes to pancreatic acinar-to-ductal metaplasia and early PanIN progression through IL-17RA-dependent signalling in dysplastic epithelium (74, 75). IL-17 further amplifies immunosuppression by promoting MDSCs, tumour associated neutrophils, Treg maturation and CAF activation (76).

IL-17 also acts upstream of IL-6 production. Tc17 cells (IL-17A producing CD8$^+$ T cells) can induce iCAF-associated gene expression through TNF and IL-17A synergy, driving the conversion of resident PSCs into inflammatory CAFs (77, 78), a major source of IL-6 in PDAC. Thus, IL-17 functions as an amplifier of IL-6-rich stromal inflammation. In turn, IL-6R-STAT3 signalling reinforces RORγt expression and IL-17 production in Th17-like Tregs, establishing a feed-forward inflammatory loop in which IL-6 occupies a dominant position.

Although IL-6 and IL-17 are classically viewed as pro-inflammatory cytokines, in PDAC they cooperate to sustain a largely immunologically "cold" tumour microenvironment. Rather than promoting effective anti-tumour immunity, this inflammatory state preferentially expands suppressive immune populations and tumour-supportive stromal programmes, thereby facilitating disease progression.

7 IL-6 signalling and the IDO$^{+/-}$-deficient dendritic cell circuit

7.1 The IDO-TGF-β self-amplification loop in IDO$^+$ dendritic cells

The metabolic enzyme Indoleamine 2,3-dioxygenase (IDO) catalyses the rate-limiting first step of tryptophan catabolism (79), converting tryptophan into kynurenines (Kyn), and is a critical

regulator of peripheral immune tolerance (Figure 3). Constitutively expressed at high levels in plasmacytoid dendritic cells (pDCs), IDO shapes the phenotype of neighbouring cell populations, most notably $CD4^+$ T cells, in a manner that favours tolerance. Consistent with this, Ruders, JH et al. has reported circulating TGF-β peptide specific $CD4^+$ T cell in PDAC patients (80). Central to this tolerogenic programme is TGF-β self-amplification loop (81), whereby TGF-β signalling in dendritic cells activates the Fyn tyrosine kinase, which phosphorylates immunoreceptor tyrosine-based inhibitory motif domains in IDO, creating docking sites for phosphatases SHP-1 and SHP-2. This TGF-β/IDO/SHP signalling axis drives non-canonical nuclear factor-κB (NF-κB) activation through p52/ReIB pathway, in part by suppressing *interleukin-1 receptor-associated* kinase 1 (IRAK1), thereby preventing transcriptional induction of IL-6 (82).

The net result is a shift in DC secretory output away from pro-inflammatory cytokines (82). Production of type I interferons and TGF-β is instead favoured, generating positive feedback that promotes the differentiation of naïve $CD4^+$ T cells into Foxp3+ Tregs (81). This self-reinforcing circuit actively suppresses IL-6 production within the tolerogenic niche (83).

7.2 IL-6 receptor-SOCS3 results in IDO-deficient dendritic cells

However, IL-6 receptor (IL-6R) signalling counters the IDO circuit through SOCS3, which binds to the immunoreceptor tyrosine-based inhibitory motifs (ITIMS) of IDO protein, and recruits E3 ubiquitin ligase complex for proteasomal degradation (84). By collapsing IDO protein abundance in DCs, this results in immunogenic IDO-deficient DCs which are less capable of secreting Kyn, that would favour Th17-like Tregs (81, 84).

The phenotypic plasticity of Tregs and Th17-like Tregs has been reported in PDAC patients (47, 81, 85). Environmental cytokine cues, particularly the balance between TGF-β and IL-6, profoundly influence interconversion between these subtypes. Reduced Kyn secreted from IDO-deficient DCs present a fundamentally altered antigenic and cytokine landscape that can mediate lineage conversion of Tregs to Th17-like Treg cells (83).

Hence IL-6R signalling promotes IDO degradation in dendritic cells via SOCS3, reducing Kyn secretion. This shifts the main Kyn-producing cell types to PDAC (see section 8.1), which plays a critical role in the balance and plasticity of $CD4^+$ T cells.

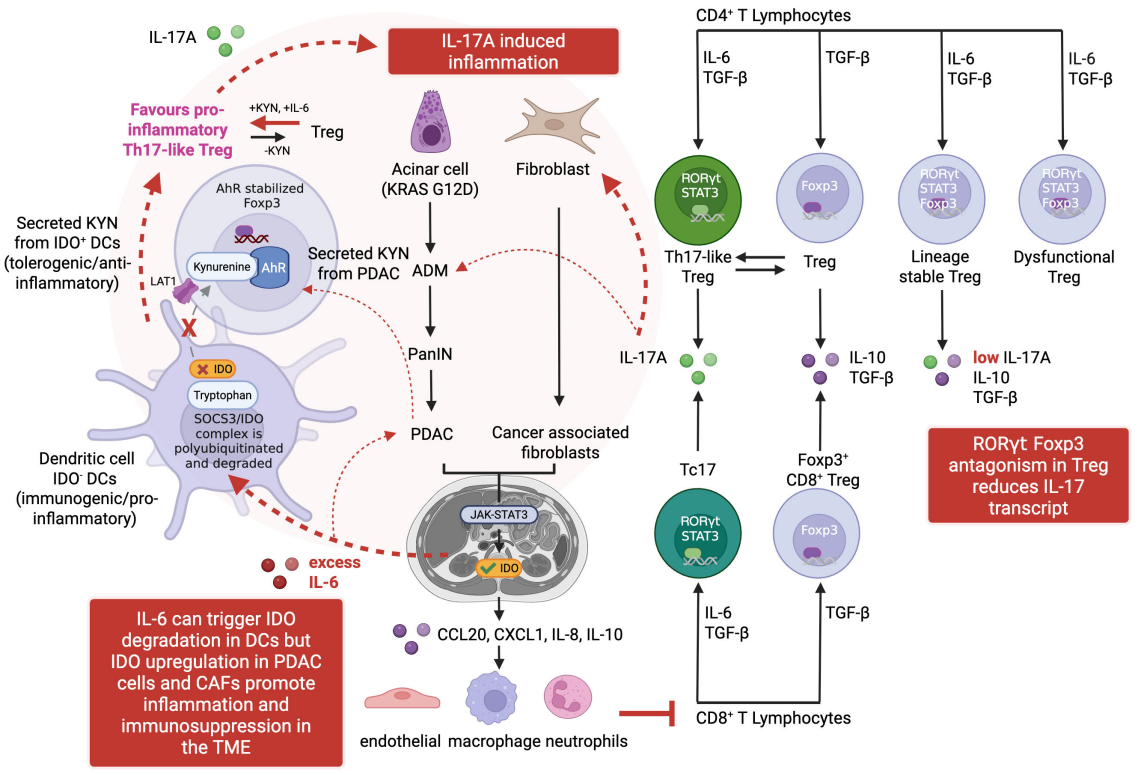


FIGURE 3
IL-6 driven interplay among IDO-dependent immune plasticity, inflammation and immunosuppression in PDAC. IL-6 produced in excess within the tumour microenvironment orchestrates a complex network of pro-tumourigenic signal across multiple cell types. In dendritic cells, excess IL-6 triggers IDO degradation while paradoxically upregulating IDO in PDAC cells and CAFs via JAK-STAT3 signalling, promoting concurrent inflammation and immune evasion. In the absence of IDO in dendritic cells, PDAC cells themselves secrete kynurenine which shifts kynurenine metabolism towards AhR-mediated Foxp3 stabilization, favouring conversion of conventional Tregs towards a pro-inflammatory Th17-like Treg phenotype. KRAS G12D-driven acinar-to-ductal metaplasia and subsequent PanIN progression to PDAC, alongside fibroblast activation into CAFs, amplify IL-17A induced inflammation. In the adaptive immune compartment, combined IL-6 and TGF-β signalling from $CD4^+$ T cells drives differentiation into functionally distinct Treg subsets-characterized by varying expression of RORγt, STAT3 and Foxp3. Collectively, these mechanisms illustrate how IL-6 functions as a central hub coordinating immunosuppression and tumour-promoting inflammation in PDAC. IDO, indoleamine 2,3-dioxygenase; KYN, kynurenine; ADM, acinar-to-ductal metaplasia; PanIN, pancreatic intraepithelial neoplasia; AhR, aryl hydrocarbon receptor.

7.3 Epigenetic maintenance of Foxp3 lineage commitment

Stable Foxp3 expression is the defining feature of committed Tregs and is maintained by epigenetic mechanisms centred on the conserved non-coding sequence 2 (CNS2), also termed the Treg-specific demethylated region (TSDR), within the Foxp3 locus (86–89). Demethylation of CNS2 is required for stable, heritable Foxp3 expression independent of exogenous TGF-β. In comparison, TGF-β-dependent STAT5 activation facilitates the initial chromatin opening at methylated CNS2, inducing Foxp3 expression (90). Accordingly, abrogation of IL-2R signalling or loss of STAT5 activity is sufficient to destabilize Foxp3 expression (91).

Beyond STAT5-mediated chromatin access, TGF-β signalling promotes the proteasomal degradation of ubiquitin-like, containing PHD and RING finger domains 1 (Uhrf1), a critical epigenetic regulator of DNA methylation maintenance (92, 93). Loss of Uhrf1 triggers rapid passive demethylation of CNS2, providing a direct mechanism by which TGF-β stabilizes Foxp3 expression at the epigenetic level (92). The kynurenine pathway adds a further layer: Kyn, the principal product of IDO-mediated tryptophan catabolism, binds and stabilizes AhR in Tregs (94), and AhR protein complex directly induces Foxp3 transcription while enhancing chromatin accessibility at the Foxp3 locus (95).

7.4 IL-6 STAT3 antagonizes the TGF-β-STAT5-AhR axis to destabilize Foxp3

IL-6-STAT3 competes with TGF-β-STAT5 for transcriptional control of Foxp3, TGF-β stabilizes Foxp3 expression through STAT5 activation and cooperative binding with CREB and AP-1 at the CNS2 locus of the Foxp3 gene (90). IL-6 driven STAT3 directly antagonizes this by competing with STAT5 for overlapping binding sites across the *Il17* genetic locus (96)— STAT3 activation suppresses STAT5-dependent Foxp3 transcription, effectively undermining the transcriptional reinforcement that maintains Treg identity.

