Hallmarks of pancreatic cancer: spotlight on TAM receptors

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Summary

Pancreatic ductal adenocarcinoma (PDAC) represents the most prevalent type of pancreatic cancer and ranks among the most aggressive tumours, with a 5-year survival rate of less than 11%. Projections indicate that by 2030, it will become the second leading cause of cancer-related deaths. PDAC presents distinctive hallmarks contributing to its dismal prognosis: (i) late diagnosis, (ii) heterogenous and complex mutational landscape, (iii) high metastatic potential, (iv) dense fibrotic stroma, (v) immunosuppressive microenvironment, and (vi) high resistance to therapy. Mounting evidence has shown a role for TAM (Tyro3, AXL, MerTK) family of tyrosine kinase receptors in PDAC initiation and progression. This review aims to describe the impact of TAM receptors on the defining hallmarks of PDAC and discuss potential future directions using these proteins as novel biomarkers for early diagnosis and targets for precision therapy in PDAC, an urgent unmet clinical need.

Keywords: PDAC; Pancreatic cancer; TAM receptors; Diagnosis; Treatment

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the most prevalent type of pancreatic cancer, and it stands out as one of the most aggressive tumours, displaying a median 5-year survival rate of less than 11% across all clinical stages.[1] It is the third leading cause of cancer-related deaths, and is anticipated to ascend to the second position by 2030.[2] The grim prognosis associated with PDAC arises from several key hallmarks: (i) late diagnosis due to nonspecific symptoms and the lack of reliable diagnostic biomarkers, resulting in delayed tumour detection; (ii) heterogenous and complex mutational landscape, with KRAS mutations showing a pivotal role; (iii) high metastatic potential, with early dissemination of tumour cells; (iv) dense fibrotic stroma comprising over 80% of the tumour mass producing a strong crosstalk between malignant cells with the host; (v) immunosuppressive tumour microenvironment, characterised by the absence of T effector cells and an abundance of anti-inflammatory macrophages, myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs); and (vi) high resistance to therapy, mostly due to the intricate tumour-stroma interactions (Fig. 1).

Despite important advances in understanding PDAC biology and disease mechanisms in recent decades, no significant improvements in diagnosis or therapy have been achieved. Currently, most patients are diagnosed at very advanced stages and receive standard chemotherapy and radiotherapy, yielding modest benefits.[3,4] Several clinical trials have been launched to explore targeted approaches for both epithelial and stromal components,[5] including the tumour's immune landscape. However, to date, these trials have demonstrated very limited success, though some are still ongoing.[3,4,6] Therefore, it is crucial to identify innovative, target-driven therapeutic strategies and early diagnostic biomarkers to improve outcomes for patients with PDAC.

A possible target is the TAM receptor system. TAM receptors (Tyro3, AXL, MerTK) share a similar domain structure (Fig. 2a)[7] and play crucial roles in reproductive, immune, vascular, and nervous systems. They facilitate key cellular functions like communication, adhesion, secretion control, apoptotic cell clearance, and tissue repair.[7,8,10] Although not vital in development, TAM receptors exhibit specific expression profiles in adult tissues.[10] The TAM system is implicated in a diverse range of pathological conditions including infections and sepsis,[11] autoimmune and chronic inflammatory diseases,[12] and cancer.[8,13] For AXL and MerTK, metalloproteases can recognize a cleavage site at the extracellular domain (Fig. 2a), leading to ectodomain

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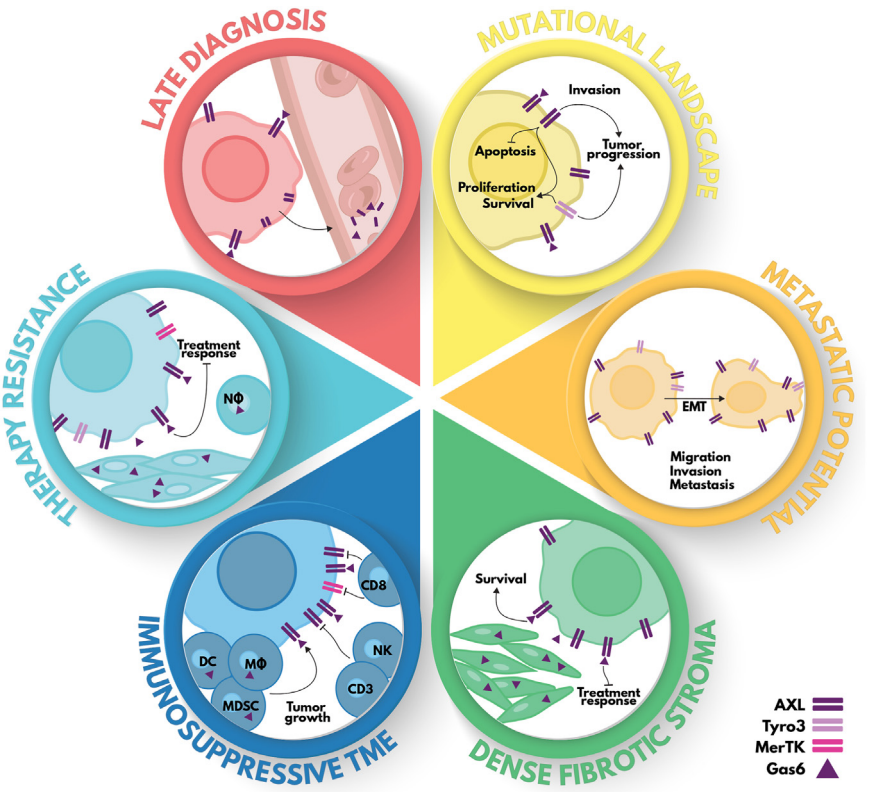

***Fig. 1:* TAM receptors role in PDAC hallmarks.** PDAC display unique characteristics that are crucial for understanding the aggressiveness of the disease and challenges in clinical management. These hallmarks include: (i) late diagnosis, (ii) heterogeneous and complex mutational landscape, (iii) high metastatic potential, (iv) dense fibrotic stroma, (v) immunosuppressive tumour microenvironment, and (vi) high resistance to therapy. The most notable functions of each member of the TAM receptors (Tyro3, AXL, MerTK) or their ligands (in particular Gas6) in relation to each hallmark have been included. TME, tumour microenvironment.

