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Review Article

Dual targeting of TAM receptors Tyro3, Axl, and MerTK: Role in tumors and the tumor immune microenvironment

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Abstract

In both normal and tumor tissues, receptor tyrosine kinases (RTKs) may be pleiotropically expressed. The RTKs not only regulate ordinary cellular processes, including proliferation, survival, adhesion, and migration, but also have a critical role in the development of many types of cancer. The Tyro3, Axl, and MerTK (TAM) family of RTKs (Tyro3, Axl, and MerTK) plays a pleiotropic role in phagocytosis, inflammation, and normal cellular processes. In this article, we highlight the cellular activities of TAM receptors and discuss their roles in cancer and immune cells. We also discuss cancer therapies that target TAM receptors. Further research is needed to elucidate the function of TAM receptors in immune cells toward the development of new targeted immunotherapies for cancer.

Keywords: *Axl, MerTK, Tyro3, Axl, and MerTK receptors, Tumor immune microenvironment, Tyro3*

Introduction

The Tyro3, Axl, and MerTK (TAM) proteins belong to the receptor tyrosine kinase (RTK) subclass of protein kinases. TAMs are ligand-activated transmembrane proteins that mediate signal transduction from an extracellular receptor through the cytoplasm to the nucleus and trigger expression of various oncogenes [1]. Many tyrosine kinase inhibitors (TKIs) have been synthesized for cancer treatment, and several inhibitors of TAM receptors have been developed for various cancers. The TAM receptors have similar domain structures and functions. Unlike other RTKs, TAM receptors play important roles in tissue conservation, inflammation, and phagocytosis, as well as in cell development, growth, migration, and survival [2,3]. Thus, the deregulation of TAM signaling is linked to various autoimmune diseases and cancers. In this review, we discuss the structure and function of TAM receptors and the roles of their ligands, growth arrest-specific 6 (Gas6), and protein S (ProS) [4]. We also explore the role of TAM receptors in immune cell function and in cancer development. Finally, we discuss TAM receptor inhibitors and their potential roles in the development of new cancer therapies.

Cloning and genomic structure of Tyro3, Axl, and MerTK receptors

Axl was first discovered as a transforming gene in chronic myelogenous leukemia (CML) patients in 1988 [5]. *Axl* is located on chromosome 19q13.2 and was cloned in 1991 [6]. The next TAM family receptor to be identified was *v-ryk*, isolated from the avian retrovirus RLP30 [7], followed by cloning of the human analog *c-Mer*. Expression of c-Mer is found in monocytes and epithelial and reproductive tissues [8]. An alias of *Mer* is *Mer* tyrosine kinase (*MerTK*), located on human chromosome 2q14.1 [9]. Murine *Tyro3* [10] and the human analog *Tyro3,* located on chromosome 15q15 [11], were cloned in 1993. *Tyro3* and *Axl* each have 20 same-sized exons [12], while Mer is encoded by 19 exons [13]. In the tyrosine kinase domain, Mer and Axl share the most similar amino acid sequences [14]. Human TAM receptors share approximately 34% and 57% amino acid sequence identity within the coding regions for the extracellular and intracellular domains, respectively, resulting in high homology in the intracellular tyrosine kinase domain [15]. However, the actual molecular weights of TAMs differ from the predicted protein size due to posttranslational modifications, including ubiquitination, phosphorylation, and glycosylation [6,12,16,17]. These modifications may cause cell- and tissue-type-specific alterations in the regulation of TAM receptor function.