SOCS3 creates a secondary antagonism. IL-6-STAT3 upregulates SOCS3, which suppresses STAT5 signalling further and drives proteasomal degradation of IDO (84). SOCS3-mediated IDO collapse in DCs reduces both Kyn availability in the TME and AhR activation in Tregs, whereby AhR signalling is a known co-stabilizer of Foxp3 through epigenetic mechanisms, so its loss, downstream of IL-6 removes a second reinforcing input to Foxp3 stability. As Foxp3 protein levels and stability drop, the cells lose their suppressive functions and begin upregulating Th17-associated markers (e.g., IL-17A, CCR6, and RORγt) to become Th17-like Tregs (97).

Through these multi-layered mechanisms operating between DCs and T cells, Foxp3 stability can be reduced to trigger lineage transformation of Tregs to Th17-like Tregs (84, 98, 99).

7.5 AhR as an immune checkpoint: intersection with IL-6 driven IDO collapse

AhR knockout in PDAC cells has been found to promote MHC-I expression (48). Thus, AhR has emerged as a candidate immune checkpoint receptor, exhibiting significant positive co-expression with inhibitory receptors including CD200R1, CD47, PD-1, and TIM-3), as well as inhibitory ligands (BTLA, PD-L1, and PD-L2) (100). Active AhR signalling in DCs and Tregs reinforces suppressive phenotypes and dampens immune activation. IL-6-SOCS3-mediated IDO collapse therefore not only removes Kyn from the extracellular milieu but also functionally inactivates AhR-dependent immune checkpoint programming, converting IDO^{+} tolerogenic DCs to an immunogenic IDO-deficient state, as strong antigen-presenting cells capable of licensing effector T cell responses.

8 The paradox of IL-6 and IDO in PDAC: cell-type specific inversion

8.1 Autocrine IL-6-IDO co-amplification loop in tumour cells

Anu RI et al. has previously reviewed the immunomodulatory roles of IDO in PDAC (101). The impact of IL-6 on IDO in tumour cells is markedly distinct from its effect in DCs (see sections 7.2 and 8.2), representing a paradigmatic example of context-dependent cytokine signalling. In PDAC, IDO expression was found to be significantly elevated, and it correlated to a poor prognosis (35). Mechanistically, in tumours, IDO activity generates Kyn, which activates AhR and permits its nuclear translocation. In the nucleus, AhR dimerizes with aryl hydrocarbon receptor nuclear translocator (ARNT) and binds dioxin-responsive elements (DRE) in the promoter of target genes, including the IL-6 gene itself, thereby transcriptionally inducing IL-6 expression (Figure 4).

IL-6 produced in this manner activates STAT3, which undergoes both phosphorylation and acetylation, and activated STAT3 in turn drives further IDO expression. This creates a fully autocrine and self-reinforcing IDO-Kyn-AhR-IL-6-STAT3-IDO feedforward loop in tumour cells (102). Compounding this circuit, persistent and high-amplitude IL-6 signalling sustains chronic STAT3 activation, which itself suppresses SOCS3 expression, removing the principal brake on this loop (103). The downstream consequence is progressive tryptophan depletion in the tumour microenvironment, which impairs cytotoxic T cell proliferation and function as IDO catalyses the rate-limiting step of tryptophan catabolism.

8.2 Inversion of IL-6-IDO polarity by SOCS3 silencing in PDAC tumour cells

The cell-type specific inversion in IL-6-IDO biology between DCs and tumour cells is explained in large part by the epigenetic silencing of SOCS3 in cancer cells. In PDAC, SOCS3 is frequently subjected to hypermethylation and transcriptional silencing (104, 105), thus abolishing the canonical SOCS3-dependent IDO degradation. This is unlike SOCS3 in DCs, which drives IDO degradation (see section 7.2). In this epigenetic context, IL-6 no longer depends on the SOCS3 brake to suppress IDO, and instead operates exclusively through STAT3 to reinforce it, creating the autocrine

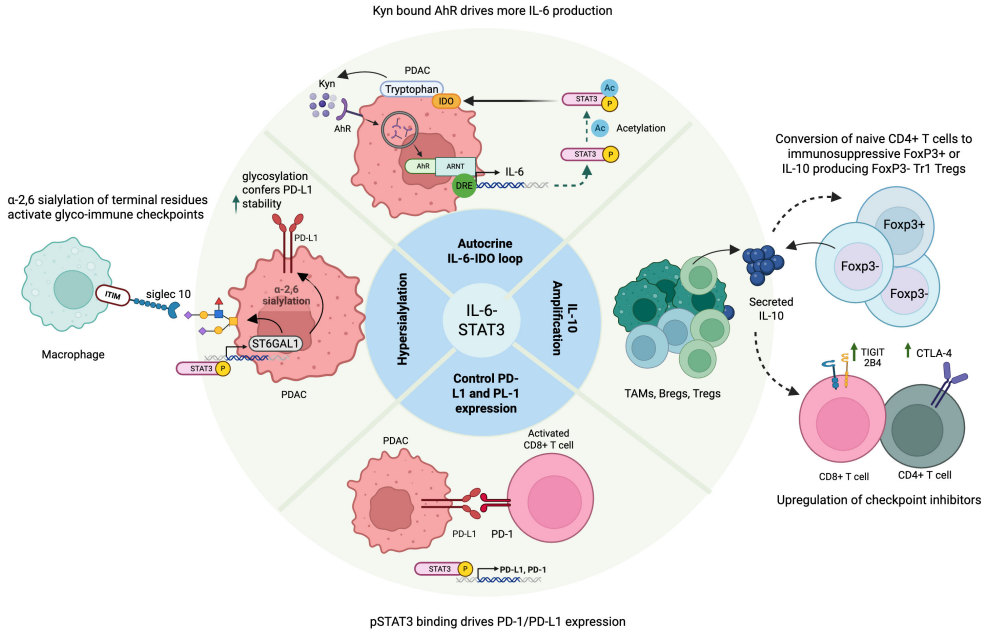


FIGURE 4
IL-6-STAT3-mediated immunosuppressive pathways in pancreatic ductal adenocarcinoma (PDAC). IL-6 signals through STAT3 to orchestrate four interconnected immunosuppressive mechanisms in the tumour microenvironment (1). Autocrine IL-6-IDO loop (top): In PDAC cells, phosphorylated STAT3 acetylation enhances IDO expression, driving tryptophan catabolism to kynurenine (Kyn). Kyn binds the aryl hydrocarbon receptor (AhR), which heterodimerizes with ARNT and binds dioxin response elements (DRE) to transcriptionally upregulate IL-6, creating a self-amplifying autocrine loop (2). Hypersialylation (left): pSTAT3 transcriptionally induces ST6GAL1, promoting α-2,6 sialylation of terminal residues on PD-L1, conferring glycoprotein stability. Hypersialylated PD-L1 engages Siglec-10 on tumour-associated macrophages via ITIM-mediated inhibitory signalling, activating glyco-immune checkpoints (3). Control of PD-L1/PD-1 expression (bottom): pSTAT3 directly binds promoter elements to transcriptionally upregulate PD-L1 on PDAC cells and PD-1 on activated $CD8^+$ T cells, suppressing cytotoxic T cell activity (4). IL-10 amplification (right): IL-6-STAT3 signalling expands tumour-associated macrophages (TAMs), regulatory B cells (Bregs), and regulatory T cells (Tregs), which secrete IL-10 to convert naïve $CD4^+$ T cells into immunosuppressive Foxp3+ Tregs or IL-10-producing Foxp3– Tr1 cells. IL-10 further upregulates checkpoint inhibitors TIGIT, 2B4, and CTLA-4 on $CD8^+$ and $CD4^+$ T cells, collectively dampening anti-tumour immunity. Together, these pathways position IL-6-STAT3 signalling as a central hub of immune evasion in PDAC.

amplification loop described above. Together, these opposing cell-type specific outcomes illustrate a PDAC paradox in which the presence or absence of functional SOCS3 acts a molecular switch deciding whether IL-6 dismantles or amplifies IDO-dependent immunosuppression.

9 IL-6-STAT3 control of PD-L1 and PD-1 expression

9.1 Multi-level transcriptional regulation of PD-L1 by IL-6

The immune checkpoint molecules PD-1 and PD-L1 form a central axis of adaptive immunosuppression, inhibiting effector T cell activation while simultaneously reinforcing the immunosuppressive capacity of Tregs (106). Transcriptional and post-transcription control of PD-L1 is highly complex in cancer, with multiple transcription factors — including STAT3, STAT1, c-Jun, HIFs, or NF-κB — binding discrete regulatory elements in the CD274 (PD-L1) gene promoter to induce its expression in tumours (36)and stromal fibroblasts (107, 108). Li et al. has reported that STAT3 can also directly stabilize PD-L1 by preventing ubiquitination and degradation in PDAC (Figure 4) (36).

Both IL-6 and IL-10 signalling activates STAT3 downstream that can strongly induce PD-L1, and these effects are additive in certain cell types, particularly macrophages (109). IL-6 further amplifies this programme by triggering IL-10 production in MDSCs, regulatory B (110), creating a cytokine relay that broadens and sustains STAT3-driven PD-L1 induction across multiple cellular compartments of the tumour microenvironment.

9.2 Post-translational stabilization of PD-L1 by JAK1-mediated glycosylation

Beyond transcript-level control, IL-6-activated JAK1 phosphorylates Tyr112 of PD-L1 protein. This phosphorylation events recruits the endoplasmic reticulum-associated N-glycosyltransferase STT3A, which catalyses PD-L1 glycosylation and stabilizes the protein against proteasomal degradation (111, 112). Glycosylated PD-L1 is substantially more stable and displays enhanced surface expression, thereby amplifying checkpoint suppression independently of transcriptional induction. This dual transcriptional-post-translational mechanism ensures robust PD-L1 accumulation in the IL-6 rich PDAC microenvironment (Figure 4). IL-17, produced by Th17-like Tregs cells arising from IL-6 driven Treg reprogramming, has also been observed to upregulate PD-L1 expression through a mechanism that remains to be fully delineated (113), potentially extending the immunosuppressive reach of IL-6 signalling network.

