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REVIEW

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Recent advances in TAM mechanisms in lung diseases

Jiaqi Ban[1†], Jiayi Qian[1†], Chi Zhang[2†] and Jun Li[1*]

Abstract

TYRO3, MERTK, and AXL receptor tyrosine kinases, collectively known as TAM receptors, play a vital role in maintaining lung tissue homeostasis by regulating integrity and self-renewal. These receptors activate signalling pathways that inhibit apoptosis, promote cell proliferation and differentiation, mediate cell adhesion and migration, and perform other essential biological functions. Additionally, TAM receptors are implicated in mechanisms that suppress anti-tumor immunity and confer resistance to immune checkpoint inhibitors. Disruption of the homeostatic balances can lead to pathological conditions such as lung inflammation, fibrosis, or tumors. Recent studies highlight their significant role in COVID-19-induced lung injury. However, the exact mechanisms by which TAM receptors contribute to lung diseases remain unclear. This article reviews the potential mechanisms of TAM receptor involvement in disease progression, focusing on lung inflammation, fibrosis, cancer, and COVID-19-induced lung injury. It also explores future research aspects and the therapeutic potentials of targeting TAM receptors, providing a theoretical foundation for understanding lung disease mechanisms and identifying treatment targets.

Keywords Lung diseases, TYRO3, MERTK, AXL, COVID-19

Introduction

Lung diseases primarily encompass lung inflammation, fibrosis, and tumors. Lung inflammation involves the accumulation of immune cells, which are phagocytized by macrophages during apoptosis. However, secondary necrosis of these apoptotic cells can trigger uncontrolled inflammatory activity [1]. Pulmonary fibrosis can develop when lung inflammation persists and inflammatory activities worsens. It is a chronic, progressive disease, and the interstitial pneumonias are classified into three categories based on pathomorphological variants: major idiopathic interstitial pneumonias, rare idiopathic interstitial pneumonias, and non-classifiable idiopathic interstitial pneumonias [2]. The main effector cells in pulmonary fibrosis are fibroblasts, myofibroblasts, and differentiated fibroblasts. The primary cause of fibrosis is the imbalance of extracellular matrix (ECM) protein homeostasis and the dysfunction of fibroblasts and myofibroblasts [3, 4]. Lung cancer remains the leading cause of cancer-related deaths worldwide, with non-small cell lung cancer (NSCLC) being the commonest type [5]. The therapeutic targets for lung diseases for instance pneumonia, pulmonary fibrosis, and lung cancer are not yet well understood and require further investigation. Additionally, the pathogenesis of lung diseases is not fully elucidated, necessitating comprehensive research to explore their mechanisms and identify effective therapeutic targets.

Numerous studies indicate that TAM receptors play a significant role in lung homeostasis regulation, making them a potential therapeutic target for lung diseases.

†Jiaqi Ban, Jiayi Qian and Chi Zhang contributed equally to this work

*Correspondence:
Jun Li
gygwlj@163.com
[1] School of Public Health, The key Laboratory of Environmental Pollution Monitoring and Disease Control, Ministry of Education, Guizhou Medical University, No.6 Ankang Road, Guian New Area, Guiyang 561113, Guizhou, China
[2] School of Clinical Medicine, Ministry of Education, Guizhou Medical University, Guiyang, Guizhou 561113, People's Republic of China

TAM, a transmembrane receptor protein that includes TYRO3, AXL, and MERTK, consists of extracellular, transmembrane, and intracellular regions. It belongs to one of the 20 subfamilies of receptor tyrosine kinases (RTKs) [6]. Under normal physiological conditions, TAM performs various functions, including inhibiting cell apoptosis, promoting proliferation, and facilitating cell adhesion and migration. The ligand Gas6 (gene 6) aids TAM in regulating inflammatory responses and fibrosis [7, 8]. However, in pathological states, TAM is overexpressed in damaged tissues, disrupting homeostasis and contributing to conditions like inflammation, fibrosis, and immune responses, evident in chronic obstructive pulmonary disease (COPD) and small cell lung cancer. In lung inflammation, TAM is vital for hemostasis and regulating macrophage activity and anti-inflammatory responses through its interaction with Gas6 [9, 10]. In lung fibrosis, AXL and TYRO3 activate lung fibroblasts [11], while MERTK is involved in myofibroblast activation [12]. AXL also regulates extracellular matrix homeostasis and the functions of fibroblasts and myofibroblasts, influencing fibrosis progression. In lung tumors, AXL and Gas6 regulate cancer growth, metastasis, and epithelial-mesenchymal transition (EMT), creating a favourable environment for tumor development [13]. This suggests that the Gas6/AXL pathway is a promising target for lung cancer therapy, offering anti-tumor effects, reducing invasion, and inhibiting migration [14–17]. MERTK can contribute to cancer development through overexpression or inappropriate activation of ligands like Gas6 and PROS1 (protein S), alterations in chimeric receptor signalling (e.g., Colony-Stimulating Factor 1 (CSF-1)), and activation of signalling pathways such as PI3K (phosphatidylinositol 3-kinase), ERK (extracellular regulatory protein kinase), p38 (p38 mitogen-activated protein kinase), and MEK (mitogen-activated extracellular signal-regulated kinase) [18]. TYRO3, by binding to PROS1, can influence local coagulation, proliferation, or differentiation and may play a role in the advance or progression of lung cancer [19]. Additionally, since the COVID-19 pandemic, there has been robust research into how the viral infections damage lung tissues. This damage may involve lung injury, abnormal wound healing, the activation of pro-inflammatory and pro-fibrotic signals [20]. The Gas6/TAM system plays a significant role in the pathological processes of diseases [21, 22], highlighting its critical importance in understanding COVID-19 pathogenesis. This review explores the potential mechanisms of TAM in lung diseases, focusing on four key areas: lung inflammation, fibrosis, cancer, and COVID-19-related injury. It underscores TAM's impact on the development of lung inflammation and fibrosis, triggering new insights for targeted therapeutic strategies in treating lung diseases.