release.[7,8] The two TAM ligands, Gas6 and Protein S (Pros1), are vitamin K-dependent proteins that share unusual structural features crucial for their functions (Fig. 2b).[7] Gas6 targets all three TAM receptors with the highest affinity for AXL, while Pros1 shows more affinity for Tyro3 and MerTK, and its interaction with AXL is controversial.[7,13]

Upon ligand engagement, TAM receptors promote cell cycle progression and survival, migration and invasion, cell plasticity and epithelial–mesenchymal transition (EMT), cancer dormancy, cancer stemness, pro-tumoural angiogenesis, and metastatic progression.[14] TAM receptors are also implicated in immune surveillance escape, reducing the recognition and elimination by cytotoxic lymphocytes and inducing the secretion of pro-tumoural cytokines and immunosuppressive chemokines.[15] Moreover, TAM receptors can favour the recruitment of immunosuppressive cells (MDSCs, Tregs) and/or block the entrance of anti-tumoural immune cells (CD8+ T cells, and natural killer [NK] cells) at the tumour.[16] The role of TAM receptors in the crosstalk with the tumour microenvironment extends beyond immune cells, also involving interactions with cancer-associated fibroblasts (CAFs).[17]

While TAM receptors' overexpression in cancer has been extensively studied, their role in PDAC has only recently garnered attention (Table 1).[18,20,25,26] AXL is overexpressed in over 70% of pancreatic cancers and in around 75% of PDAC-derived cell lines from patients.[18,20,26] Moreover, PDAC subtypes associated with poor prognosis, in particular the basal subtype, exhibit high levels of AXL RNA.[22] Likewise, patients with PDAC with higher Tyro3 expression have worse outcomes.[26] Although no systematic study on MerTK expression in PDAC has been published, MerTK is significantly upregulated in tumour-associated macrophages linked to a worse prognosis.[27]

In alignment with Hanahan and Weinberg's seminal work on the hallmarks of cancer,[28] this review adopts a similar framework tailored to PDAC, delineating its six most distinctive features, while comprehensively exploring the intricate involvement of the TAM receptor family in each hallmark (Fig. 1). By integrating the latest findings, we provide fresh insights into the potential

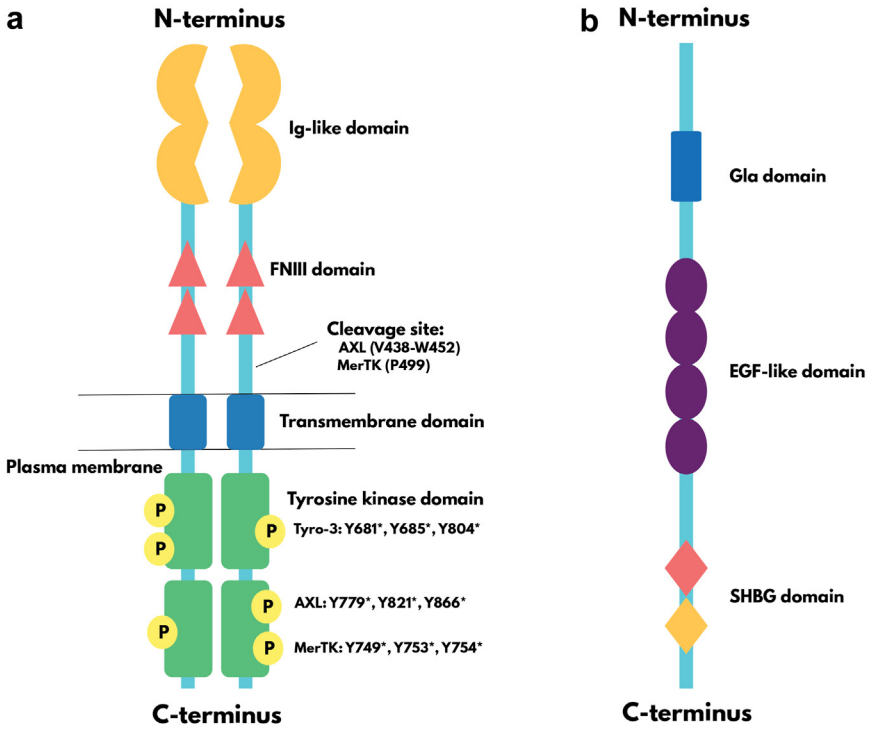

***Fig. 2:* Schematic representation of TAM receptor and ligands structure**. (a) **TAM receptors**. TAM receptors have a unique domain architecture with an extracellular region comprising two immunoglobulin (Ig)-like domains, two fibronectin type III (FNIII) domains and an intracellular kinase domain with a conserved KWIAIES sequence. Asterisks indicate autophosphorylation sites.[7–9] For AXL and MerTK a metalloprotease cleavage site has been identified.[8,9] (b) TAM ligands. The Gas6 and Pros1 TAM ligands share a similar structure that includes an N-terminal glutamic-acid rich (Gla) domain, four EGF-like domains and a C-terminal sex hormone-binding globulin (SHGB)-like domain, which mediates dimerization with the receptor and kinase activation.[7,8]

value of TAM receptors in diagnostic and therapeutic opportunities for PDAC, paving the way for future research directions in this critical area.

Hallmark (i): late diagnosis

Diagnosis of PDAC currently relies exclusively on image-based tests, as the symptoms are usually non-specific, such as abdominal and back pain, weight loss and fatigue. However, the localization of the pancreas makes the diagnosis challenging, resulting in late-stage detection and poor prognosis. The only FDA-approved blood biomarker, carbohydrate antigen 19–9 (CA19-9), has limited sensitivity and specificity, restricting its use to monitor treatment response and recurrence.[29,30] Consequently, accurate and early diagnostic markers remain an unmet clinical need for PDAC.[31]

TAM receptors can be turned off through ectodomain-shedding mediated by ADAM10 and ADAM17 proteases, releasing soluble forms detectable in plasma and cellular conditioned medium. Under physiological conditions, soluble AXL (sAXL) acts as a decoy, limiting ligand availability and AXL activation.[32,33]However, elevated levels of sAXL have been associated with progression of various pathologies, suggesting additional functions that are still poorly understood.