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Tyro3, Axl, and MerTK receptor protein structure and associated ligands

TAM receptors are RTKs that are widely expressed in the nervous, immune, vascular, and reproductive systems and regulate cell growth, survival, differentiation, adhesion, and motility. TAM receptors contain two immunoglobulin (Ig)-like domains, two type III fibronectin (FN III) domains within the extracellular domain, and one conserved KW (I/L) A (I/L) ES sequence within the intracellular domain [Figure 1a] [1]. TAM receptor ligands include Vitamin K-dependent Gas6 and ProS, which have similar domain structures, such as a C-terminal sex hormone-binding globulin, four epidermal growth factor (EGF)-like repeats, and an N-terminal γ–carboxyglutamic acid (Gla)-rich domain. Gas6 and ProS demonstrate Ca^{2+}-dependent binding to phosphatidylserine (PtdSer)-presenting cell membranes carrying a negative charge, and these protein ligands share 43% amino acid sequence identity [18]. In apoptotic cells, the binding of TAM receptor dimers occurs via interaction with paired Gas6 or ProS molecules bound to the interacting cell membrane via PtdSer, thereby forming a tetrameric complex [Figure 1b]. Gas6 can interact with all TAM receptors, while ProS binds MerTK and Tyro3 only [19]. TAM receptors have overlapping expression patterns and functions. However, TAM-deficient and triple gene knockout mice are viable [12]. Among the RTKs, the Tie (Tie1), Tek (Tie2), fibroblast growth factor receptor, vascular endothelial growth factor receptor (VEGFR), and platelet-derived growth factor receptor families contain extracellular domains that include both Ig-like and FNIII domains or an Ig-like domain alone. The MET RTK family (including Met and Ron) is most closely related to TAMs based on amino acid sequence of the kinase domain [14]. MET RTKs can signal through TAM receptors to activate common RTK signaling pathways and achieve functional redundancy [18,20].

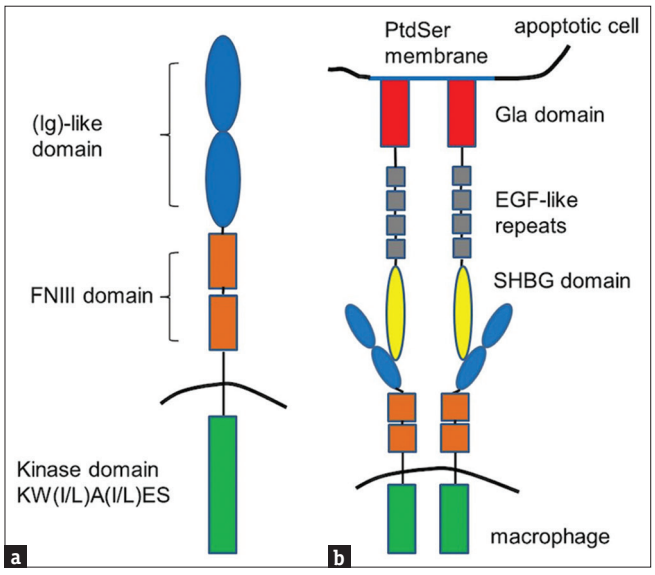

Figure 1: Structure of (a) Tyro3, Axl, and MerTK receptors and (b) the interaction between Tyro3, Axl, and MerTK receptors and ligands Gas6 and ProS. FNIII: Type III fibronectin, Gla: γ–carboxyglutamic acid-rich, (Ig)-like: Immunoglobulin-like, PtdSer membrane: Phosphatidylserine-presenting, SHBG: Sex hormone-binding globulin

Therefore, differences in the extracellular domain versus the intracellular kinase domain lead to distinct effects on cellular function.