9.3 STAT3-mediated prolongation of PD-1 expression on CD8$^+$ T cells

The IL-6-STAT3 axis also targets PD-1 expression on cytotoxic T cells. During cognate T cell receptor engagement, IL-6-dependent STAT3 binds directly to regulatory elements of *pdcd1* (encoding PD-1), prolonging PD-1 expression on activated CD8$^+$ T cells (114) (Figure 4). This sustains PD-1-mediated inhibitory signalling, thus contributing to T cell exhaustion in the chronic inflammatory milieu of PDAC. In this manner, IL-6 simultaneously induces the ligand (PD-L1) on tumour and stromal cells and prolongs receptor (PD-1) expression on effector T cells, reinforcing checkpoint suppression at both ends of the PD-L1-PD-1 axis.

10 IL-6-STAT3-ST6GAL1 mediated sialylation and glyco-immune checkpoints

10.1 ST6GAL1: IL-6-driven sialylation as immune evasion

Aberrant tumour hypersialylation has emerged as a glyco-immune checkpoint mechanism, enabling cancer cells to evade immune responses by engaging inhibitory receptors on immune effector cells (115). Sialic acid–binding immunoglobulin-like lectins (Siglecs), expressed on T cells, DCs, macrophages, and B cells mediate this effect (116, 117). These Siglecs signal through immunoreceptor tyrosine-based inhibitory or switch motifs (ITIM/ITSM), leading to suppressed cytotoxic activity of CD8$^+$ T cells and NK cells, impaired DC maturation and T cell priming, and favour Treg induction and TAMs polarization (118).

In PDAC, IL-6, drives ST6GAL1 overexpression *via* STAT3, binding to the P3 promoter of the sialytransferase gene (Figure 4) (37). ST6GAL1 is a critical enzyme for adding sialic acid residues to terminal N-glycosylated proteins via α2-6-linkage, fundamentally altering glycoprotein structure and function (37, 119). ST6GAL1-mediated sialylation generates sialoglycans recognised by Siglec-2, -3, -9 and -10 (120), and elevated α2,3- and α2,6- sialylation was among the dominant glycomic modifications in PDAC patients (121).

10.2 Siglec-mediated suppression of TAMs and tolerogenic antigen presentation

Recently, Saini et al. reported that Siglec-10 expressed on TAMs engages its sialoglycoprotein ligand α3β1 on PDAC cells, which suppresses macrophage-mediated phagocytosis, and thereby promotes immune evasion (122). Another consequential aspect of IL-6 driven hypersialylation is its impact on antigen presentation. Perdicchio et al. reported that sialylated tumour antigens taken up by DCs endows a tolerogenic response, inducing *de novo* Tregs while dampening T effector expansion and IFN-γ production (123).This mechanism directly links IL-6 driven ST6GAL1 activity to antigen specific tolerance in the PDAC tumour microenvironment, a glycoimmune barrier that reinforces resistance to immunotherapies by promoting Sia-antigen-specific tolerance.

11 IL-6–Blimp-1–IL-10 axis and broad co-inhibitory receptor programming

11.1 STAT3-driven Breg induction and IL-10 amplification

Under the quiescent conditions, B cells produce minimal IL-10 (124). However, STAT3 signalling induces IL-10-competent regulatory B (Breg) programme through cooperation with IRF4 and PRDM1/Blimp-1–associated transcriptional networks. Breg are the most prominent B cell subset identified in PDAC (124, 125), and exert broad immunosuppressive effects not through lineage identity but through secretion of anti-inflammatory cytokines including IL-10, TGF-β and IL-35. These mediators directly sustain MDSCs and TAMs (125, 126), and Bregs can expand Treg populations or converting naive T cells into Foxp3+ Tregs or IL-10 producing Foxp3- Tr1 regulatory cells (127–129).Supporting a role for Tr1-like cells in PDAC, tumour-associated DCs have been shown to induce CD4$^+$ T cells expressing Tr1-associated markers including CD39, CD49b, IL-10, and AhR within the pancreatic tumour microenvironment, and overall creating an immunosuppressive environment (130).

IL-6 additionally triggers IL-10 production in MDSCs and other myeloid cells, creating a broader cytokine relay that sustains STAT3 activity across multiple cell types. In macrophages, IL-10 downregulates co-stimulatory molecules CD86, ICAM1, and MHC class II expression, via induction of the E3 ubiquitin ligase March-I (131–133), directly limiting the capacity for effective antigen presentation and T cell priming. Beyond antigen presentation, IL-10 signalling promotes CTLA-4 expression on CD4$^+$ T cells and TIGIT and 2B4 (CD244) on CD8$^+$ T cells (134). Consistent with this immunosuppressive phenotype, PDAC-infiltrating T cells exhibit elevated expression of TIGIT (41), and high soluble CTLA-4 levels are associated with advanced PDAC severity (42). CTLA-4 outcompetes with costimulatory receptor CD28 for the shared ligands CD80 and 86, for which it has a higher affinity and avidity, thereby attenuating further T cell activation (135). Collectively, IL-10 driven upregulation of CTLA-4, TIGIT and 2B4 compounds the PD-1 exhaustion programme driven directly by IL-6-STAT3, blanketing cytotoxic T cells with multiple co-inhibitory signals.

11.2 TIM-3-STAT3 feedforward loop in cDC2-like immunosuppressive dendritic cells

Chronic inflammatory signalling through IL-6 and IL-10 reprograms tumour-infiltrating DCs towards a cDC2-like

immunosuppressive phenotype. TIM-3, a co-inhibitory receptor expressed on this DC subset as well as Foxp3+ Tregs (136), reinforces STAT3 activation in reprogrammed DCs, which drives further IL-10 production. IL-10 in turn signals through c-Src to activate the transcription factors Ets1, Ets2, USF1, and USF2, propagating TIM-3 expression and establishing a TIM-3-STAT3-IL-10 positive feedback loop (137). These cDC2-like DCs skew T cell differentiation towards Th2- and Treg responses, further entrenching the immunosuppressive tumour microenvironment (137).

11.3 IL-6-mediated impairment of DC differentiation and the cDC2 enrichment paradox in PDAC

Elevated IL-6 within the PDAC tumour microenvironment contributes to defective dendritic cell differentiation and function through aberrant STAT3 activation, thereby suppressing DC maturation (49). In PDAC patients, cDC2s are the predominant infiltrating DC subtype, yet this population is markedly depleted relative to healthy tissue and displays reduced expression of co-stimulation receptors (138–140). This creates a paradox of relative cDC2 enrichment and overall DC scarcity and functional impairment: the remaining DC pool is disproportionately composed of functionally compromised cDC2-like subset, which is then further reprogrammed by the IL-6-IL-10 axis toward immunosuppressive phenotypes (141). The new consequence is a profound distortion of the antigen-presenting cell landscape, with vast downstream implications for $CD4^+$ and $CD8^+$ T cell differentiation, effector function, and exhaustion within the PDAC tumour microenvironment.

12 Clinical translation of IL-6 pathway targeting: Lessons from the trial landscape

12.1 IL-6(R) blockade in PDAC: a pattern of clinical failure

Despite the mechanistic rationale described above, direct targeting of IL-6 or its receptor in PDAC has not translated into meaningful clinical benefits. Two prospective trials have tested IL-6R or IL-6 blockade in combination with immune checkpoint inhibitors in this disease (Table 2), and neither demonstrated the efficacy required for continued development.

In a Phase Ib/II trial combining the anti-IL-6 antibody siltuximab with the anti-PD-1 antibody spartalizumab in patients with late-stage or metastatic PDAC, no measurable tumour regression was observed across either dose cohort. The low-dose cohort achieved a median progression-free survival (PFS) of 1.9 months and a median overall survival (OS) of 9.3 months; the high-dose cohort fared worse, with a median PFS of 2.1 months and a markedly reduced median OS of 3.1 months. The absence of meaningful clinical activity precluded further trial progression.

The Phase II 'TRIPLE-R' trial evaluated a more aggressive quadruplet regimen of radiotherapy combined with ipilimumab (anti-CTLA-4), nivolumab (anti-PD-1) and tocilizumab (anti-IL-6R) in patients with progressive pancreatic cancer. Despite multimodal checkpoint co-inhibition, the trial failed to meet its prespecified expansion criteria, recording a median PFS of 1.6 months and median OS of 5.3 months. Together, these outcomes highlight a

TABLE 2 Clinical trials of IL-6(R) pathway targeting in PDAC versus RAS-directed strategies.

Study/ref	Population	Intervention	Targets	Key outcomes	Conclusion
Phase Ib/II (142)	Late-stage/ metastatic PDAC (n = 31)	Siltuximab, Spartalizumab	IL-6, PD-1	Low dose: • Median progression-free survival (PFS): 1.9 months Median overall survival (OS): 9.3 months• High dose: • Median PFS: 2.1 • Median OS: 3.1	Absence of measurable tumour regression in treated patients. Cannot progress due to no meaningful clinical activity.
Phase II trial 'TRIPLE-R' (143)	Refractory pancreatic cancer (n = 26)	Radiotherapy, Ipilimumab, Nivolumab, Tocilizumab	IL-6R, CTLA-4, PD-1	• Median PFS: 1.6 months • Median OS: 5.3 months	Did not meet the criteria for the study to expand and continue.
Phase III RASolute 302 (144)	Previously treated Metastatic PDAC (n = 500)	Daraxonrasib	Multiple RAS variants	• Median OS of 13.2 months • Median PFS: undisclosed	Met all primary and key secondary endpoints.
Interim Phase 1/2 (AMPLIFY-7P) (145)	mKRAS-driven PDAC (n = 158)	Peptides: ELI-002 7P	mKRAS	• Median recurrence-free survival of 16.33 months • Median OS: 28.94 months	*Disease-free survival analysis to be released in 2026.*

consistent pattern in which IL-6R blockade, even combined with established immune checkpoint inhibitors, fails to reprogram the immunosuppressive PDAC tumour microenvironment at clinically advanced disease stages.