The detection of higher soluble forms of TAM receptors, or their ligands, in patients with cancer, in comparison with healthy individuals, has raised the possibility of using them to achieve early diagnosis, monitor progression and treatment effectiveness, and predict recurrence. For instance, sAXL and Gas6 have been evaluated as biomarkers in hepatocellular carcinoma (HCC),[34,35] though the performance is limited by increased levels in liver fibrosis, cirrhosis, and other liver diseases. In patients with melanoma, higher sAXL levels correlate with disease progression and shorter survival after ipilimumab treatment.[36] Overall, plasma soluble TAM receptors and ligand concentrations may reflect tumour presence, phenotype, and treatment efficacy, although not in all cases.[37]

The TAM receptor system has also been explored in PDAC,[25] with recent studies demonstrating the predictive value of sAXL for early diagnosis of PDAC and discrimination from chronic pancreatitis (CP).[22] Our group analysed sAXL plasma levels in two independent cohorts, finding significantly higher plasma levels in

Member	Expression profile	Reference
AXL	Increased IHC staining in 54 out of 99 (55%) PDAC tissue samples. Increased expression in Panc-1, CFPAC1, PK9, MiaPaCa-2 and SU86.86 versus HPNE cell lines.	18
	Increased IHC staining in 38 out of 54 (70%) PDAC tissue samples. Positive expression in 9 out of 12 (75%) PDAC cell lines	19
	Increased IHC staining in 32 out of 42 (76%) PDAC tissue samples. Expression in Panc-1, BxPC3, MiaPaCa-2 and Capan-1 cell lines, detected by WB.	20
	Analysis of the expression of AXL mRNA in Panc-1, MiaPaCa2 and BxPC3 cell lines.	21
	Increased IHC staining and mRNA expression in PDAC versus normal tissue. Increased mRNA expression in the squamous/basal-like/quasi-mesenchymal versus classical tumour subtype (Bailey, Moffit and Collison classifications). Elevated sAXL levels in PDAC plasma versus control samples, without differences among PDAC stages (II, III and IV). Analysis of protein and mRNA expression in Panc-1, Hs766T, RWP-1, SK-PC-1 and Capan-1 cell lines.	22
MerTK	Increased MerTK mRNA expression in tumour versus normal pancreatic samples. No differential expression between classical versus basal PDAC subtypes.	GEPIA2 (TCGA database)
	Increased IHC staining in human pancreatic cancer tissue samples. Detection of MerTK expression by WB in Panc-1 and MiaPaCa2 cell lines.	23
	Analysis of the expression of MerTK mRNA in Panc-1, MiaPaCa2 and BxPC3 cell lines.	21
Tyro3	High expression of Tyro3 protein in Panc-1, MiaPaCa2, BxPC3, AsPC-1 and K9 versus HPDE cell lines, detected by WB.	24
	Increased Tyro3 mRNA expression in pancreatic tumour samples versus normal samples.	GEPIA2 (TCGA database)
	Analysis of the expression of Tyro3 mRNA in Panc-1, MiaPaCa2 and BxPC3 cell lines.	21
Gas6	Increased Gas6 mRNA expression in pancreatic tumour versus normal samples. No differential expression in classical versus. basal PDAC subtypes.	GEPIA2 (TCGA database)
	Analysis of the expression of Gas6 and Pros1 mRNA in Panc-1, MiaPaCa2 and BxPC3 cell lines.	21
Pros1	Increased Pros1 mRNA expression in tumour versus normal samples. No differential expression in classical versus basal PDAC subtypes.	GEPIA2 (TCGA database)
	Analysis of the expression of Gas6 and Pros1 mRNA in Panc-1, MiaPaCa2 and BxPC3 cell lines.	21

Summary of the expression pattern of TAM receptors and ligands in published studies and TCGA database. Abbreviations: GEPIA2, Gene Expression Profiling Interactive Analysis; IHC, Immunohistochemistry; TGCA, The Cancer Genome Atlas.

Table 1: **Expression profile of TAM family members in PDAC.**

patients with PDAC than in healthy controls and patients with CP. sAXL expression is upregulated from the earliest phases of PDAC, and no significant differences have been observed across PDAC stages. These results are supported by findings in mouse models, showing a specific increase of sAXL in mice developing PDAC but not preneoplastic lesions or other pancreatic cancer types (acinar carcinomas).[22] ROC analysis showed that sAXL outperformed CA19-9 in discriminating PDAC from CP.[29] Detection of both CA19-9 and sAXL in the blood increases the accuracy in diagnosing PDAC versus healthy controls (91.3% sensitivity, 100% specificity) and PDAC versus CP (89.9% sensitivity, 100% specificity).[22] These findings indicate that sAXL is a promising biomarker in the diagnosis and clinical management of patients with PDAC.[38]

Hallmark (ii): heterogeneous and complex mutational landscape

The genetic landscape of PDAC is characterized by frequent activating mutations of the KRAS gene (present in >90% of tumours) and alterations in tumour suppressor genes like p53, CDKN2A, and SMAD4. Moreover, recent molecular profiling has allowed the identification of PDAC subtypes on the basis of distinct molecular signatures, paving the way for precision therapeutic approaches.[30]

KRAS-mutant lung cancer cells respond to KRAS inhibition by upregulating AXL,[39] and combination of RAF/MEK and AXL inhibitors yields a synergistic anti-proliferative effect.[40] These findings suggest a connection between KRAS mutations and AXL, which may be applicable to the PDAC context. Furthermore, recent reports indicate a correlation between AXL and p53, where AXL can diminish p53 activity and expression in malignant mesotethelioma,[41] or conversely, p53 may suppress AXL, as shown in B-cell chronic lymphocytic leukemias.[42] However, the specific mechanisms underlying this AXL-p53 interplay remain unexplored in the context of pancreatic tumours.

