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Targeting TAM to tame pancreatic cancer

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Abstract

Pancreatic cancer is expected to become the second leading cause of cancer related death within the next few years. Current therapeutic strategies have limited effectiveness and therefore there is an urgency to develop novel effective therapies. The receptor tyrosine kinase subfamily TAM (Tyro3, Axl, MerTK) is directly implicated in the pathogenesis of the metastatic, chemoresistant, and immunosuppressive phenotype in pancreatic cancer. TAM inhibitors are promising investigational therapies for pancreatic cancer due to their potential to target multiple aspects of pancreatic cancer biology. Specifically, recent mechanistic investigations and therapeutic combinations in the preclinical setting suggest that TAM inhibition with chemotherapy, targeted therapy, and immunotherapy should be evaluated clinically.

1. Introduction

Pancreatic cancer is expected to become the second leading cause of cancer related death within the United States in the next few years (1). Unfortunately, there is no screening test for pancreatic cancer and patients are most commonly diagnosed with advanced disease (2,

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3). Current standard of care treatment for metastatic pancreatic cancer includes conventional cytotoxic chemotherapy with 5-fluorouracil-based treatment (e.g. FOLFIRINOX) or gemcitabine-based treatment, which achieve at best modest responses (4). The recent approval of olaparib represented the first biomarker specific approval for pancreatic cancer for patients harboring germline BRCA mutations (5). Advances in the understanding of pancreatic cancer biology should allow for the development of further targeted therapies.

The TAM (Tyro3, Axl, MerTK) family of receptor tyrosine kinases (RTKs) are involved in immune, vascular, reproductive, hematopoietic, and nervous system functions (6). The TAM receptors are composed of an extracellular ligand binding domain, a transmembrane domain, and a conserved cytoplasmic tyrosine kinase domain that is responsible for intracellular signaling (7, 8).

The control of TAM expression is not fully understood and may differ for each TAM member. The most well studied is Axl, the expression of which is positively regulated by numerous endogenous signaling molecules known to bind to the Axl promoter region, including HIF, SP-1/3, AP-1/2, MZF-1, and YAP/TAZ/TEAD (8–19). Interestingly, it has been observed that the Axl ligand, Protein S, can cause Axl overexpression (20). Conversely, Axl expression is thought to be negatively regulated by TAZ, YAP, microRNA (miR)-432, miR-34a and miR-199a/b, EZH2, and merlin (8–19, 21). Tyro3 is widely expressed in the nervous system and some other tissues and MerTK is expressed in a large number of organ systems and tissues, notably monocytes, dendritic cells, natural killer cells and platelets (22). The regulation of Tyro3 and MerTK expression remain understudied (23).

TAM activation is precipitated by a promiscuous extracellular receptor domain which can transduce signals by homo- or hetero-dimerization on binding of endogenous ligand complexed with phosphatidylserine, inducing auto-phosphorylation of the intra-cellular domain (8, 15). Canonical TAM ligands include the vitamin-K dependent carboxylated proteins growth arrest-specific gene 6 (Gas6) and Protein S (23). Protein S has higher affinity for MerTK and Tyro3, while Gas6 has higher affinity for Axl (8). Protein S has been shown to specifically function as a ligand for the TAM family in macrophages and specifically for MerTK in T cells (24, 25), and Gas6 has been shown to bind to each respective TAM family member in dendritic cells to initiate a signaling pathway required for suppression of inflammation (26). Many intracellular transduction partners have been identified down-stream of the TAM receptors, including GRB2, PI3K, SRC, PLC γ , JAK Akt, PKC, MAPK, MEK, RAK, mTORC, NF κ B, and STAT1 pathways (6, 27, 28). Ultimately, this complex network affects a wide variety of contact dependent cellular activities including regulation of inflammation, inactivation of natural killer cells (6, 27, 29), and epithelial-mesenchymal transition (EMT) (30, 31).

Increased TAM pathway activity is often observed in metastatic pancreatic cancer, conferring proliferative, migratory, invasive, chemoresistant, and immunosuppressive properties via multiple signaling pathways (32, 33). This review will highlight TAM biology, specifically related to cancer biology and pancreatic cancer, and comment on future directions in the development of TAM inhibitors as investigational therapeutic options for pancreatic cancer.

2 TAM cancer biology and therapy

Upregulation of Axl expression has been observed in cancer for over 20 years (34–38). There is now an increasing body of evidence suggesting that increased Axl expression and Axl signaling is associated with cancer. Recent studies also implicate increased MerTK and Tyro 3 expression and signaling in cancer pathogenesis (34–38).