12.2 Redefining the therapeutic horizon: RAS-directed strategies in PDAC

The repeated failure of IL-6(R) blockade in PDAC has prompted a re-evaluation of which molecular targets are tractable in this disease. Mounting evidence from two distinct RAS-directed therapeutic strategies—one targeting the oncogenic driver directly at the protein level and one harnessing the immune system against it—offers a compelling mechanistic contrast and potentially transformative clinical results. Daraxonrasib (RMC-6236) is an orally bioavailable, RAS (ON) multi-selective, non-covalent tri-complex inhibitor that targets the active, GTP-bound state of RAS. This modality confers pan-RAS selectivity across the broad spectrum of RAS G12X and other variants present in PDAC—including G12D, G12V, G12R, G12A, G12S and G12C—addressing a limitation that has historically constrained allele-specific inhibitor development in this disease. The clinical impact of this mechanism was demonstrated in the Phase III RASolute 302 trial (NCT06625320). Whereas daraxonrasib targets RAS oncoproteins directly, ELI-002 7P (Elicio Therapeutics) takes an orthogonal immunological approach: activating the patient's own adaptive immune system against mutant KRAS neoantigens. ELI-002 7P is a seven-valent amphiphile (Amph) cancer vaccine comprising Amph-modified long peptides encoding seven common KRAS/NRAS driver mutations (G12D, G12R, G12V, G12A, G12C, G12S, and G13D) combined with an Amph-modified Toll-like receptor 9 (TLR9) agonist adjuvant (CpG-7909). ELI-002 7P is being evaluated in the Phase 1/2 AMPLIFY-7P trial (NCT05726864) as adjuvant monotherapy in patients with mKRAS-positive PDAC (and other solid tumours). Notably, antigen spreading to personalised tumour neoantigens beyond mKRAS was detected in a subset of patients—a signal suggesting that vaccine-induced T cells are killing tumour cells and releasing new antigens, broadening the immune response beyond the vaccine's encoded targets.

A mechanistic distinction between these two RAS-directed approaches is noteworthy in the context of this Review. Daraxonrasib acts *upstream* of the immunosuppressive programme described herein — suppressing oncogenic RAS signalling that drives IL-6 production, IDO induction, STAT3 activation, and ST6GAL1 overexpression — and thereby has the potential to dismantle the tumour-intrinsic feedforward loop at its source. ELI-002 7P acts *in parallel*, seeking to generate mKRAS-specific cytotoxic T cells capable of recognising and killing PDAC cells that express these neoantigens. In principle, these strategies are not mutually exclusive: reducing oncogenic RAS activity with daraxonrasib could alleviate T cell exclusion and immune suppression in the tumour microenvironment, while vaccine-induced mKRAS-specific T cells could target residual or resistant tumour clones. The clinical viability of such combinations remains to be tested.

12.3 Timing, tumour architecture, and the limits of late-stage IL-6 targeting

IL-6 has a prominent role in pancreatic tumourigenesis, including promotion of inflammatory signalling, myeloid-cell recruitment, impaired dendritic-cell differentiation, STAT3 activation, and early immune tolerance. However, by the time most patients present with advanced or metastatic PDAC, the tumour microenvironment is often already shaped by dense desmoplasia, T cell exclusion, stromal compartmentalisation, and multiple overlapping immunosuppressive pathways. In this setting, IL-6/IL-6R blockade alone is unlikely to fully reprogramme the established stromal–myeloid network or restore effective antitumour immunity. Its value may therefore depend less on broad late-stage use and more on rational combinations, earlier intervention windows, or biologically selected patients.

The absence of biomarker-guided patient selection compounds this challenge. Patients with high circulating IL-6, high intratumoural IL-6 pathway activity, or tumours with demonstrable STAT3-dependent immune suppression may represent more plausible candidates for IL-6-directed therapy, although these markers remain investigational rather than validated predictors. In unselected PDAC, using immune checkpoint inhibition as the therapeutic backbone without first addressing T-cell exclusion, stromal barriers, and myeloid-mediated suppression is likely to limit the efficacy of any added immunomodulatory intervention.

12.4 Implications for trial design: earlier intervention, rational combinations, and patient selection

Collectively, these findings suggest that IL-6 blockade may be better suited to earlier disease stages – neoadjuvant or resectable settings – where the tolerogenic programme is still being established and where prevention of immune suppression is mechanistically achievable. Rational multi-modal strategies that simultaneously address stromal barriers (for example, with CXCR4 or TGF-β inhibitors), deplete immunosuppressive myeloid populations, and engage T cell priming alongside IL-6R blockade may more closely match the biological complexity of the PDAC tumour microenvironment. Finally, prospective biomarker stratification — selecting patients with demonstrably IL-6 dependent STAT3 activation, high ST6GAL1 expression, or SOCS3 competent intratumoural DCs — represents an important and as yet untested approach to identifying the subpopulation most likely to benefit from IL-6 pathway inhibition.

To operationalize this approach, we propose a multi-parameter biomarker framework for patient selection in future IL-6 directed trials. Candidate stratification markers include (i) serum IL-6 (>10 pg/mL) as a provisional threshold, to be defined prospectively; (ii) pSTAT3-positive tumour cells by immunohistochemistry (>10% of tumour cells); (iii) SOCS3 promoter methylation status in tumour biopsy (methylation indicating IDO-amplifying PDAC context); (iv) ST6GAL1 protein expression by IHC or RNA *in situ*

hybridization; (v) glycosylated PD-L1 as detected by glycan-specific antibody; (vi) Siglec ligand abundance by lectin histochemistry; and (vii) T-cell exclusion score e.g. $CD8^+$ T-cell density at tumour margin vs centre. Therefore patients with high IL-6 pathway activation (markers i-iii positive), evidence of glyco-immune checkpoint activity (markers iv-vi), and profound T-cell exclusion (marker vii) represent the stratum for IL-6-STAT3 co-targeting strategies.

13 Conclusion

IL-6 is a multi-armed cytokine whose immunosuppressive impact in PDAC extends far beyond any single pathway. Acting primarily through STAT3, and reinforced by IL-10, Kyn–AhR, and JAK1 kinase activity, IL-6 drives a coordinated programme that disrupts tolerogenic DC function, sustains an IDO–IL-6 autocrine loop in SOCS3-silenced tumour cells, stabilizes PD-L1 protein and prolongs PD-1 on exhausted T cells, promotes tumour-surface hypersialylation to engage Siglec-mediated checkpoints, and expands Breg–IL-10 circuits that suppress antigen presentation and co-stimulation. These pathways are interconnected and mutually reinforcing.

Consistent with this biological complexity, earlier clinical trials of IL-6R/IL-6 blockade in PDAC have repeatedly failed to achieve meaningful responses, in contrast to the more encouraging responses reported for RAS-directed strategies. This divergence likely reflects differences in tumour immune architecture and the multiplicity of upstream inputs converging on STAT3 in PDAC. Against this backdrop, RAS-directed strategies in PDAC, including RAS(ON) multi-selective inhibitor daraxonrasib and mKRAS/NRAS peptide vaccines, are generating more promising early clinical signals.

Translating the mechanistic understanding into clinical benefits will require a fundamental shift in trial design strategy, rather than adding IL-6 or IL-6R blockade onto a single immunotherapy backbone, future trials should be designed around the interconnected biology described here: combining IL-6 pathway inhibition with agents that simultaneously dismantle stromal barriers, restore DC function, and counteract glyco-immune checkpoints. The proposed multi-parameter biomarker framework — incorporating serum IL-6, pSTAT3 tumour burden, SOCS3 methylation status, ST6GAL1 expression and T-cell exclusion score — offers a tractable path towards identifying the patient subpopulation most likely to benefit, rather than applying IL-6(R) blockade in an unselected population. The convergence of RAS-directed strategies with IL-6 pathway co-targeting represents a compelling combination hypothesis: as RAS(ON) inhibitors reshape tumour-intrinsic signalling and reduce IL-6 transcription. Realising this potential will depend on prospective biomarker stratification, mechanistically rational combination design, and willingness to test these hypotheses in earlier stage disease where immune intervention has the greatest chance of altering the natural history of PDAC.

Author contributions

JW: Writing – original draft. JT: Writing – review & editing. VS: Writing – review & editing. JL: Conceptualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declared that financial support was received for this work and/or its publication. This work was supported by Singapore Immunology Network, Agency for Science, Technology and Research (A*STAR).

Acknowledgments

Figures were created with BioRender.com.

Conflict of interest

JL is a co-founder of Otter-Bio Pte Ltd, which did not contribute to this study.

The remaining author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Yu-Meng T. The bare truth of pancreatic cancer. *Mount Elizabeth Health Plus*. (2016). doi: 10.1007/978-0-387-92988-0_20

2. Borz P-C, Borz MB, Borz O-C, Zaharie T, Hagiu C, Munteanu L, et al. Improving outcomes in pancreatic adenocarcinoma: a systematic review of immunotherapy in multimodal treatment. *Med (B Aires)*. (2025) 61:1076. doi: 10.3390/medicina61061076

3. Pandey V, Storz P. Targeting the tumor microenvironment in pancreatic ductal adenocarcinoma. *Expert Rev Anticancer Ther*. (2019) 19:473–82. doi: 10.1080/14737140.2019.1622417

4. Zhang T, Ren Y, Yang P, Wang J, Zhou H. Cancer-associated fibroblasts in pancreatic ductal adenocarcinoma. *Cell Death Dis*. (2022) 13:897. doi: 10.1038/s41419-022-05351-1

5. Boeker V, Wilke L, Mansourkiaei A, Le VMH, Church KA, Czigany Z, et al. The influence of clinical risk factors on the classification of human cancer-associated fibroblasts in PDAC and pancreatitis patients. *BJC Rep*. (2025) 3:44. doi: 10.1038/s44276-025-00150-5

6. Von Hoerschelmann E, Neumann CCM, Felsenstein M, Gogolok J, Reutzel-Selke A, Sauer IM, et al. Cancer associated fibroblasts derived from pancreatic adenocarcinoma and their role in cell migration. *Anticancer Res*. (2021) 41:4229–38. doi: 10.21873/anticanres.15227

7. Yang L, Qiao S, Zhang G, Lu A, Li F. Inflammatory processes: key mediators of oncogenesis and progression in pancreatic ductal adenocarcinoma (PDAC). *Int J Mol Sci*. (2024) 25:10991. doi: 10.3390/ijms252010991