This complex mutational landscape is responsible for the high aggressiveness of PDAC, leading to uncontrolled cell proliferation and activation of survival mechanisms. The role of TAM receptors in these processes has been studied in detail. AXL ligand inactivation using warfarin, a vitamin K antagonist that inhibits the activity of Gas6 and Pros1 ligands, blocks cell proliferation *in vitro*, and cancer progression in vivo.[21,43] Additionally, bemcentinib (also named BGB324 or R428), a selective AXL inhibitor, exhibits a marked reduction in the proliferation rate of PDAC cell lines[44,45] and PDAC cells from patient-derived xenografts (PDXs).[45] Similarly, mice implanted with orthotopic PDAC cells and treated with an AXL inhibitor (TP-0903) show a reduction in tumour growth and extended survival.[46] Also, monoclonal anti-AXL antibodies reduce tumour growth of subcutaneous pancreatic tumour xenografts.[20] AXL silencing abolishes Gas6 AKT-mediated activation in PDAC-derived cells, promoting apoptosis.[26]

Expression of hematopoietic progenitor kinase 1 (HPK1) seems to provide a downregulatory mechanism to limit AXL overexpression. HPK1 interacts with the AXL receptor reducing AXL-mediated signalling and decreasing the invasion capability of PDAC cells.[19]

Apart from AXL, Tyro3 has also been associated with PDAC proliferation and survival. Morimoto et al. observed that Tyro3 silencing with shRNA suppressed the downstream growth signals and tumour progression *in vitro* and PDAC cell proliferation. Moreover, Tyro3 silencing in vivo mitigates PDAC tumourigenicity in orthotopic subcutaneous injections in mouse preclinical models.[24]

These studies demonstrate the involvement of TAM receptors in the intricate mutational landscape of PDAC and highlight the potential of targeting them, particularly AXL and Tyro3, as promising avenues for therapeutic intervention in this disease.

Hallmark (iii): high metastatic potential

Metastatic disease, rather than the primary tumour, is the leading cause of mortality in solid cancers. In PDAC, the most common metastatic sites are the liver, lung, and peritoneum.[47,48] Several studies have demonstrated the critical role of EMT and cellular plasticity in the metastatic process of PDAC. TAM receptors have been found among the key players in EMT. In patients with PDAC, AXL overexpression correlates with distant metastases and poor prognosis and overall survival.[18] Accordingly, AXL depletion inhibits the EMT program[18,26,49] and reduces migration, invasion, and extracellular matrix (ECM) enzymes, contributing to a reduction in the number of metastases.[18,26,50] Singular mechanisms implicating TAM receptor signalling could contribute to the aggressive phenotype observed in PDAC (Fig. 3). For instance, the axon guidance receptor ROBO3 can initiate the STAT-3 signalling pathway through AXL activation, contributing to the prometastatic program in the basal/mesenchymal aggressive subtype.[45] A second mechanism has been recently proposed, in TANK-binding kinase 1 (TBK1), activated by AXL, binds and phosphorylates the AKT3 isoform, driving the nuclear localization and activation of the core EMT-activating transcription factors slug/snail (Fig. 3).[44,50,51] Furthermore, specific epigenetic mechanisms, such as mRNA acetylation, can enhance the metastatic potential of PDAC cells by enhancing AXL expression.[56]

Inhibition of TAM receptors has been employed as an approach to study their role in EMT and metastasis in PDAC. Zhang et al. reported that inhibition of AXL using the small-molecule inhibitor TP-0903 reduced the number of liver metastases in a mouse model of PDAC using a mutant p53 as secondary driver mutation. The effect of AXL inhibition was associated with increased epithelial markers, reduced clonogenic capacity, and a more differentiated tumour cell phenotype.[46] Similarly, treatment with the AXL-specific inhibitor bemcentinib, either alone or in combination with gemcitabine, decreased distant metastases in PDAC murine models.[45] Furthermore, Ireland et al. demonstrated that the pharmacological blockade of Gas6, secreted by stromal cells, inhibited the metastatic outgrowth of PDAC cells in mice.[57] The same study showed that depletion of stromal-derived Gas6 also altered the EMT signature.[57] Similarly, a low dose of warfarin, a vitamin K antagonist that inhibits Gas6 formation, reduce the EMT signature, migration, and invasive capacity of PDAC cells (Table 2).[43]

The role of the other two TAM receptors, Tyro3 and MerTK, in metastasis and cell plasticity remains underexplored in PDAC. However, a recent study by Morimoto et al. has evaluated the oncogenic functions of Tyro3 in pancreatic cancer. Tyro3 activation leads to AKT and MAPK pathway activation, mirroring the activity observed for AXL. The authors reported that silencing of Tyro3 in PDAC cell lines led to a reduction in their invasion ability. Tyro3 knockdown also decreased cell invasion ability *in vitro* and the levels of the EMT-inducing transcription factor Snail, suggesting that Tyro3 is implicated in EMT and migration, similarly to AXL.[24]

Therefore, TAM receptors, particularly AXL and Tyro3, play a crucial role in driving EMT and metastatic spread in PDAC.

Hallmark (iv): dense fibrotic stroma

One of the most distinctive hallmarks of PDAC is its remarkably abundant stroma, often constituting more than 80% of the total tumour volume. Comprising a complex network of CAFs, extracellular matrix (ECM), endothelial cells, and infiltrating immune cells,[61,62] the PDAC stroma has emerged as a focal point of research due to its pivotal role in both the onset and progression of the disease.[63] The dynamic bidirectional crosstalk between stroma and cancer cells is a key driver of PDAC initiation, progression, metastasis, immune infiltration, and drug resistance.[52,64,65] As such, modulating the pancreatic stroma has emerged as a promising therapeutic strategy, with several ongoing clinical trials targeting stromal components.[66]

The presence of TAM receptors and their ligands in both stromal and cancer cells has led researchers to investigate their role in the tumour-stroma interactions in PDAC. For example, recent data have shown that components of the ECM, such as the LAMC2 laminin, can increase the expression of AXL via AKT pathway activation.[67] The Gas6/AXL signalling axis is implicated in the bidirectional communication between PDAC cells and CAFs, the predominant stroma cell type. $KRAS^{G12D}$-driven PDAC cells induce Gas6 production in CAFs and IGF1 through the production of soluble factors such as Shh, which in turn activates the IGFR1/AXL-AKT pathway, promoting survival and treatment