2.1 TAM cancer biology

2.1.1 Hypoxia and apoptosis lead to increased TAM signaling activity in the tumor microenvironment—The nature of TAM overexpression in cancer is not fully understood, but is not related to fusion genes, activating mutations, or genomic amplification (39). Hypoxia in the Tumor microenvironment (TME) induces the expression of hypoxia-inducible factor (HIF), which directly binds to the Axl promoter and results in increased Axl expression (41). Additionally, release of phosphatidylserine by cancer cell death has been shown to augment TAM receptor activity on remaining tumor cells through increased Axl signaling and cellular motility *in vitro* (44). Compared to Axl activation, the availability of phosphatidylserine from apoptotic bodies appears even more important for the efficacy of MerTK activation and signaling (45). In conclusion, TME factors including hypoxia, generation of reactive oxygen species (ROS), nutrient deprivation, and apoptosis have been found to result in increased TAM signaling activity (40–43).

2.1.2 TAM overexpression is associated with metastatic phenotypic tumor changes—Cancer metastasis is associated with a number of biological phenotypic changes, including tumor EMT, resulting in increased cell motility and metastasis (46). Knockdown of Axl in cancer cell lines reduces the expression of EMT mediators Snail, Slug, N-Cadherin, and Vimentin, therefore suggesting that Axl may play a role in EMT (47). Vimentin expression in an EMT model is associated with an increase in Axl expression, which promotes increased Slug expression and signaling and the EMT phenotype (46, 48). In addition to Axl, Tyro3 signaling promotes cancer cell motility and invasion by inducing the expression of Snail (49, 50). MerTK has also been shown to play a role in cancer migration by inducing FAK and Rho A GTPase signaling altering cytoskeletal organization and promoting cellular motility (51).

Together, these data suggest the TAM signaling pathway is inextricably involved in the initiation and maintenance of metastatic behavior through the process of EMT. Multiple preclinical studies demonstrate that inhibition of Axl can reverse these metastatic phenotypic properties in multiple cancer models suggesting a possible role in cancer therapy (41, 52, 53).

2.1.3 TAM signaling leads to chemoresistance—TAM signaling is consistently associated with resistance to chemotherapy and targeted inhibition of other receptor tyrosine kinases. Increased Axl expression and signaling promotes resistance to conventional chemotherapy in association with the expression of EMT promoting regulators and DNA repair regulators. While the precise mechanism of chemoresistance is unknown, it is thought that increased expression of DNA repair enzymes impair the DNA toxicity effects of chemotherapy that would otherwise lead to cell death (54–56). Additionally, an ectopically

expressed MerTK and Tyro3 cell line confers Akt mediated chemoprotection by an unknown mechanism (45, 57). While the precise mechanism remains elusive, early evidence suggests overexpression of TAM family members may promote a compensatory stress response through induction of autophagy allowing escape of apoptosis, a reduction of co-stimulatory phosphatidylserine, and chemo-resistance (9,70). Most intriguingly, early data suggests this chemoresistance can be overcome by targeted inhibition of TAM kinases suggesting a possible role in improving the observed response to current cytotoxic therapy (58–61).

Multiple studies have found that Axl is overexpressed in tyrosine kinase inhibitor (TKI) resistant cancer cell lines (62–64). In an EGFR inhibitor resistant cell line, Axl expression was found to be responsible for persistent EGFR activation (65). In renal cell carcinoma, overexpression of Axl may result in targeted therapy resistance by complexing with the intracellular SRC proto-oncogene, which results in lateral activation of MET signaling similar to the observed crosstalk with the HER-family of receptors (41). Interestingly, preclinical models of EGFR resistance have provided early data suggesting TAM family receptors provide a pathway of redundant activation of Akt allowing cancer to circumvent attempts at EGFR inhibition (59–63). Multiple preclinical studies have found that Axl inhibition can sensitize TKI resistant cancer models (11, 66–70). These studies highlight the role of TAM in the development of resistance to chemotherapy and targeted therapy and the preclinical rationale to trial TAM inhibition in the clinical setting to prevent or treat chemoresistance.