TAM

Structure of TAM

TAM receptors, members of the receptor tyrosine kinase family, include TYRO3, AXL, and MERTK [6] These transmembrane proteins consist of an extracellular region, a transmembrane domain, and an intracellular region. The extracellular region features two tandem immunoglobulins like domains and two fibronectin type III repeats, which enable ligand binding. The transmembrane region contains cleavage sites for ADAM17 (in AXL and MERTK) and ADAM10 (in AXL), allowing proteolytic processing. The intracellular region includes a tyrosine kinase catalytic domain, a conserved KWIAIES motif, and three tyrosine autophosphorylation sites [23], which are critical for signal transduction [24, 25]. The tyrosine kinase domain is implicated in oncogenic activity and can be activated both dependently and independently of extracellular stimuli [26].

TAM is activated by binding to its ligand's growth inhibition specific gene 6 and PROS1 [27]. Compared to TYRO3, AXL exhibits higher structural similarity to MERTK receptors, with 31%—36% amino acid homology in the extracellular region and 54%—59% in the intracellular region [28]. TYRO3, AXL, and MERTK are homologous type I RTKs, sharing a conserved kinase domain sequence [KW (I/L) and (I/L) ES] and similar extracellular structures, including two immunoglobulin-like domains and two fibronectin III domains [29]. TAM is expressed in monocytes, macrophages, dendritic cells (DCs), phagocytes, as well as in natural killer (NK) and natural killer T (NKT) cells [30, 31] (Fig. 1).

Mechanisms of AXL in disease

Activation of AXL under physiological conditions requires homodimerization of its ligand and is fully achieved through interaction with phosphatidylserine [32]. Binding of AXL to its ligand triggers autophosphorylation, receptor dimerization, and trans-autophosphorylation of tyrosine residues in the cytoplasmic domains [33]. Oxidative stress can also induce AXL phosphorylation, enhancing cell migration [15]. AXL activates downstream signalling pathways that promote processes such as proliferation, survival, migration, plasticity, and immunosuppression. In lung tissue, AXL expressed in platelet [34], endothelial cell, [35] and bronchial epithelial cell [19], affecting normal cell growth and immune regulation of the body [36]. For instance, AXL mediates contact dependent activation and platelet stabilization through interactions with