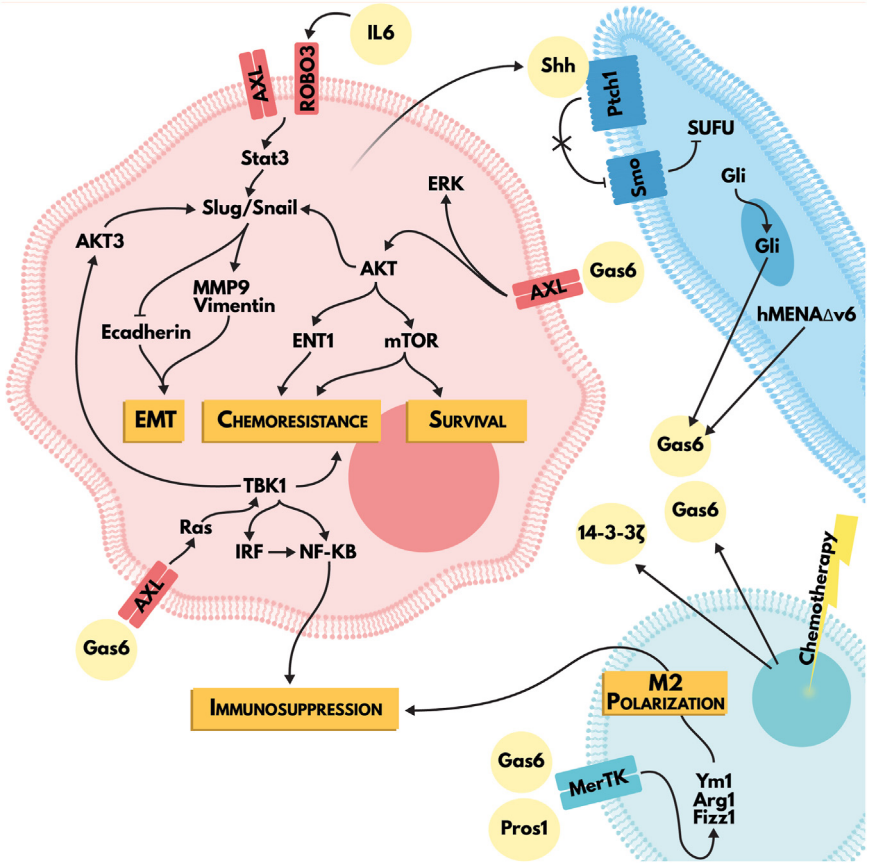

***Fig. 3:* Molecular mechanisms of TAM receptors and ligands in PDAC cancer cells and TME.** TAM receptors, similar to other RTKs, activate the PKB/AKT/mTOR and MAPK signalling pathways in the context of tumour pancreatic cancer cells.[18] The activation of these pathways provides pro-metastatic and survival signalling. They also induce chemoresistance which is, at least in part, mediated by upregulation of the nucleoside transporter ENT1.[49] Upon AXL activation, tumour cells undergo an EMT program, mediated by upregulation of the transcription factors Slug and Snail.[45,46,49] EMT is mediated by a complex change in the transcriptome including production of ECM remodelling enzymes, and decreasing epithelial markers such as E-cadherin. Furthermore, AXL is able to activate TANK-binding kinase-1 (TBK1) through the GRB2/RAS/RALB pathway.[44,50] TBK1 activation is known to regulate innate immunity through the interaction with the NF-kB pathway and interferon regulatory factors. Induction of cytokine genes by TBK1 can activate MDSCs and suppress anti-tumoural responses.[44] Furthermore, AXL-mediated TBK1 activation is essential in establishing the EMT program through its regulation of Slug/Snail activity in PDAC cells.[50] A recent study showed that TBK1 activates AKT3, one of the isoforms of AKT. Activated AKT3 interacts with Snail and carries it to the nucleus to induce EMT and favouring metastasis.[51] In combination with ROBO3, AXL activates an STAT3 signalling pathway supporting a pro-metastatic program associated with a basal-like phenotype.[45] This pathway is mediated by the induction of IL-6 from stromal sources in a reciprocal signalling loop. Similarly, AXL is reciprocally activated by Gas6 and 14-3-3ζ secreted by stromal fibroblasts/stellate cells and macrophages in a non-cell autonomous signalling loop.[52,53] Induction of the actin regulator hMENA expression in CAFs by tumour cells increases the production of GAS6.[17] Chemotherapy, possibly through the induction of apoptosis in the tumour, induces the production of Gas6 in neutrophils[54] and macrophages, as well as a 14-3-3ζ by macrophages,[52] which in turn would potentiate AXL activity in the tumour.[53] MerTK activation induces M2 polarization in tumour associated macrophages, being important in the immunosuppressive properties of PDAC.[55]

resistance (Fig. 3).[52] Another cross-talk mechanism is mediated by the actin regulatory protein hMENA, which is overexpressed by CAFs and increases Gas6 secretion. Reciprocally, hMENA upregulates AXL expression in tumour cells, thus sustaining tumour-stroma crosstalk and cancer progression through paracrine activation of the Gas6/AXL axis.[17] Beyond CAFs, AXL also mediates the crosstalk between tumour cells and other stromal components, such as macrophages,[53] NK cells,[57] neutrophils,[54] and mesenchymal stromal cells.[68] In response to the induction of apoptosis in the tumour by chemotherapy, tumour-associated macrophages secrete the 14-3-3ζ protein that activates AXL receptor in PDAC cells, inducing pro-survival mechanisms through the AKT/mTOR pathway (Fig. 3).[53] Also, Gas6 mainly produced by tumour-associated macrophages and fibroblasts mediates NK cell activation in PDAC.[57] The Gas6/AXL axis has also been linked to the regrowth of

Target	Drug	Type	Animal model	Reference
AXL	Bemcentinib	Small molecule	KIC mouse & syngeneic mouse models. Human pancreatic cancer PDX subcutaneous implanted in nu/nu athymic mice.	44
	TP-0903	Small molecule	KPfC, KPC and syngeneic models (combination with gemcitabine, anti-PD1 or gemcitabine + anti-PD1).	46
	α-AXL D9 and E8	mAb	Subcutaneous or orthotopic injection of MiaPaCa-2 and BxPC-3 human cell lines in athymic mice.	20
	ADCT-601	ADC	Subcutaneous injection of pancreatic cancer PDX in athymic nude mice.	58
MerTK	Sitravatinib	Small molecule	Subcutaneous injection of an isogenic KPfC-derived cell line in C57BL/6 mice (combination with anti-PD1).	55
Gas6	MYD1-72	Decoy soluble receptor	Orthotopic and subcutaneous model of murine pancreatic cancer.	59
Gas6/Pros1	Warfarin	Vitamin-K antagonist	Orthotopic implantation of a KPfC-derived isogenic cell lines in C57BL/6 mice.	57
			KIC and orthotopic Pan02 implantation immunocompetent mice models. Orthotopic implantation of human cell lines in NOD/SCID mice.	43
			Subcutaneous injection of Panc02-SIY murine in MerTK−/− and C57BL/6 mice. Tumors from Panc02-SIY murine PDAC model grafted in wild-type and MerTK−/− mice.	60

Summary of the main studies with preclinical data on compounds targeting TAM receptors or their ligands. Abbreviations: mAb, monoclonal Antibody; ADC, Antibody Drug Conjugate; NOD/SCID Non-Obese Diabetic/Severe Combined Immunodeficiency; PD1, Programme cell Death proten-1; PDX, Patient-Derived Xenograft.