Biological functions of Tyro3, Axl, and MerTK receptors

TAM receptors mediate the phagocytosis and engulfment of apoptotic cells, viral infection, homeostasis of blood vessel integrity, autoimmunity, and oncogenic processes [21,22]. In cell biology, apoptotic cell death and subsequent phagocytosis to clear the apoptotic bodies is important to reduce necrosis and intracellular organoid release that may lead to inflammation and autoantibody creation. Loss of TAM receptor function has been linked to autoimmune disease resulting from failure to clear apoptotic cells [23]. TAM receptors, especially MerTK, function as bridges between phagocytes (e.g., macrophages and dendritic cells) and the apoptotic cells that they engulf. MerTK is expressed on the phagocytes and binds the ligands linked to the PtdSer-presenting apoptotic cells [Figure 1b] [24]. Intriguingly, enveloped viruses present PtdSer residues, mimicking apoptotic cells, and infect innate immune cells, resulting in decreased expression of type I interferon (IFN) [25]. Blockage of TAM receptors impairs the infectivity of viruses such as dengue, West Nile, Ebola, and Zika and reduces viral replication in dendritic cells [26-28]. TAM receptors also function as pleiotropic inhibitors of immune cells [29]. Reduced TAM signaling through down-regulation of ProS may contribute to the progression of autoimmune diseases, including multiple sclerosis and systemic lupus erythematosus [30,31]. Furthermore, TAM receptors, especially Axl and MerTK, are highly expressed in various cancers, driving conventional RTK signaling and playing an oncogenic role [2]. Downstream signaling molecules of TAM receptors include PI3K-Akt-mTOR, MEK-ERK, p38, FAK, STAT5, NFκB, and other proteins that regulate cell proliferation, migration, survival, epithelial–mesenchymal transition (EMT), and chemoresistance [3,32-37]. The functions of TAM receptors are both in regulating cancer cells and immune cells, which provide as good dual targets for cancer drug development.

Tyro3, Axl, and MerTK receptors in cancer

TAM receptors have been linked to various types of cancer. The expression and role of Axl has been studied extensively, whereas data on the role of Tyro3 in cancer are scarce. Axl is overexpressed in most solid tumors and hematologic malignancies, and MerTK overexpression has been observed in breast, gastric, glioblastoma, lung, and prostate cancers, as well as melanoma and multiple myeloma. Overexpression of Tyro3 only occurred in select hematopoietic malignancies, such as acute myeloid leukemia and multiple myeloma [Table 1]. Among the TAM receptors, Axl is a risk factor for poor prognosis, including lymph node metastasis, reduced disease-free survival, and reduced overall survival in various types of cancer [Table 1]. In addition, activation of TAM receptors suppresses pro-inflammatory cytokines and decreases inflammation, creating an immune-tolerant environment for tumor

Table 1: Association of Tyro3, Axl, and MerTK receptors in cancers

Cancer types	Axl	MerTK	Tyro3	Associated outcomes	References
Breast	+	+		Axl: poor prognosis, metastasis	[38-41]
Colorectal	+			All: poor prognosis	[42]
Gastric	+	+		Axl and MerTK: poor prognosis	[43,44]
GBM	+	+		Axl: poor prognosis	[45,46]
H and N	+			Axl: poor prognosis, metastasis	[47,48]
HCC	+			Axl: poor prognosis	[49,50]
Lung	+	+		Axl: poor prognosis, metastasis	[51-53]
Melanoma	+	+		Axl: drug resistance	[54-56]
Ovarian	+			Axl: poor prognosis	[57,58]
Pancreatic	+			Axl: poor prognosis	[59]
Prostate	+	+		Axl: drug resistance	[60,61]
RCC	+			Axl: poor prognosis	[62-64]
AML	+		+	Axl: poor prognosis, drug resistance	[65-67]
Multiple myeloma	+	+	+		[68,69]

AML: Acute myeloid leukemia, HCC: Hepatocellular carcinoma, H and N: Head and neck cancer, GBM: Glioblastoma, RCC: Renal cell carcinoma

growth [70]. The oncogenic role of TAM receptors is well studied, with supportive evidence in various types of cancer. Furthermore, the inhibitors of TAM receptors, especially Axl, are under developing for treating cancers.