2.1.4 TAM overexpression is immunosuppressive—Recent decades have seen substantial advances in the understanding of the relationship between cancer and the immune system. Immune dysregulation is now thought to be a key driver of cancer biology (71). These advances have led to the development of immune checkpoint inhibitors, which have revolutionized the treatment for many cancers. Unfortunately, immune checkpoint inhibitors alone had little activity in pancreatic cancer (72). It is now clear that interplay between the tumor immune microenvironment and the host immune system is critical in determining cancer response to immunotherapy (71). TAMs are an important regulatory component of innate immune checkpoints surveilling cancer development and progression. TAM activity can promote immunosuppressive cytokine signaling to reduce T cell recruitment, inactivate natural killer cells, inactivate antigen presenting dendritic cells, and induce immune tolerance (73). Conversely, Axl inhibition has been observed to promote the inflammatory M1 macrophage state, relieve suppression of Toll-like receptor (TLR) responses by antigen presenting cells, and increase natural killer cell activity (23, 59).

PD-L1 is an immunosuppressive cancer biomarker used for predicting response to immune checkpoint inhibitors. Overexpression of MerTK in preclinical models has been associated with increased PD-L1 expression. Further, the addition of apoptotic cellular debris to MerTK cancer lines increased cancer cell PD-L1 expression, suggesting that availability of phosphatidylserine may potentiate the effects of MerTK (45). In other cancer cell models, overexpression of Tyro3, Axl, and MerTK have all demonstrated the ability to upregulate PD-L1 expression with varied degrees of phosphatidylserine dependence (74). Accordingly, treatment of leukemic cell lines with MerTK inhibitor was observed to reduce PD-L1 expression on immune cells in leukemia (75). Tumor infiltrating lymphocytes are higher in

MerTK knockout models reflecting an increase in immune surveillance and checkpoint activity (76). Culturing macrophages in the presence of PDAC cell lines were found to induce activity of Axl (77).

These emerging data suggest that TAMs contribute to tumor immunosuppression via dysregulation of cytokine signaling, impaired innate and adaptive immune cell function, and reduced efficacy of the immune surveillance checkpoint.

3 Pancreatic Cancer Biology

While there are several histological subtypes of pancreatic cancer, over 90% of cases comprise ductal adenocarcinoma (78). There are several known risk factors for developing pancreatic cancer, such as smoking, obesity, family history, pancreatitis, and germline mutations in BRCA and PALB2 (78). Pancreatic ductal adenocarcinoma (PDAC) is thought to most commonly arise from pancreatic intraepithelial neoplasia precursor lesions that usually harbor KRAS mutations, and sometimes CDKN2A, TP53, and SMAD4 mutations, all of which occur in the majority of tumors that progress to PDAC (78, 79). The development of PDAC results in alteration in the TME and growth of a specific tumor-associated stroma (Figure 1) (2, 80). This stroma is composed of cancer associated fibroblasts, immune cells, endothelial cells, nerve cells, and the extracellular matrix which may provide a physical barrier to cancer metastasis as well as soluble factors promoting tumor growth, vascularization, immunosuppression, and metastatic escape (80). Advances in the molecular characterization of pancreatic cancer indicate that classification of molecular subtypes may allow for selection of subtypes with specific therapeutic vulnerabilities (78). Unfortunately, resistance to standard treatment is frequently observed in PDAC, which is thought to result from multiple factors including EMT, propagation of pancreatic cancer stem cells, and metabolic dysregulation (81, 82),

Despite the success of immune checkpoint inhibitors revolutionizing the standard of care treatment for many cancers, clinical trials with immunotherapy in pancreatic cancer thus far have found limited benefit (83–85). PDAC appears to exhibit less immunogenicity compared to other solid cancers, and this may be due to the immunosuppressive properties of the TME (84). PDAC also appears to confer localized immunosuppression through alteration of the TME as demonstrated by the observed recruitment of M2 macrophages (86). Together, these data provide additional evidence that TAM overexpression in pancreatic cancer may contribute to the immunosuppressive phenotype.

3.1 TAM are overexpressed in pancreatic cancer

Axl is overexpressed in 70% of Stage II PDAC tissue, 75% of PDAC cell lines, and is associated with distant metastatic disease and reduced overall survival (32). Multiple Axl knockdown studies in PDAC models show reduced Akt activation and downstream Slug and Snail pathways, with associated reduced cell invasion and migration properties (32, 33). Treatment of PDAC xenografts with monoclonal antibodies directed against the extracellular ligand binding domain of Axl (anti-Axl mAbs D9 and E8) inhibit homo-dimerization necessary for Axl autophosphorylation and downstream Akt signaling, reducing tumor growth (87). Interestingly, PDAC metastases can respond differently to Axl inhibition than

the primary pancreatic tumor when modelled in vitro. This reduced efficacy at some metastatic sites suggests a complex interaction requiring additional investigation (88).