Table 2: **Pre-clinical studies in PDAC of inhibitors of the TAM family.**

disseminated PDAC cells after chemotherapy withdrawal. These cells produce the neutrophil-chemoattractant CXCL1/2, stimulating the recruitment of Gas6-secreting neutrophils to the liver, a common site of PDAC metastases. These neutrophils activate the AXL receptor on tumour cells, thereby promoting their proliferation in a feedback loop.[54]

To summarize, TAM receptors, in particular AXL, and their ligands are key mediators of the intricate crosstalk between tumour and stroma cells, influencing immune infiltration, tumour progression and therapy response. Overexpression of AXL (and possibly Tyro3) by PDAC tumour cells creates a node of reciprocal signalling that can sense and utilize signals from the stroma.[52] Therefore, targeting TAM members emerges as a promising stromal-based therapeutic approach against PDAC.

Hallmark (v): immunosuppressive microenvironment

PDAC is often described as an "immunologically cold" tumour because of the highly immunosuppressive nature of its microenvironment. It is characterised by the presence of anti-inflammatory macrophages, MDSCs, and Tregs. Moreover, immune cells involved in tumour rejection, such as effector CD4+ and CD8+ T cells, NK cells, and pro-inflammatory macrophages, are nearly absent.[4,69,70] This immunosuppressive landscape significantly limits the efficacy of immunotherapies in PDAC, including immune checkpoint blockade.[71,72]

Several reports have implicated TAM receptors in the modulation of the PDAC immune landscape, contributing to immune evasion. For instance, depletion of AXL induces upregulation of anti-tumour immune pathways, reducing tumour-associated macrophages and increases the presence of NK and CD3+T cells.[49] Similarly, selective pharmacological inhibition of AXL also alters the immunosuppressive tumour microenvironment.[32,57,61] Monoclonal anti-AXL antibodies trigger antibody-dependent cellular cytotoxicity (ADCC) *in vitro*, reducing the growth of subcutaneous pancreatic tumour xenografts.[20] Moreover, AXL in vivo blockade by bemcentinib modifies the secretion of chemokines and cytokines in the PDAC tumour environment, potentially through modulation of the TBK1/NF-κB signalling pathway.[44,50] Inhibiting AXL with bemcentinib also alters the immune landscape of PDAC by reducing the tumour infiltration of MDSCs and tumour-associated macrophages.[44,53] TP-0903, another AXL selective inhibitor, also leads to a more active anti-tumour immune microenvironment by decreasing the infiltration of tumour-associated neutrophils and increasing intra tumour pro-inflammatory macrophages and CD8+T cells.[46] These results indicate that pharmacological inhibition of AXL restores PDAC immune surveillance.

Beyond AXL, MerTK has also been implicated in the immunosuppressive PDAC microenvironment. Recent studies using bulk and single-cell RNA sequencing data from PDAC databases have shown that MerTK is upregulated in tumours exhibiting high infiltration of M2 tumour-associated macrophages, which are associated with worse prognosis (Fig. 3).[27] These results indicate that MerTK is a potential target for PDAC therapy given its involvement in macrophage polarization and tumour progression. Nevertheless, although not in PDAC but in melanoma, MerTK can act as a co-stimulatory signal for CD8+ T cells, enhancing tumour-infiltrating lymphocyte expansion and cytotoxic activity against cancer cells.[73] These findings suggest caution in the development of MerTK inhibitors for cancer treatment.

Finally, studies of TAM ligands' contribution to PDAC immune environment are limited. However, recent evidence demonstrates that a neutralizing antibody against the TAM ligand Gas6 enhances the presence of NK cells in both tumour-draining lymph nodes

and lung metastasis.[57] These findings underscore the potential of targeting the TAM receptor-Gas6 axis to reduce PDAC metastasis and suggest that the activation status of NK cells could be used as a novel biomarker to monitoring response to anti-AXL/Gas6 treatments.

In conclusion, activation of TAM members, particularly AXL, MerTK or Gas6, can significantly contribute to the PDAC immune suppressive landscape, highlighting the therapeutic potential of disrupting the TAM receptor-ligand axis to restore immune surveillance and improve treatment outcomes.

Hallmark (vi): high resistance to therapy

PDAC is highly resistant to treatment and fails to respond to conventional chemotherapy, radiotherapy, targeted therapies, and immunotherapies. Numerous studies have identified the overexpression of components of the TAM system as a key factor for the resistance, leading to treatment failure and cancer recurrence.[74] In particular, AXL activation promotes anti-apoptotic/survival mechanisms, being key in driving chemotherapy resistance in PDAC. Accordingly, its selective inhibition increases the efficacy of chemotherapies. Bemcentinib sensitizes pancreatic tumours to the standard of care gemcitabine therapy, both in *in vitro* and in vivo preclinical models, including PDXs.[44,45] Also, TP-0903 has demonstrated a synergic action in combination with gemcitabine or with the immune checkpoint inhibitor anti-PD1.[46] Similarly, in vivo inhibition with the small molecule SGI-7079 increases significantly the effects of gemcitabine in PDAC.[53] TAM receptor-ligand interaction has also been targeted as a strategy to overcome therapy resistance. Blocking Gas6/AXL axis using the receptor decoy MYD1-72, leads to an accumulation of DNA damage, increasing the efficacy of chemotherapy with gemcitabine (Table 2).[59] Kirane et al. have also shown that AXL inhibition using a low dose of warfarin increased the sensitivity to chemotherapy.[43] Similarly, AXL deficiency improves gemcitabine efficacy in preclinical PDAC models by reversing the reduced expression of nucleoside transporters, caused by AXL upregulation, favouring chemotherapeutics' entry.[49] Furthermore, silencing the ROBO3 receptor disrupts the AXL/p-STAT3 signalling axis enhancing therapy sensitivity to gemcitabine.[45]

AXL also promotes drug resistance by participating in the tumour-stroma crosstalk. For instance, the activation of AXL through its interaction with the14-3-3ζ protein, secreted by tumour-associated macrophages upon exposure to chemotherapy-induced apoptotic PDAC cells, promotes resistance to nab-paclitaxel and gemcitabine in PDAC.[53] Also, Gas6 secreted by CAFs[17] or by neutrophils[54] can activate AXL in PDAC cancer cells, inducing their resistance to chemotherapy. In addition, AXL depletion diminishes the survival of a panel of PDAC cells treated with radiotherapy.[26]