8. Tsukamoto H, Nishikata R, Senju S, Nishimura Y. Myeloid-derived suppressor cells attenuate TH1 development through IL-6 production to promote tumor progression. *Cancer Immunol Res*. (2013) 1. doi: 10.3389/conf.fimmu.2013.02.00696

9. Beury DW, Parker KH, Nyandjo M, Sinha P, Carter KA, Ostrand-Rosenberg S, et al. Cross-talk among myeloid-derived suppressor cells, macrophages, and tumor cells impacts the inflammatory milieu of solid tumors. *J Leukoc Biol*. (2014) 96:1109–18. doi: 10.1189/jlb.3a0414-210r

10. Skartsis N, Peng Y, Ferreira LMR, Nguyen V, Ronin E, Muller YD, et al. IL-6 and TNFα drive extensive proliferation of human Tregs without compromising their lineage stability or function. *Front Immunol*. (2021) 12. doi: 10.3389/fimmu.2021.783282

11. Korn T, Hiltensperger M. Role of IL-6 in the commitment of T cell subsets. *Cytokine*. (2021) 146:155654. doi: 10.1016/j.cyto.2021.155654

12. Błogowski W, Deskur A, Budkowska M, Sałata D, Madej-Michniewicz A, Dąbkowski K, et al. Selected cytokines in patients with pancreatic cancer: a preliminary report. *PloS One*. (2014) 9:e97613. doi: 10.1371/journal.pone.0097613

13. Ramsey ML, Talbert E, Ahn D, Bekaii-Saab T, Badi N, Bloomston PM, et al. Circulating interleukin-6 is associated with disease progression, but not cachexia in pancreatic cancer. *Pancreatology*. (2019) 19:80–7. doi: 10.1016/j.pan.2018.11.002

14. Holmer R, Goumas FA, Waetzig GH, Rose-John S, Kalthoff H. Interleukin-6: a villain in the drama of pancreatic cancer development and progression. *Hepatobiliary Pancreatic Dis Int*. (2014) 13:371–80. doi: 10.1016/s1499-3872(14)60259-9

15. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. *Cold Spring Harb Perspect Biol*. (2014) 6:a016295–a016295. doi: 10.1101/cshperspect.a016295

16. Grebenciucova E, VanHaerents S. Interleukin 6: at the interface of human health and disease. *Front Immunol*. (2023) 14. doi: 10.3389/fimmu.2023.1255533

17. Rašková M, Lacina L, Kejík Z, Venhauerová A, Skaličková M, Kolář M, et al. The role of IL-6 in cancer cell invasiveness and metastasis—overview and therapeutic opportunities. *Cells*. (2022) 11:3698. doi: 10.3390/cells11223698

18. Grant TJ, Hua K, Singh A. Molecular pathogenesis of pancreatic cancer. (2016) 241–75. doi: 10.1016/bs.pmbts.2016.09.008

19. Moini J, Badolato C, Ahangari R. Pancreatic tumors. In: *Epidemiology of Endocrine Tumors*. Amsterdam, Netherlands: Elsevier (2020). p. 335–58. doi: 10.1016/B978-0-12-822187-7.00012-8

20. Barcellini A, Peloso A, Pugliese L, Vitolo V, Cobianchi L. Locally advanced pancreatic ductal adenocarcinoma: challenges and progress. *Onco Targets Ther*. (2020) 13:12705–20. doi: 10.2147/OTT.S220971

21. Lin Z, Adeniran EA, Cai Y, Qureshi TA, Li D, Gong J, et al. Early detection of pancreatic cancer: current advances and future opportunities. *Biomedicines*. (2025) 13:1733. doi: 10.3390/biomedicines13071733

22. Halbrook CJ, Lyssiotis CA, Pasca di Magliano M, Maitra A. Pancreatic cancer: advances and challenges. *Cell*. (2023) 186:1729–54. doi: 10.1016/j.cell.2023.02.014

23. Marstrand-Daucé L, Lorenzo D, Chassac A, Nicole P, Couvelard A, Haumaitre C. Acinar-to-ductal metaplasia (ADM): on the road to pancreatic intraepithelial neoplasia (PanIN) and pancreatic cancer. *Int J Mol Sci*. (2023) 24:9946. doi: 10.3390/ijms24129946

24. Quoc-Huy Trinh V, Ankenbauer KE, Torbit SM, Taranto CP, Liu J, Batardiere M, et al. Mutant GNAS drives a pyloric metaplasia with tumor suppressive glycans in intraductal papillary mucinous neoplasia. *Cell Rep*. (2025) 44:116684. doi: 10.2139/ssrn.5242140

25. van Duijneveldt G, Griffin MDW, Putoczki TL. Emerging roles for the IL-6 family of cytokines in pancreatic cancer. *Clin Sci*. (2020) 134:2091–115. doi: 10.1042/cs20191211

26. Nusrat F, Khanna A, Jain A, Jiang W, Lavu H, Yeo CJ, et al. The clinical implications of KRAS mutations and variant allele frequencies in pancreatic ductal adenocarcinoma. *J Clin Med*. (2024) 13:2103. doi: 10.3390/jcm13072103

27. Graham S, Dmitrieva M, Vendramini-Costa DB, Francescone R, Trujillo MA, Cukierman E, et al. From precursor to cancer: decoding the intrinsic and extrinsic pathways of pancreatic intraepithelial neoplasia progression. *Carcinogenesis*. (2024) 45:801–16. doi: 10.1093/carcin/bgae064

28. Hu Q, Zhu Y, Mei J, Liu Y, Zhou G. Extracellular matrix dynamics in tumor immunoregulation: from tumor microenvironment to immunotherapy. *J Hematol Oncol*. (2025) 18:65. doi: 10.1186/s13045-025-01717-y

29. Ahmad RS, Eubank TD, Lukomski S, Boone BA. Immune cell modulation of the extracellular matrix contributes to the pathogenesis of pancreatic cancer. *Biomolecules*. (2021) 11:901. doi: 10.3390/biom11060901

30. Wu YS, Chung I, Wong WF, Masamune A, Sim MS, Looi CY. Paracrine IL-6 signaling mediates the effects of pancreatic stellate cells on epithelial-mesenchymal transition via Stat3/Nrf2 pathway in pancreatic cancer cells. *Biochim Biophys Acta (BBA) - Gen Subj*. (2017) 1861:296–306. doi: 10.1016/j.bbagen.2016.10.006

31. Iliopoulos D, Hirsch HA, Struhl K. An epigenetic switch involving NF-κB, Lin28, Let-7 microRNA, and IL6 links inflammation to cell transformation. *Cell*. (2009) 139:693–706. doi: 10.1016/j.cell.2009.10.014

32. Caligiuri G, Tuveson DA. Activated fibroblasts in cancer: perspectives and challenges. *Cancer Cell*. (2023) 41:434–49. doi: 10.1016/j.ccell.2023.02.015

33. Huang L, Guo Z, Wang F, Fu L. KRAS mutation: from undruggable to druggable in cancer. *Signal Transduct Target Ther*. (2021) 6:386. doi: 10.1038/s41392-021-00780-4

34. Hannifin S, Mello AM, Ngodup T, Kim NH, Pasca di Magliano M, Lee KE. Hypoxia-induced fibroblast IL-6 promotes immunosuppressive macrophage phenotypes in pancreatic cancer. *Cells*. (2026) 15:683. doi: 10.3390/cells15080683

35. Zhang T, Tan X-L, Xu Y, Wang Z-Z, Xiao C-H, Liu R. Expression and prognostic value of indoleamine 2,3-dioxygenase in pancreatic cancer. *Chin Med J (Engl)*. (2017) 130:710–6. doi: 10.4103/0366-6999.201613

36. Li Z, Otkur W, Qi H, Li J, Li S, Ling T, et al. Glutamine homeostasis regulates PD-L1 level through STAT3 in pancreatic cancer. In: *Genes Dis* Amsterdam, Netherlands: Elsevier B.V. (2026). p. 102092. doi: 10.1016/j.gendis.2026.102092

37. Silva AD, Hwang J, Marciel MP, Bellis SL. The pro-inflammatory cytokines IL-1β and IL-6 promote upregulation of the ST6GAL1 sialyltransferase in pancreatic cancer cells. *J Biol Chem*. (2024) 300:107752. doi: 10.1007/978-3-540-29807-6_2910

38. Lesina M, Kurkowski MU, Ludes K, Rose-John S, Treiber M, Klöppel G, et al. Stat3/Socs3 activation by IL-6 transsignaling promotes progression of pancreatic intraepithelial neoplasia and development of pancreatic cancer. *Cancer Cell*. (2011) 19:456–69. doi: 10.1016/j.ccr.2011.03.009

39. Taniguchi K, Karin M. IL-6 and related cytokines as the critical lynchpins between inflammation and cancer. *Semin Immunol*. (2014) 26:54–74. doi: 10.1016/j.smim.2014.01.001

40. Kitamura F, Semba T, Yasuda-Yoshihara N, Yamada K, Nishimura A, Yamasaki J, et al. Cancer-associated fibroblasts reuse cancer-derived lactate to maintain a fibrotic and immunosuppressive microenvironment in pancreatic cancer. *JCI Insight*. (2023) 8 (20). doi: 10.1172/jci.insight.163022

41. Heiduk M, Klimova A, Reiche C, Digomann D, Beer C, Aust DE, et al. TIGIT expression delineates T-cell populations with distinct functional and prognostic impact in pancreatic cancer. *Clin Cancer Res*. (2023) 29:2638–50. doi: 10.1158/1078-0432.ccr-23-0258

42. Hassan M, Elhusseny Y, Agamy FE, Azmy MM, Balata M. Soluble CTLA-4 and high-risk genetic variants: a new frontier in pancreatic ductal adenocarcinoma (PDAC) biomarkers. *Biochem Biophys Rep*. (2025) 44:102304. doi: 10.1016/j.bbrep.2025.102304

43. Wan YY, Flavell RA. 'Yin–Yang' functions of transforming growth factor-β and T regulatory cells in immune regulation. *Immunol Rev*. (2007) 220:199–213. doi: 10.1111/j.1600-065X.2007.00565.x