Tyro3, Axl, and MerTK receptors in immune cells and the tumor microenvironment

TAM receptors are also play an important role in certain immune cells, including dendritic cells, macrophages, nature killer (NK) cells, and platelets [1]. TAM-deficient NK cells demonstrated poor cytotoxic activity, 10-fold lower than normal NK cells, and have a lower number of NK cells, indicating that TAM receptors could regulate NK cell differentiation [71]. TAM receptors have been shown to inhibit Toll-like receptor-induced proinflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor (TNF), type I IFNs, and IL-12, driving the transition to an immunosuppressive state [23]. As indicated above, loss of TAM receptors in macrophages caused decreased clearance of apoptotic cells, as TAM receptors on macrophages interact with Gas6-linked apoptotic cells and mediate phagocytosis. These phagocytosis phenomena or so-called efferocytosis could further promote M2 polarization of macrophages by secreting IL-10, IL-4, and TGF-β and contribute to tumor progression. On the other hand, the M1 polarization cytokines, TNF-α, IL-1, and IL-12, were decreased, and subsequently reduced the antitumor activity of M1 macrophages [72]. Furthermore, activation of Axl by Gas6 binding can increase the suppressive function of regulatory T cells (Treg) through upregulation of forkhead box P3 expression *in vitro* and *in vivo* [73]. Even though studies have shown that TAM receptors play an important role in immune system function, there has been little research into the immunological effects of TAM receptor inhibitors in cancer. So far, we know that inhibition of MerTK significantly increased inflammatory cytokines in serum and increased the number of cytotoxic cells in the TME [74]. In addition, mature NK cells were shown to express TAM receptors, and upon ligand (Gas6) activation, NK cell proliferation and IFNγ production were suppressed [75]. Furthermore, Gas6 secreted from tumor-educated stromal cells resulted in negative regulation of antitumor immunity, contributing to tumor progression [76]. In contrast, inhibition of TAM receptors showed a pro-tumorigenic effect in colitis-driven colorectal cancer [77]. Nevertheless, inhibition of TAM receptors is needed as a mechanism to control the side effects of excessive inflammation and other immune disorders associated with cancer therapy. In summary, the research of the role of TAM receptors on tumor-associated macrophages, NK cells, dendritic cells, and T cells in cancer TME are needed to further elucidated.

Tyro3, Axl, and MerTK receptor inhibitors

Since the concept of TKIs was raised in 1988, which was focus on epidermal growth factor receptor (EGFR) [78]. However, the first TKI drug was imatinib, which is on the market for treating CML in 2001 [79]. Henceforth, the TKI drugs among targets, such as HER2, VEGF, FGF, PDGF, MET, c-kit, ALK, and second or third generation of them, are under development worldwide. TAM receptors belong to RTK. MerTK and Axl have been studied as therapeutic targets in various cancers, but more research is needed to assess these TAMs relative to tumor-associated macrophages and other cells, particularly immune cells in the TME. There are some TAM inhibitors under development in the preclinical stage and in each stage of clinical trial [Table 2]. Many inhibitors are used to block Axl and/or MerTK, but they also have inhibitory effects on other RTKs, such as VEGFR, c-Met, and Flt3, leading to reduced cell proliferation, migration, and other properties of tumor progression *in vitro* and in a mouse xenograft model; the next step is to advance testing via clinical trials. In addition to small molecules, several anti-Axl monoclonal antibodies, such as YW327.62S [111] and 20G7-D9 [112], and nucleotide aptamers, e.g., GL21.T [113], are under investigation at the preclinical stage. Thus, TAM inhibitors have great potential as cancer therapy; however, the associated effects on immune cells are limiting. Recently, a newly synthesized small molecule (UNC4241) has been shown to inhibit both TAM receptors and myeloid-derived suppressor cells, thereby enhancing anti-PD-1 therapy for

Table 2: Development of the inhibitors of Tyro3, Axl, and MerTK receptors

Inhibitor	IC50 (nM)			Other targets	Clinical phase	References
	Axl	MerTK	Tyro3			
Amuvatinib (MP-470)	10			c-kit, PDGFR, Flt3, RET	Phase 2	[80,81]
Bemcentinib (R428, BGB324)	14				Phase 2	[82,83]
Bosutinib (SKI-606)				Src, Abl	Phase 2	[84,85]
Cabozantinib (XL184)	7			VEGFR2, c-Met, c-kit, Flt3	Phase 3	[86-89]
Dubermatinib (TP-0903)	27				Phase 2	[90]
Foretinib (XL880)	11			VEGFR2, c-Met, Tie-2, Ron	Phase 2	[91]
Gilteritinib (ASP2215)	0.73			Flt3	Phase 3	[92,93]
Glesatinib (MGCD265)				c-Met, VEGFR1/2/3, Ron	Phase 2	[94,95]
Merestinib (LY2801653)	11			c-Met, TEK, Ron	Phase 2	[96,97]
Sitravatinib (MGCD516)	1.5	2		DDR2, EPHA3, Flt4	Phase 2	[98]
BMS 777607	1.1		4.3	c-Met, Ron	Phase 2	[99,100]
CEP-40783 (RXDX-106)	7			c-Met	Phase 1	[101]
LDC1267	29	<5	8	c-Met, Aurora B, LCK	Preclinical	[75]
NPS-1034	10.3			c-Met	Preclinical	[102]
RU-301, RU-302					Lead compound	[103]
S49076	7	2		c-Met, FGFR1/2/3	Phase 1	[104]
SGI-7079					Phase 2	[105,106]
UNC2025	14	0.74	17	Flt3	Lead compound	[107]
UNC2250		1.7			Lead compound	[108]
UNC2541		4.4			Lead compound	[109]
UNC2881		22			Lead compound	[110]