Beyond AXL, other TAM receptors can also mediate therapy resistance in PDAC. Tyro3 mediates chemoresistance to gemcitabine and 5-fluorouracil in an autophagy-dependent manner.[23] The effects of MerTK targeting, particularly in the context of radiotherapy, have been recently explored in PDAC.[60,75] Some studies suggest that MerTK inhibition can promote a pro-inflammatory macrophage signature and enhance the adaptive immune response. Indeed, in murine models of PDAC, MerTK deficiency increased antigen-specific T cells responses after the combination of radiotherapy and agonist antibodies anti-OX40.[60] These results indicate that MerTK inhibition together with conventional treatments could have beneficial effects in PDAC.[60]

Last but not least, PDAC also exhibits high resistance to immunotherapies, including PD-1/PD-L1 and CTLA-4 immune checkpoints inhibitors, cancer vaccines, and adoptive cell therapy. One major contributor to this resistance is the immunosuppressive environment of PDAC (see hallmark (v)). As outlined earlier, several TAM members support PDAC immune evasion by modulating both innate and adaptive immune responses, potentially contributing to immunotherapy resistance. Consequently, pharmacological inhibition of AXL, MerTK or Gas6 restore anti-tumour immune responses,[27,44,46,49,57] highlighting the potential utility of targeting the TAM receptor family to enhance responses to PDAC immunotherapy. Furthermore, in murine models of PDAC, inhibiting multiple TAM receptors with the multi-kinase inhibitor sitravatinib potentiated the anti-tumour effects of anti-PD1 by preventing M2 macrophage polarization and promoting a pro-inflammatory tumour micro-environment.[55,76]

Altogether, these studies underscore the significance of TAM receptor family in fostering drug resistance and provide a compelling rationale for targeting these molecules in clinical studies aimed at preventing refractoriness.

Concluding remarks

The overexpression of TAM receptors in the majority of patients with PDAC and their correlation with poor prognosis underscore their oncogenic potential. PDAC is a complex tumour with unique hallmarks that drives its high aggressiveness and often fatal outcome. Within this intricate landscape, the TAM receptor family emerges as a pivotal player, exerting significant influence on disease progression and therapeutic results. From facilitating early diagnosis through the potential utility of soluble proteins as blood biomarkers to modulating the intricate tumour-stroma crosstalk, TAM receptors exhibit multifaceted roles in shaping the PDAC microenvironment. Their involvement extends to promoting metastasis, inducing therapy resistance, and orchestrating immunosuppressive mechanisms.

Consequently, targeting TAM receptors presents a promising avenue for therapeutic intervention in PDAC. Preclinical studies (Table 2) demonstrate the efficacy of TAM inhibition in sensitizing tumours to chemotherapy, overcoming immunotherapy resistance, and reshaping the tumour immune microenvironment towards an anti-tumour response. Moving forward, clinical studies (Table 3) exploring TAM inhibitors in combination therapies hold considerable promise for mitigating refractoriness and advancing precision treatment strategies in PDAC.

Outstanding questions and future directions

TAM receptors play a crucial role in several hallmarks of PDAC, making it essential to include these proteins as promising biomarkers for the diagnosis and targets for the therapy of PDAC. However, there are fundamental unresolved questions that need to be addressed before transitioning to the clinical setting.

First, while sAXL has emerged as a reliable biomarker for early PDAC diagnosis, there are limitations to its clinical utility. On the one hand, AXL overexpression is present in 70% of patients with PDAC, raising concerns about detecting false negatives in the remaining AXL^{low} subgroup. Combining sAXL and CA19-9 detection can enhance sensitivity significantly.[22] Exploring additional blood proteins in future studies may help identify a panel of biomarkers to boost PDAC diagnosis sensitivity. On the other hand, elevated sAXL levels are also detected in non-tumour pathologies,[82] underscoring the need to identify AXL cancer-specific variants or isoforms to develop novel more sophisticated tools for improving the specificity of AXL as a PDAC biomarker. Furthermore, the potential use of other TAM receptors, such as MerTK or Tyro3, in PDAC diagnosis or prognosis remains unexplored.

Second, preclinical studies on TAM-based therapies have shown promising results, but translation to clinics is not trivial and needs to overcome several limitations, such as toxicity or generation of resistance, before being successful. Furthermore, careful analysis of the expression and functions of TAM receptors in the complex context of human disease is necessary for successful clinical trial design. Inhibiting TAM receptors can be achieved through different strategies, including

Clinical trial	Drug (Target)	Regimen	Disease	Phase	Status	Results (reference)
NCT03649321	Bemcentinib (AXL, small molecule)	Monotherapy/ Combination (G/ NP/CPt)	Metastatic PDAC	Phase Ib/II	Terminated	9 patients with PDAC enrolled. 5 patients experienced an adverse event of grade 3 or higher. Study finished after the Phase 1b completed and prior to Phase 2 initiation.[44]
NCT05052723	Cabozantinib (AXL, small molecule)	Combination (Pembrolizumab)	Metastatic PDAC	Phase II	Active, not recruiting	21 patients with PDAC enrolled. No results posted
NCT00940225	Cabozantinib (AXL, small molecule)	Combination (G)	Advanced PDAC	Phase I	Completed	12 patients with PDAC enrolled. MTD for the combination not established due to toxicity and small sample size[77]
NCT00940225	Cabozantinib (AXL, small molecule)	Monotherapy	Advanced tumors	Phase II	Completed	20 patients with PDAC enrolled. Few or no responders in the PDAC cohort. Phase III programs were initiated in CRPC and HCC[78]
NCT04820179	Cabozantinib (AXL, small molecule)	Combination (Atezolizumab)	Metastatic, Refractory PDAC	Phase II	Recruiting	29 patients with PDAC enrolled (estimated). No results posted
NCT05389462	ADCT-601 (AXL, ADC)	Monotherapy/ Combination (G)	Solid tumors	Phase II	Recruiting	No information about number of patients with PDAC enrolled. No results posted
NCT03425279	BA3011 (AXL, ADC)	Monotherapy/ Combination	Advanced solid tumours	Phase I/II	Recruiting	No information about number of patients with PDAC enrolled. No results posted.
NCT02219711	Sitravatinib (MerTK, small molecule)	Monotherapy	Advanced solid tumours	Phase I/Ib	Completed	3 patients with PDAC recruited. 90.2% of total patients experienced adverse effects (severe & therapy discontinuation in 13.5%)[79]
NCT03510104	MRX-2843 (MerTK, small molecule)	Monotherapy	Relapsed/refractory advanced and/or metastatic solid tumours	Phase I	Active, not recruiting	No information about number of patients with PDAC enrolled. No results posted
NCT02791334	Merestinib (AXL, Tyro3 & MerTK, small molecule)	Combination (Anti-PD-L1 Antibody LY3300054)	Advanced, refractory pancreatic cancer	Phase Ia/b	Active, not recruiting	12 patients with PDAC recruited. 33.3% stable disease, 50% clinical progression[80]
NCT04983407	Batiraxcept (Gas6, AXL fragment-Ig fusion protein)	Combination (G/ NP)	PDAC	Phase Ib/II	Terminated	34 patients with PDAC recruited Higher doses in combination with G/NP are under study[81]
NCT03536208	Warfarin (Gas6/ Pros1)	Monotherapy	PDAC	Early Phase I	Withdrawn	No patients enrolled. No results posted