44. Hossain DMS, Pal SK, Moreira D, Duttagupta P, Zhang Q, Won H, et al. TLR9-targeted STAT3 silencing abrogates immunosuppressive activity of myeloid-derived suppressor cells from prostate cancer patients. *Clin Cancer Res*. (2015) 21:3771–82. doi: 10.1158/1078-0432.ccr-14-3145

45. Mundry CS, Triplett AA, Shah OS, Chaitankar V, McAndrews KL, Ly QP, et al. Single-cell RNA-sequencing of human spleens reveals an IDO-1+ tolerogenic dendritic cell subset in pancreatic cancer patients that is absent in normal individuals. *Cancer Lett*. (2024) 607:217321. doi: 10.1016/j.canlet.2024.217321

46. Li F, Wang M, Li X, Long Y, Chen K, Wang X, et al. Inflammatory-miR-301a circuitry drives mTOR and Stat3-dependent PSC activation in chronic pancreatitis and PanIN. *Mol Ther Nucleic Acids*. (2022) 27:970–82. doi: 10.1016/j.omtn.2022.01.011

47. Chellappa S, Hugenschmidt H, Hagness M, Line PD, Labori KJ, Wiedswang G, et al. Regulatory T cells that co-express RORγt and FOXP3 are pro-inflammatory and immunosuppressive and expand in human pancreatic cancer. *Oncoimmunology*. (2016) 5:e1102828. doi: 10.1080/2162402x.2015.1102828

48. Mei W, Ding Y, Bian C, Jia Y, Qu C, Fang Z, et al. The aryl hydrocarbon receptor inhibits antigen presentation to promote progression of pancreatic ductal adenocarcinoma. In: *J. Adv. Res* Amsterdam, Netherlands: Elsevier (2025). doi: 10.1016/j.jare.2025.10.079

49. Bharadwaj U, Li M, Zhang R, Chen C, Yao Q. Elevated interleukin-6 and G-CSF in human pancreatic cancer cell conditioned medium suppress dendritic cell differentiation and activation. *Cancer Res*. (2007) 67:5479–88. doi: 10.1158/0008-5472.can-06-3963

50. Fan C, Li J, Li Y, Jin Y, Feng J, Guo R, et al. Hypoxia-inducible factor-1α regulates the interleukin-6 production by B cells in rheumatoid arthritis. *Clin Transl Immunol*. (2023) 12. doi: 10.1002/cti2.1447

51. Xiong J, Xiao R, Zhao J, Zhao Q, Luo M, Li F, et al. Matrix stiffness affects tumor-associated macrophage functional polarization and its potential in tumor therapy. *J Transl Med*. (2024) 22:85. doi: 10.1186/s12967-023-04810-3

52. Liu L, Wang R, Alifu A, Xiao Y, Liu Y, Qian C, et al. Hypoxia-driven M2-polarized macrophages facilitate the epithelial-mesenchymal transition of glioblastoma via extracellular vesicles. *Theranostics*. (2024) 14:6392–408. doi: 10.7150/thno.95766

53. Mukhopadhyay S, Encarnación-Rosado J, Lin EY, Sohn ASW, Zhang H, Mancias JD, et al. Autophagy supports mitochondrial metabolism through the regulation of iron homeostasis in pancreatic cancer. *Sci Adv*. (2023) 9(16). doi: 10.1126/sciadv.adf9284

54. Schaaf MB, Garg AD, Agostinis P. Defining the role of the tumor vasculature in antitumor immunity and immunotherapy. *Cell Death Dis*. (2018) 9:115. doi: 10.1038/s41419-017-0061-0

55. Liu H, Liang Z, Zhou C, Zeng Z, Wang F, Hu T, et al. Mutant KRAS triggers functional reprogramming of tumor-associated macrophages in colorectal cancer. *Signal Transduct Target Ther*. (2021) 6:144. doi: 10.1038/s41392-021-00534-2

56. Zeng Y, Tao Y, Du G, Huang T, Chen S, Fan L, et al. Advances in the mechanisms of HIF-1α-enhanced tumor glycolysis and its relation to dedifferentiation. *Prog Biophys Mol Biol*. (2025) 197:1–10. doi: 10.1016/j.pbiomolbio.2025.05.003

57. Feng J, Li J, Wu L, Yu Q, Ji J, Wu J, et al. Emerging roles and the regulation of aerobic glycolysis in hepatocellular carcinoma. *J Exp Clin Cancer Res*. (2020) 39:126. doi: 10.1186/s13046-020-01629-4

58. Zhang Q, Cao Z, Yan S, Chen B, Wu H, Cao H, et al. Metabolic and immune crosstalk between cancer-associated fibroblasts and pancreatic cancer cells. *J Transl Med*. (2025) 23:1118. doi: 10.1186/s12967-025-07164-0

59. Sheehan C, Muir A. What's on the menu?: metabolic constraints in the pancreatic tumor microenvironment. *J Clin Invest*. (2025) 135(14):e191940. doi: 10.1172/jci191940

60. Fu Y, Liu S, Yin S, Niu W, Xiong W, Tan M, et al. The reverse Warburg effect is likely to be an Achilles' heel of cancer that can be exploited for cancer therapy. *Oncotarget*. (2017) 8:57813–25. doi: 10.18632/oncotarget.18175

61. Gao F, Sun K, Wang S, Zhang X, Bai X. Lactate metabolism reprogramming in PDAC: Potential for tumor therapy. *Biochim Biophys Acta (BBA) - Rev Cancer*. (2025) 1880:189373. doi: 10.1016/j.bbcan.2025.189373

62. Hakim N, Patel R, Devoe C, Saif MW. Why HALO 301 failed and implications for treatment of pancreatic cancer. *Pancreas – Open J*. (2019) 3:e1–4. doi: 10.17140/poj-3-e010

63. Long KB, Tooker G, Tooker E, Luque SL, Lee JW, Pan X, et al. IL6 receptor blockade enhances chemotherapy efficacy in pancreatic ductal adenocarcinoma. *Mol Cancer Ther*. (2017) 16:1898–908. doi: 10.1158/1535-7163.mct-16-0899

64. Ware MB, Phillips M, McQuinn C, Zaidi MY, Knochelmann HM, Greene E, et al. Dual IL-6 and CTLA-4 blockade regresses pancreatic tumors in a T cell– and CXCR3-dependent manner. *JCI Insight*. (2023) 8(8):e155006. doi: 10.1172/jci.insight.155006

65. Kang S, Tanaka T, Narazaki M, Kishimoto T. Targeting interleukin-6 signaling in clinic. *Immunity*. (2019) 50:1007–23. doi: 10.1016/j.immuni.2019.03.026

66. Heink S, Yogev N, Garbers C, Herwerth M, Aly L, Gasperi C, et al. Trans-presentation of IL-6 by dendritic cells is required for the priming of pathogenic TH17 cells. *Nat Immunol*. (2017) 18:74–85. doi: 10.1038/ni.3632

67. Diao Y, Wang X, Wu Z. SOCS1, SOCS3, and PIAS1 promote myogenic differentiation by inhibiting the leukemia inhibitory factor-induced JAK1/STAT1/STAT3 pathway. *Mol Cell Biol*. (2009) 29:5084–93. doi: 10.1128/mcb.00267-09

68. Liu T, Zhang L, Joo D, Sun S-C. NF-κB signaling in inflammation. *Signal Transduct Target Ther*. (2017) 2:17023. doi: 10.1038/sigtrans.2017.23

69. Faggioli L. Activation of the interleukin-6 promoter by a dominant negative mutant of c-Jun. *Biochim Biophys Acta (BBA) - Mol Cell Res*. (2004) 1692:17–24. doi: 10.1016/s0167-4889(04)00041-2

70. Yang J-L, Lin W-L, Tai S-B, Ciou Y-S, Chung C-L, Chen J-J, et al. Suppression of TGFβ-Induced Interleukin-6 Secretion by Sinulariolide from Soft Corals through Attenuation of the p38–NF-kB Pathway in Carcinoma Cells. *Int J Mol Sci*. (2023) 24:11656. doi: 10.3390/ijms241411656

71. Cheng H, Nan F, Ji N, Ma X, Zhang J, Liang H, et al. Regulatory T cell therapy promotes TGF-β and IL-6-dependent pro-inflammatory Th17 cell generation by reducing IL-2. *Nat Commun*. (2025) 16:7644. doi: 10.1038/s41467-025-62628-7

72. Laurence A, Tato CM, Davidson TS, Kanno Y, Chen Z, Yao Z, et al. Interleukin-2 signaling via STAT5 constrains T helper 17 cell generation. *Immunity*. (2007) 26:371–81. doi: 10.1016/j.immuni.2007.02.009

73. Cui H, Wang N, Li H, Bian Y, Wen W, Kong X, et al. The dynamic shifts of IL-10-producing Th17 and IL-17-producing Treg in health and disease: a crosstalk between ancient 'Yin-Yang' theory and modern immunology. *Cell Commun Signaling*. (2024) 22:99. doi: 10.1186/s12964-024-01505-0

74. Liu W, Wang X, Wu W. Role and functional mechanisms of IL-17/IL-17R signaling in pancreatic cancer (Review). *Oncol Rep*. (2024) 52:144. doi: 10.3892/or.2024.8803

75. Li H, Liu D, Li K, Wang Y, Zhang G, Qi L, et al. Pancreatic stellate cells and the interleukin family: Linking fibrosis and immunity to pancreatic ductal adenocarcinoma (Review). *Mol Med Rep*. (2024) 30:159. doi: 10.3892/mmr.2024.13283

76. Wang S, Wang J, Wu S, Fu Y, Li M. The central role of IL-17 in cancer stemness and immune evasion: A novel axis for overcoming immune checkpoint inhibitor resistance. *Crit Rev Oncol Hematol*. (2026) 217:104999. doi: 10.1016/j.critrevonc.2025.104999

77. Picard FSR, Lutz V, Brichkina A, Neuhaus F, Ruckenbrod T, Hupfer A, et al. IL-17A-producing CD8+ T cells promote PDAC via induction of inflammatory cancer-associated fibroblasts. *Gut*. (2023) 72:1510–22. doi: 10.1136/gutjnl-2022-327855