In a PDAC model treated with a MEK1 inhibitor, members of the RTK-family Axl, PDGFR, and HER1–2 are overexpressed rescuing Akt signaling and promoting chemo-resistance (89). Addition of MEK1 inhibition to Axl, PDGFR, and HER1–2 inhibition can re-establish treatment efficacy as measured by reduced cell proliferation and increased apoptosis (89). This raises a concern that in PDAC, a complex regulatory system exists in which tumors can derive resistance to targeted therapy by their own constitutive changes in oncogenic signals and through changes in the tumor stromal environment. MerTK and Tyro3 expression, and TAM ligand expression and activity have been understudied in pancreatic cancer, but there is active work aiming to further elucidate the pathogenesis and importance of these pathways in pancreatic cancer (90). It was recently shown that Tyro3 is important in pancreatic cancer growth in a mouse xenograft model and was required for pancreatic cancer progression (91). In addition, pancreatic cancer patients with higher Tyro3 expression had worse outcomes (91). The pan-TAM inhibitor sitravatinib was found to have activity in a pancreatic cancer cell line, suggesting the importance of the TAM pathway activity in pancreatic cancer preclinical models (92). Recently, it was shown that cancer associated fibroblasts and macrophages are the primary sources of Gas6 in pancreatic cancer, and that inhibition of Gas6 alters the EMT phenotype (93).

There is extensive evidence that suggests the TME is a critical barrier to the success of current and novel therapies in pancreatic cancer. As described above, the TAM subfamily is involved in many known pathophysiological properties associated with the TME including EMT, chemoresistance, and immunosuppression. Alteration of the TME with TAM inhibition should therefore be investigated clinically in patients with pancreatic cancer.

4 TAM inhibitor development in pancreatic cancer

There are several therapeutic strategies aiming at targeting TAM pathway activity. While antibodies, aptamers, and decoy receptors have been developed and may prove useful, the most promising agents investigated thus far are small molecule TAM inhibitors targeting the ATP binding site. Most of the small molecule inhibitors that have been developed to clinical trial stage are Axl inhibitors, as Axl is the most widely altered in malignancy and subsequently the best studied member of the TAM family. There are also now MerTK inhibitors in clinical trials ([NCT03510104](#)).

There are several TKIs with activity against multiple kinases including Axl. The most notable of these are cabozantinib and foretinib. Cabozantinib was initially developed as a c-MET and VEGFR2 inhibitor, and has been approved for use in medullary thyroid cancer and renal cell carcinoma (94, 95). Cabozantinib was evaluated clinically in combination with gemcitabine in PDAC, but toxicity limited the feasibility of further study (96). Foretinib (GSK1363089) is another multi-kinase inhibitor (MKI) targeting MET, ROS, RON, Axl, TIE-2, Tyro-3, and VEGFR2 that has demonstrated efficacy in early trials across multiple cancer types including metastatic renal cell carcinoma, hepatocellular carcinoma, and adenocarcinoma of the breast with reported partial response (PR) and stable disease (SD)

rates of 22.9% and 82.% in the single-agent setting (97–99). Despite promising pre-clinical data, clinical trials were halted due to excessive toxicity in the completed phase II trials (100). There are a number of additional MKIs in development that may provide future opportunities in PDAC treatment (101).

Selective TAM inhibitors have also been developed, the most advanced is bemcentinib (also known as BGB324 and R428), the first in class selective Axl inhibitor (102). In PDAC models, bemcentinib induced epithelial differentiation, returned the tumor microenvironment to an immunostimulatory phenotype, and sensitized PDAC to chemotherapy (102). Early phase clinical trials evaluating bemcentinib in combination with standard of care cytotoxic chemotherapy are ongoing across a variety of malignancies including PDAC. Initial observations from [NCT03184571](#) presented at Society for Immunotherapy of Cancer (SITC) 2019 suggest a significant prolongation in progression free survival when BGB324 is added to the immune checkpoint inhibitor pembrolizumab (103). Perhaps most interestingly, the benefit of Axl inhibition was observed independent of PD-L1 expression and most tightly correlated to ‘composite Axl expression’ and TGFb mRNA levels, both previously demonstrated predictors of immune checkpoint inhibitor failure.

A number of other selective- and multi-TAM inhibitors (e.g. RXDX-106, TP-0903) are being developed, but studies in PDAC are limited (101). Preliminary results from the Phase Ia dose-escalation trial [NCT02729298](#) of TP-0903 reported at ESMO 2019 suggest a 37% response rate with a best response of stable disease across a mixed population of advanced solid tumors (104). Clinical investigation of the pan-TAM inhibitor RXDX-106 has been halted since early termination of the sole phase 1 trial. Warfarin is a small molecule inhibitor that inhibits γ -carboxylation of glutamic acid residues on Protein S and Gas6 thus reducing TAM activation, has preclinical efficacy in PDAC models, and may be worth pursuing clinically (105).