List of the therapeutic approaches in PDAC targeting TAM receptors or their ligands, encompassing interventions tested in preclinical studies and those currently under investigation in clinical trials, as documented on https://clinicaltrials.gov. Abbreviations: ADC, Antibody Drug Conjugated; G, Gemcitabine; NP, Nab-Paclitaxel; CPt, Cisplatin; MTD, Maximum Tolerated Dose; CRPC, Castration Resistant Prostate Cancer; HCC, Hepatocellular Carcinoma.

Table 3: **Clinical trials of TAM family inhibitors in PDAC.**

monoclonal antibodies, aptamers, decoy receptors, and small inhibitory molecules.[25] Although AXL has received the most attention for the development of inhibitory strategies, inhibitors of MerTK, Tyro3, and TAM ligands are also being evaluated for their potential to halt cancer progression in various tumour models.[15,83] Regarding PDAC, several TAM receptor/ligand inhibitors have been evaluated in preclinical models (Table 2) and clinical trials (Table 3). While several of these clinical trials are still ongoing, the interpretation of efficacy from those already concluded is limited due to trial discontinuation (resulting from toxicity or other reasons, Table 3, NCT03649321) or because they include a low number of patients with PDAC (Table 3).[79,80] Notably, some of these studies demonstrated clinical activity in other tumours, progressing to phase III.[78] This failure in patients with PDAC may be due to several factors, such as the increased stroma in this tumour, which may hamper drug delivery and require higher doses (Table 3),[81] or the high intra- and inter-tumour heterogeneity, which can affect the expression of TAM receptors. For example, as previously mentioned, AXL is overexpressed in approximately 70% of patients with PDAC, so patient stratification based on AXL levels is crucial for trial design and precision medicine. Additionally, uncovering a potential role of the p53-AXL axis in PDAC could provide an alternative approach to personalized medicine, enabling the selection of p53-inactive tumours as suitable candidates for AXL-targeted therapies. Ongoing research and clinical trials continue to explore new TAM family-based therapeutic approaches to improve outcomes for PDAC patients.

Third, the identification of immune checkpoints has revolutionized the treatment of various tumours, yet there is currently no evidence of clinical benefit in patients with PDAC. Considering the role of the TAM family in immune modulation and the promising results observed in mouse models, where dual AXL and PD1 inhibition restored tumour immune surveillance,[46,55,76] inhibitors of TAM receptors may be incorporated into the arsenal of anti-tumour drugs for combination therapies with immune checkpoints. In fact, the broad TAM inhibitor merestinib is currently in a phase Ia/b trial for advanced/refractory PDAC in combination with an anti-PD-L1 checkpoint antibody (Table 3)[80] Furthermore, chimeric antigen receptor T cell (CAR-T) immunotherapy has been ground-breaking for haematological malignancies, although its application in solid tumours remains challenging. A recent study shows that Gas6-CAR-T cells display strong anti-tumour activity against PDAC, inducing *in vitro* cell death of TAM-positive PDAC cell lines and suppression of xenografts and PDXs growth in vivo.[84] These encouraging results underscore the potential of TAM receptors in immunotherapy and present new avenues for PDAC therapeutic interventions. However, attention must be paid to potential side effects and toxicity, considering the broad physiological functions in immune regulation of the TAM family.

Lastly, significant alterations in cellular metabolism are a key hallmark of PDAC, being crucial for cancer cell survival and tumour progression. The unique fibrotic stroma of PDAC restricts nutrient access for tumour cells, prompting adaptation through metabolic reprogramming. PDAC metabolism relies on enhanced glycolysis and the utilization of fatty acids, cholesterol, and several amino acids, as alternative fuel sources. Additionally, non-canonical metabolic pathways, such as macropinocytosis and autophagy, are essential to support tumour growth.[85] These distinct metabolic requirements are seen as potential vulnerabilities in PDAC, offering new therapeutic opportunities. TAM receptors have been implicated in cancer metabolism. Specifically, AXL inhibition has been linked to reduced glycolysis,[86] and increased cholesterol biosynthesis in ovarian cancer.[87] In the same line, AXL limits cholesterol mobilization in dendritic cells, avoiding proper maturation and favouring tumour immunosuppression.[88] These changes can impact the efficacy of cancer treatments by altering chemosensitivity,[86] DNA stability,[87] and immune response.[88] Future research will help elucidate whether TAM receptors also contribute to PDAC metabolic dysregulation, potentially introducing a new dimension to its fundamental hallmarks.

Search strategy and selection criteria

Data for this Review were identified by searches of PubMed and MEDLINE and references from relevant articles using the search "PDAC", "pancreatic cancer", "TAM receptors", "diagnosis", "treatment" and "inhibition". Abstracts and reports from meetings were included only when they related directly to previously published work. Only articles published in English between 2013 and 2023 were included.

Contributors

PGF and PN contributed to the concept and design of this review. NV-B, PGF and PN performed the literature search and reviewed and selected the papers for inclusion. NV-B wrote the first draft. NV-B, PGF and PN wrote and edited the manuscript. NM-B created the figures and critically revised the manuscript, the figures and tables. All authors read and approved the final version of the manuscript.

Declaration of interests

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

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