78. Chen Z, Qiao S, Yang L, Sun M, Li B, Lu A, et al. Mechanistic insights into the roles of the IL-17/IL-17R families in pancreatic cancer. *Int J Mol Sci*. (2023) 24:13539. doi: 10.3390/ijms241713539

79. Passarelli A, Pisano C, Cecere SC, Di Napoli M, Rossetti S, Tambaro R, et al. Targeting immunometabolism mediated by the IDO1 Pathway: A new mechanism of immune resistance in endometrial cancer. *Front Immunol*. (2022) 13. doi: 10.3389/fimmu.2022.953115

80. Ruders JH, Ahmad SM, Mortensen REJ, Met Ö, Byrdal M, Chen IM, et al. Rationale for multi-epitope TGFβ vaccination in pancreatic cancer: evidence from immunologic and clinical correlates. *Signal Transduct Target Ther*. (2026) 11:107. doi: 10.1038/s41392-026-02626-3

81. Orabona C, Pallotta MT, Grohmann U. Different partners, opposite outcomes: A new perspective of the immunobiology of indoleamine 2,3-dioxygenase. *Mol Med*. (2012) 18:834–42. doi: 10.2119/molmed.2012.00029

82. Mbongue J, Nicholas D, Torrez T, Kim N-S, Firek A, Langridge W. The role of indoleamine 2, 3-dioxygenase in immune suppression and autoimmunity. *Vaccines (Basel)*. (2015) 3:703–29. doi: 10.3390/vaccines3030703

83. Sharma MD, Hou D-Y, Liu Y, Koni PA, Metz R, Chandler P, et al. Indoleamine 2,3-dioxygenase controls conversion of Foxp3+ Tregs to TH17-like cells in tumor-draining lymph nodes. *Blood*. (2009) 113:6102–11. doi: 10.1182/blood-2008-12-195354

84. Orabona C, Pallotta MT, Volpi C, Fallarino F, Vacca C, Bianchi R, et al. SOCS3 drives proteasomal degradation of indoleamine 2,3-dioxygenase (IDO) and antagonizes IDO-dependent tolerogenesis. *Proc Natl Acad Sci*. (2008) 105:20828–33. doi: 10.1073/pnas.0810278105

85. Mickael M-E, Kubick N, Miftari K, Horbańczuk JO, Atanasov AG, Binçe K, et al. The role of th17/treg axis in retinal pathology associated with diabetes and treatment options. *Biol (Basel)*. (2025) 14:275. doi: 10.3390/biology14030275

86. Deng G, Song X, Fujimoto S, Piccirillo CA, Nagai Y, Greene MI. Foxp3 post-translational modifications and treg suppressive activity. *Front Immunol*. (2019) 10. doi: 10.3389/fimmu.2019.02486

87. Cameron JJ, Colson TR, Li X. Dot1L licenses DNA demethylation to establish regulatory T cell identity. (2025). doi: 10.64898/2025.12.03.692152

88. Li J, Sha J, Sun L, Zhu D, Meng C. Contribution of regulatory T cell methylation modifications to the pathogenesis of allergic airway diseases. *J Immunol Res*. (2021) 2021:1–8. doi: 10.1155/2021/5590217

89. Kasper IR, Apostolidis SA, Sharabi A, Tsokos GC. Empowering regulatory T cells in autoimmunity. *Trends Mol Med*. (2016) 22:784–97. doi: 10.1016/j.molmed.2016.07.003

90. Ogawa C, Tone Y, Tsuda M, Peter C, Waldmann H, Tone M. TGF-β–mediated foxp3 gene expression is cooperatively regulated by stat5, creb, and AP-1 through CNS2. *J Immunol*. (2014) 192:475–83. doi: 10.4049/jimmunol.1301892

91. Murawski MR, Litherland SA, Clare-Salzler MJ, Davoodi-Semiromi A. Upregulation of foxp3 expression in mouse and human treg is IL-2/STAT5 dependent. *Ann N Y Acad Sci*. (2006) 1079:198–204. doi: 10.1196/annals.1375.031

92. Sun X, Cui Y, Feng H, Liu H, Liu X. TGF-β signaling controls Foxp3 methylation and T reg cell differentiation by modulating Uhrf1 activity. *J Exp Med*. (2019) 216:2819–37. doi: 10.1084/jem.20190550

93. Kong X, Chen J, Xie W, Brown SM, Cai Y, Wu K, et al. Defining UHRF1 domains that support maintenance of human colon cancer DNA methylation and oncogenic properties. *Cancer Cell*. (2019) 35:633–648.e7. doi: 10.1016/j.ccell.2019.03.003

94. Labadie BW, Bao R, Luke JJ. Reimagining IDO pathway inhibition in cancer immunotherapy via downstream focus on the tryptophan–kynurenine–aryl hydrocarbon axis. *Clin Cancer Res*. (2019) 25:1462–71. doi: 10.1158/1078-0432.ccr-18-2882

95. Quintana FJ, Iglesias AH, Farez MF, Caccamo M, Burns EJ, Kassam N, et al. Adaptive autoimmunity and foxp3-based immunoregulation in zebrafish. *PloS One*. (2010) 5:e9478. doi: 10.1371/journal.pone.0009478

96. Yang X-P, Ghoreschi K, Steward-Tharp SM, Rodriguez-Canales J, Zhu J, Grainger JR, et al. Opposing regulation of the locus encoding IL-17 through direct, reciprocal actions of STAT3 and STAT5. *Nat Immunol*. (2011) 12:247–54. doi: 10.1038/ni.1995

97. Wan YY. Regulatory T cells: immune suppression and beyond. *Cell Mol Immunol*. (2010) 7:204–10. doi: 10.1038/cmi.2010.20

98. Yang XO, Nurieva R, Martinez GJ, Kang HS, Chung Y, Pappu BP, et al. Molecular antagonism and plasticity of regulatory and inflammatory T cell programs. *Immunity*. (2008) 29:44–56. doi: 10.1016/j.immuni.2008.05.007

99. Murai M, Krause P, Cheroutre H, Kronenberg M. Regulatory T-cell stability and plasticity in mucosal and systemic immune systems. *Mucosal Immunol*. (2010) 3:443–9. doi: 10.1038/mi.2010.27

100. Tan N, Zhao W, Wang Y, Li P, Liu J, Sun Z, et al. AHR, a novel inhibitory immune checkpoint receptor, is a potential therapeutic target for chemoresistant glioblastoma. *J Cancer Res Clin Oncol*. (2023) 149:9705–20. doi: 10.1007/s00432-023-04894-w

101. Anu RI, Shiu K-K, Khan KH. The immunomodulatory role of IDO1-Kynurenine-NAD+ pathway in switching cold tumor microenvironment in PDAC. *Front Oncol*. (2023) 13. doi: 10.3389/fonc.2023.1142838

102. Litzenburger UM, Opitz CA, Sahm F, Rauschenbach KJ, Trump S, Winter M, et al. Constitutive IDO expression in human cancer is sustained by an autocrine signaling loop involving IL-6, STAT3 and the AHR. *Oncotarget*. (2014) 5:1038–51. doi: 10.18632/oncotarget.1637

103. Wang R, Zhao S, Chen X, Xiao Z, Wen X, Zhong X, et al. Molecular mechanisms involved in the IL-6-mediated upregulation of indoleamine 2,3-dioxygenase 1 (IDO1) expression in the chorionic villi and decidua of women in early pregnancy. *BMC Pregnancy Childbirth*. (2022) 22:983. doi: 10.1186/s12884-022-05307-5

104. Feng Y, Wang Z, Bao Z, Yan W, You G, Wang Y, et al. SOCS3 promoter hypermethylation is a favorable prognosticator and a novel indicator for G-CIMP-positive GBM patients. *PloS One*. (2014) 9:e91829. doi: 10.1371/journal.pone.0091829

105. Jiang M, Zhang W, Liu P, Yu W, Liu T, Yu J. Dysregulation of SOCS-mediated negative feedback of cytokine signaling in carcinogenesis and its significance in cancer treatment. *Front Immunol*. (2017) 8. doi: 10.3389/fimmu.2017.00070

106. Lin X, Kang K, Chen P, Zeng Z, Li G, Xiong W, et al. Regulatory mechanisms of PD-1/PD-L1 in cancers. *Mol Cancer*. (2024) 23:108. doi: 10.1186/s12943-024-02023-w

107. Zerdes I, Matikas A, Bergh J, Rassidakis GZ, Foukakis T. Genetic, transcriptional and post-translational regulation of the programmed death protein ligand 1 in cancer: biology and clinical correlations. *Oncogene*. (2018) 37:4639–61. doi: 10.1038/s41388-018-0303-3

108. Cheng Q, Zuo X, Wang Z, Lu W, Jiang Y, Liu J, et al. Intrapleural dual blockade of IL-6 and PD-L1 reprograms CAF dynamics and the tumor microenvironment in lung cancer-associated Malignant pleural effusion. *Respir Res*. (2025) 26:180. doi: 10.1186/s12931-025-03263-0

109. Copland A, Sparrow A, Hart P, Diogo GR, Paul M, Azuma M, et al. Bacillus Calmette-Guérin induces PD-L1 expression on antigen-presenting cells via autocrine and paracrine interleukin-STAT3 circuits. *Sci Rep*. (2019) 9:3655. doi: 10.1038/s41598-019-40145-0

110. Yaseen MM, Abuharfeil NM, Darmani H, Daoud A. Mechanisms of immune suppression by myeloid-derived suppressor cells: the role of interleukin-10 as a key immunoregulatory cytokine. *Open Biol*. (2020) 10(9). doi: 10.1098/rsob.200111

111. Chan L-C, Li C-W, Xia W, Hsu J-M, Lee H-H, Cha J-H, et al. IL-6/JAK1 pathway drives PD-L1 Y112 phosphorylation to promote cancer immune evasion. *J Clin Invest*. (2019) 129:3324–38. doi: 10.1172/jci126022

112. Wang Y-N, Lee H-H, Hsu JL, Yu D, Hung M-C. The impact of PD-L1 N-linked glycosylation on cancer therapy and clinical diagnosis. *J BioMed Sci*. (2020) 27:77. doi: 10.1186/s12929-020-00670-x