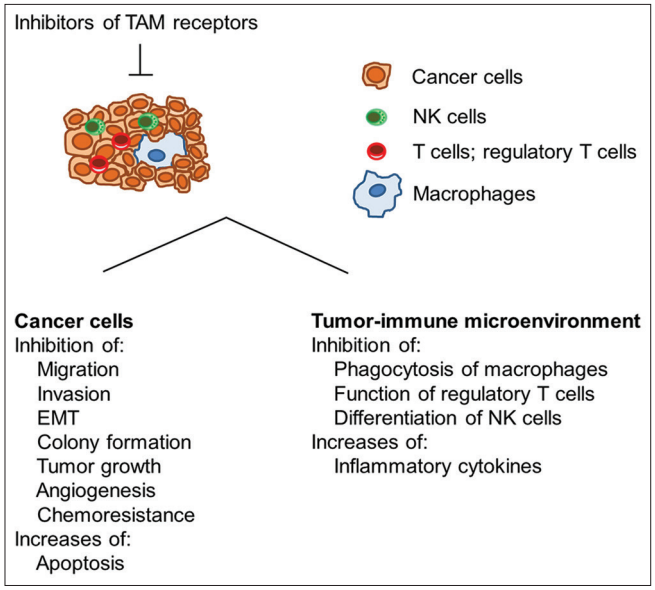

Figure 2: Dual targeting of the inhibitors of Tyro3, Axl, and MerTK receptors. Left panel: The drug effects on cancer cells. Right panel: The drug effects on tumor immune microenvironment

melanoma [114]. Above all, these pieces of evidence reveal that the treatment of inhibitors of TAM receptors in combination with anti-PD-1 antibody-drug may enhance the overall efficacy in treating cancer.

Conclusion

Overexpression of TAM receptors and their ligands, Gas6 and ProS, has been strongly linked to the growth of various cancers through regulation of cell proliferation, migration, EMT, chemoresistance, and angiogenesis. On the other hand, TAM receptors function as pleiotropic inhibitors of immune cells, regulating phagocytic clearance of apoptotic cells and limiting cytokine release, which may make the TME a more tumor-favorable niche. Initial studies of TAM inhibitors for cancer therapy showed antitumor benefits, but further study is necessary to determine the full immunologic consequences. Future research may also explore combination treatments, sequence of administration, and other considerations of therapeutic strategy to fully realize the potential benefits of TAM inhibitors in the era of individualized targeted cancer therapy.

Perspective

The inhibitory drugs of TAM receptors are under development, mostly due to the oncogenic role in the cancer progression. Indeed, blockage of TAM receptors could reduce cancer cell proliferation, migration, invasion, and tumor growth. Moreover, the effect of these drugs may not only inhibit tumor growth itself but also from TME. Inhibition of TAM receptors could decrease immunosuppressive activity, which affects macrophages, NK cells, and Treg cells. However, the side effects of the anti-immunosuppression and auto-immune diseases are needed to further consider in the future. Besides, those TKIs may also inhibit other RTK targets, which is sharing similar structures with TAM receptors. In summary, the dual targeting inhibitors of TAM receptors have great potential for treating various types of cancer [Figure 2].

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Conflicts of interest

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