Due to the demonstrated escape and chemoresistance mechanisms previously discussed, considerable effort has been given to the use of TAM inhibition in concert with standard of care therapy (106). Ongoing studies are exploring the clinical efficacy of TAM inhibition across a myriad of malignancies in combination with cytotoxic chemotherapy, targeted small molecular inhibitors, and immune checkpoint inhibitor therapy in addition to several monotherapy studies in both the palliative and adjuvant setting. The advent of targeted therapy in other malignancies has brought substantial success, particularly for non-small cell lung cancer. However, despite initial impressive responses to targeted therapy, resistance invariably develops. While there is no preclinical evidence of resistance mechanisms to TAM inhibitors, this will clearly need to be monitored. Combination therapy with TAM inhibitors and other therapy as described above may allow us to circumvent resistance mechanisms by targeting potentially resistant clones with other cancer therapy.

4 Potential toxicities of TAM inhibition

There are some safety concerns that will require monitoring throughout the development of TAM inhibitors. Inactivating mutations of MerTK introduced into mouse models have

demonstrated increased incidence of retinopathy (6, 73). Further, Axl and MerTK knockout mice have demonstrated an increased incidence of colorectal cancer likely secondary to the oncogenic effects of ongoing inflammation (107). Since Axl is a regulator of TGF β activity in osteoblasts and induces dormancy of prostate cancer, it has been speculated that TAM inhibition may paradoxically result in disease progression in this population (108). Clinical trials will need to monitor for potential adverse events given the broad function of TAM in human physiology, but particularly autoimmunity, de novo carcinogenesis, bone metastases and retinopathy (23). Studies of triple knockout Axl-/MerTK-/Tyro3- mice indicate increased autoimmunity in this model (109). This finding, in addition to the expected immunostimulatory effects of TAM inhibition mentioned above, highlight the importance of monitoring for autoimmune toxicity in clinical studies. This will be particularly critical if evaluated in combination with immune checkpoint inhibitors, which can result in deadly immune-related adverse events (110). Furthermore, since Axl and Tyro3 play important roles in platelet activation and thrombus formation, close monitoring of bleeding and thrombosis in clinical trials involving TAM inhibitors (111).

The most common dose-limiting toxicities reported in the early phase 1a dose escalation studies to date include thrombocytopenia and adverse gastro-intestinal events, most commonly diarrhea. Common reported grade 3 or higher adverse events diarrhea, vomiting, anemia, thrombocytopenia, and hyponatremia.

However, even considering these potential adverse effects, the current dismal prognosis of pancreatic cancer with a mortality/incidence ratio of 98%, means that the potential benefits of developing TAM inhibitors far outweigh the potential risks and therefore should be pursued (3).

5 Conclusions

Inhibitors of the TAM pathway can modify the TME and impart anti-cancer effects through modulation of EMT, chemoresistance, and immunosuppression. There is a strong preclinical evidence for pursuing Axl inhibition in the clinical setting for pancreatic cancer. Tyro3 and MerTK remain understudied in pancreatic cancer, but biological and preclinical studies in other cancers indicate they should also be pursued as potential targets for pancreatic cancer. The available preclinical evidence suggests that combination therapy of TAM inhibition with chemotherapy and immunotherapy may provide the most clinical benefit. Results of current and planned preclinical studies and clinical trials will help understand how to best sequence these treatments to improve the care of patients with pancreatic cancer.

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Key Points

1. The TAM receptor tyrosine kinase signaling pathway is implicated in the pathophysiology of pancreatic cancer.
2. Preclinical models demonstrate that pharmacological inhibition of TAM signaling has activity against pancreatic cancer and should be clinically evaluated.

Figure 1. Pancreatic tumor microenvironment and TAM receptors.

A: Cancer associated fibroblasts express and increase the availability of the TAM ligand Gas6. B: Cytotoxic therapies cause cancer cell death, increasing the availability of phosphatidylserine, which engages with TAM ligands Gas6 and Protein S to increase TAM activation and signaling. C: When Axl is pharmacologically inhibited, tumor-associated macrophages are polarized towards the M1 phenotype, resulting in increased production of inflammatory cytokines. M2 polarization is reduced, resulting in reduced suppression of T cell function via VISTA. D: Small molecule Axl inhibitor binding to Axl at the cytoplasmic binding domain.