113. Ying S, Wu N, Ruan Y, Ge W, Ma P, Xu T, et al. IL-17 triggers PD-L1 gene transcription in NSCLC cells via TRIM31-dependent MEF2C K63-linked polyubiquitination. *BMC Cancer*. (2025) 25:81. doi: 10.1186/s12885-025-13473-w

114. Powell MD, Lu P, Neeld DK, Kania AK, George-Alexander L-EMM, Bally APR, et al. IL-6/STAT3 signaling axis enhances and prolongs Pdcd1 expression in murine CD8 T cells. *Immunohorizons*. (2023) 6:872–82. doi: 10.4049/immunohorizons.2100112

115. Boelaars K, Rodriguez E, Huinen ZR, Liu C, Wang D, Springer BO, et al. Pancreatic cancer-associated fibroblasts modulate macrophage differentiation via sialic acid-Siglec interactions. *Commun Biol*. (2024) 7:430. doi: 10.1038/s42003-024-06087-8

116. Paulson JC, Macauley MS, Kawasaki N. Siglecs as sensors of self in innate and adaptive immune responses. *Ann N Y Acad Sci*. (2012) 1253:37–48. doi: 10.1111/j.1749-6632.2011.06362.x

117. Lim J, Sari-Ak D, Bagga T. Siglecs as therapeutic targets in cancer. *Biol (Basel)*. (2021) 10:1178. doi: 10.3390/biology10111178

118. Boelaars K, Goossens-Kruijssen L, Wang D, de Winde CM, Rodriguez E, Lindijer D, et al. Unraveling the impact of sialic acids on the immune landscape and immunotherapy efficacy in pancreatic cancer. *J Immunother Cancer*. (2023) 11: e007805. doi: 10.1136/jitc-2023-007805

119. GC S, Bellis SL, Hjelmeland AB. ST6Gal1: Oncogenic signaling pathways and targets. *Front Mol Biosci*. (2022) 9. doi: 10.3389/fmolb.2022.962908

120. Haldar B, Bhalerao N, Bellis S. Upregulated expression of the ST6GAL1 sialyltransferase in tumor cells creates sialoglycan ligands for immunosuppressive Siglec receptors. *Glycobiology*. (2022) 32:962–1063. doi: 10.1093/glycob/cwac066

121. Marciel MP, Haldar B, Hwang J, Bhalerao N, Bellis SL. Role of tumor cell sialylation in pancreatic cancer progression. (2023) 157:123–55. doi: 10.1016/bs.acr.2022.07.003

122. Saini P, Mirji G, Islam SMS, Simons LM, Bhat SA, Bonfanti AP, et al. Targeting Siglec-10/α3β1 integrin interactions enhances macrophage-mediated phagocytosis of pancreatic cancer. (2025) 86(1). doi: 10.1101/2025.05.06.652455

123. Perdicchio M, Ilarregui JM, Verstege MI, Cornelissen LAM, Schetters STT, Engels S, et al. Sialic acid-modified antigens impose tolerance via inhibition of T-cell proliferation and de novo induction of regulatory T cells. *Proc Natl Acad Sci*. (2016) 113:3329–34. doi: 10.1073/pnas.1507706113

124. Michée-Cospolite M, Boudigou M, Grasseau A, Simon Q, Mignen O, Pers J-O, et al. Molecular mechanisms driving IL-10- producing B cells functions: STAT3 and c-MAF as underestimated central key regulators? *Front Immunol*. (2022) 13. doi: 10.3389/fimmu.2022.818814

125. Senturk ZN, Akdag I, Deniz B, Sayi-Yazgan A. Pancreatic cancer: Emerging field of regulatory B-cell-targeted immunotherapies. *Front Immunol*. (2023) 14. doi: 10.3389/fimmu.2023.1152551

126. Gorosito Serrán M, Fiocca Vernengo F, Beccaria CG, Acosta Rodriguez E V., Montes CL, Gruppi A. The regulatory role of B cells in autoimmunity, infections and cancer: Perspectives beyond IL10 production. *FEBS Lett*. (2015) 589:3362–9. doi: 10.1016/j.febslet.2015.08.048

127. Lee KM, Stott RT, Zhao G, SooHoo J, Xiong W, Lian MM, et al. TGF-β-producing regulatory B cells induce regulatory T cells and promote transplantation tolerance. *Eur J Immunol*. (2014) 44:1728–36. doi: 10.1016/j.trre.2010.04.002

128. Pennati A, Ng S, Wu Y, Murphy JR, Deng J, Rangaraju S, et al. Regulatory B cells induce formation of IL-10-expressing T cells in mice with autoimmune neuroinflammation. *J Neurosci*. (2016) 36:12598–610. doi: 10.1523/jneurosci.1994-16.2016

129. Facciabene A, Motz GT, Coukos G. T-regulatory cells: Key players in tumor immune escape and angiogenesis. *Cancer Res*. (2012) 72:2162–71. doi: 10.1158/0008-5472.can-11-3687

130. Barilla RM, Diskin B, Caso RC, Lee KB, Mohan N, Buttar C, et al. Specialized dendritic cells induce tumor-promoting IL-10+IL-17+ FoxP3neg regulatory CD4+ T cells in pancreatic carcinoma. *Nat Commun*. (2019) 10:1424. doi: 10.1038/s41467-019-09416-2

131. Verma R, Balakrishnan L, Sharma K, Khan AA, Advani J, Gowda H, et al. A network map of interleukin-10 signaling pathway. *J Cell Commun Signal*. (2016) 10:61–7. doi: 10.1007/s12079-015-0302-x

132. Hovsepian E, Penas F, Siffo S, Mirkin GA, Goren NB. IL-10 inhibits the NF-κB and ERK/MAPK-mediated production of pro-inflammatory mediators by up-regulation of SOCS-3 in Trypanosoma cruzi-infected cardiomyocytes. *PloS One*. (2013) 8: e79445. doi: 10.1371/journal.pone.0079445

133. Mittal SK, Cho K-J, Ishido S, Roche PA. Interleukin 10 (IL-10)-mediated immunosuppression. *J Biol Chem*. (2015) 290:27158–67. doi: 10.1074/jbc.m115.682708

134. Guo Z, He Q, Zhang Y, Li Y, Zhang Z. Mechanisms of interleukin-10-mediated immunosuppression in viral infections. *Pathogens*. (2025) 14:989. doi: 10.3390/pathogens14100989

135. Sobhani N, Tardiel-Cyril DR, Davtyan A, Generali D, Roudi R, Li Y. CTLA-4 in regulatory T cells for cancer immunotherapy. *Cancers (Basel)*. (2021) 13:1440. doi: 10.3390/cancers13061440

136. Das M, Zhu C, Kuchroo VK. Tim-3 and its role in regulating anti-tumor immunity. *Immunol Rev*. (2017) 276:97–111. doi: 10.1111/imr.12520

137. Mishra M, Yadav M, Kumar S, Kumar R, Sen P. TIM-3 increases the abundance of type-2 dendritic cells during Leishmania donovani infection by enhancing IL-10 production via STAT3. *Cell Death Dis*. (2023) 14:331. doi: 10.1038/s41419-023-05848-3

138. James CA, Baer JM, Zou C, Panni UY, Knolhoff BL, Hogg GD, et al. Systemic alterations in type-2 conventional dendritic cells lead to impaired tumor immunity in pancreatic cancer. *Cancer Immunol Res*. (2023) 11:1055–67. doi: 10.1158/2326-6066.cir-21-0946

139. Fu Y, Tao J, Liu T, Liu Y, Qiu J, Su D, et al. Unbiasedly decoding the tumor microenvironment with single-cell multiomics analysis in pancreatic cancer. *Mol Cancer*. (2024) 23:140. doi: 10.1186/s12943-024-02050-7

140. Hegde S, Krisnawan VE, Herzog BH, Zuo C, Breden MA, Knolhoff BL, et al. Dendritic cell paucity leads to dysfunctional immune surveillance in pancreatic cancer. *Cancer Cell*. (2020) 37:289–307.e9. doi: 10.1016/j.ccell.2020.02.008

141. Tang M, Diao J, Gu H, Khatri I, Zhao J, Cattral MS. Toll-like receptor 2 activation promotes tumor dendritic cell dysfunction by regulating IL-6 and IL-10 receptor signaling. *Cell Rep*. (2015) 13:2851–64. doi: 10.1016/j.celrep.2015.11.053

142. Alese OB, Gbolahan O, Coleman KM, Cao Y, Kane S, Craven S, et al. Abstract CT136: Phase Ib study of siltuximab and spartalizumab in advanced pancreatic cancer. *Cancer Res*. (2024) 84:CT136–6. doi: 10.1158/1538-7445.am2024-ct136

143. Chen IM, Donia M, Chamberlain CA, Jensen AWP, Draghi A, Theile S, et al. Phase 2 study of ipilimumab, nivolumab, and tocilizumab combined with stereotactic body radiotherapy in patients with refractory pancreatic cancer (TRIPLE-R). *Eur J Cancer*. (2023) 180:125–33. doi: 10.2139/ssrn.4176353

144. Wolpin BM, Wainberg ZA, Garrido-Laguna I, Manji GA, Spira AI, Azad NS, et al. Trial in progress: RASolute 302—a phase 3, multicenter, global, open-label, randomized study of daraxonrasib (RMC-6236), a RAS(ON) multi-selective inhibitor, versus standard of care chemotherapy in patients with previously treated metastatic pancreatic ductal adenocarcinoma (PDAC). *J Clin Oncol*. (2025) 43. doi: 10.1200/jco.2025.43.16_suppl.tps4230

145. Wainberg ZA, Chung V, Devoe CE, George TJ, Welkowsky E, Kheoh T, et al. AMPLIFY-7P: Phase 1 and randomized phase 2 study of amphiphile immunotherapy ELI-002 7P as adjuvant treatment for subjects with G12D, G12R, G12V, G12C, G12A, G12S and G13D Kirsten rat sarcoma (KRAS)-mutated pancreatic ductal adenocarcinoma. *J Clin Oncol*. (2024) 42:TPS720–0. doi: 10.1200/jco.2024.42.3_suppl.tps720