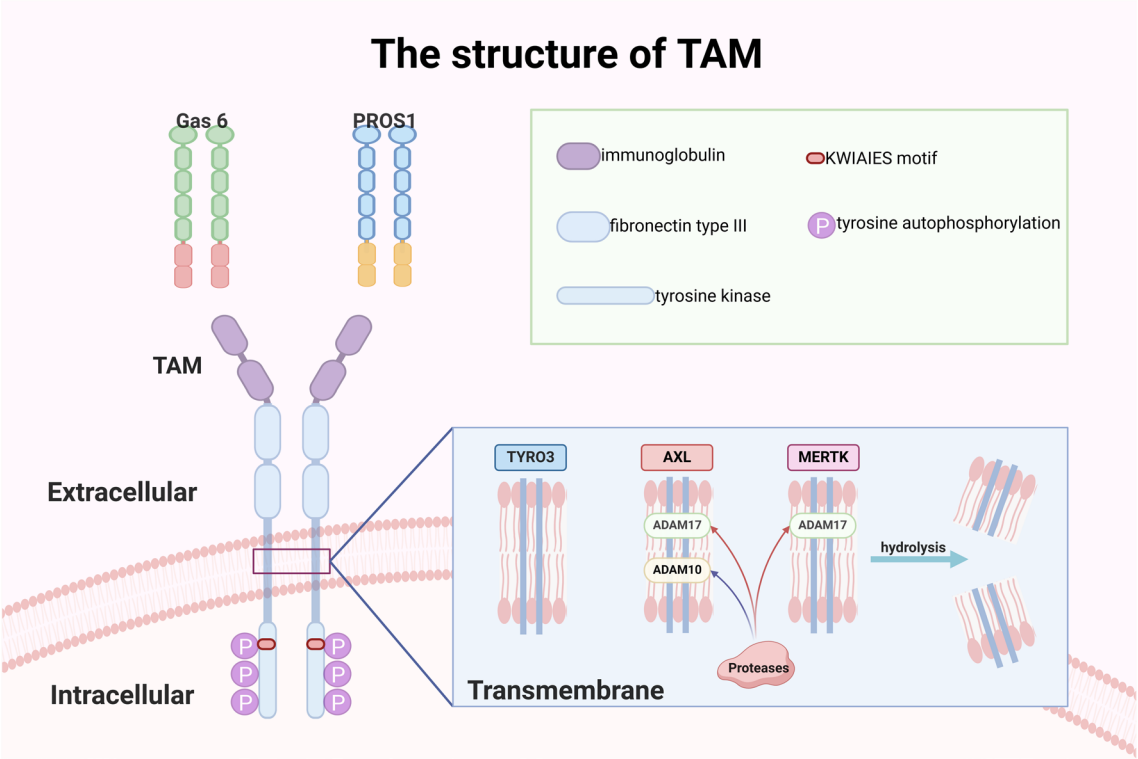

Fig. 1 Structure of TAM. TAM is a transmembrane receptor protein that consists of an extracellular region, a transmembrane region, and an intracellular region. The extracellular region is composed of two tandem immunoglobulins and two fibronectin type III repeat sequences. Transmembrane region consists of TYRO3, AXL, MERTK these 3 RTKs. The intracellular region contains the tyrosine kinase catalytic region, the highly conserved KWIAIES motif, and three tyrosine autophosphorylation sites. TAM is able to bind to ligand-specific gene 6 and protein S

Gas6 [37–39], while also promoting inflammation by enhancing leukocyte extravasation [40]. AXL in the endothelium is cleaved into its soluble form, sAXL, which is released into the bloodstream. Plasma levels of sAXL serve as indicators of inflammation severity and trends in endothelial dysfunction, as seen in conditions like COVID-19 [41].

In the context of lung tumors, AXL modulates the tumor immune microenvironment to encourage tumor growth. It regulates cancer cell properties, influencing migration, growth, survival, and chemotherapy resistance [42]. AXL also facilitates immune evasion by reducing antigen presentation and immune cell killing [43]. Additionally, it promotes the secretion of immunosuppressive cytokines and chemokines, recruits immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), and reduces the infiltration of activated immune cells like cytotoxic T cells. Furthermore, AXL drives the polarization of M1 to M2 macrophages, contributing to tumor microenvironment remodelling [26].

Mechanism of MERTK in disease

MERTK plays a critical role in various physiological processes, including lung tissue homeostasis and repair, platelet aggregation, and innate immune regulation. It is essential for phagocytosis and the efficient clearance of apoptotic cells, as macrophages lacking MERTK can recognize and bind apoptotic cells but fail to engulf them [44]. By mediating efferocytosis, MERTK suppresses inflammation, preventing the release of antigens from apoptotic cells and eliminating apoptotic debris [45]. This process also induces MERTK signalling, which promotes M2 macrophage polarization [46–49]. PROS1-mediated MERTK signalling serves as a late costimulatory signal, enhancing the proliferation and secretion of effector and memory cytokines [50]. Activated T cells expressing PROS1 and PtdSer (phosphatidylserine) can bind to MERTK on dendritic cells, further inhibiting inflammatory responses [51]. In platelet aggregation, MERTK promotes integrin signalling, fibrinogen adhesion, and platelet spreading [52–54], although its exact role in platelet activation remains unclear and requires further verification [37]. MERTK also maintains immune balance by preventing excessive

pro-inflammatory responses to pathogens or tumor cells while avoiding autoimmune reactions that could lead to tissue damage or tumorigenesis [55]. In the context of lung cancer, MERTK overexpression contributes to oncogenic processes such as cell growth, proliferation, survival, and migration. Inhibiting MERTK can induce apoptosis, suppress colony formation, enhance chemosensitivity, and reduce tumor growth [56].

Mechanism of TYRO3 in disease

The endogenous ligands for TYRO3 are Gas6 and PROS1. Gas6 is significantly upregulated following growth arrest [57], while PROS1 is linked to the proliferation and differentiation of immune cells [6]. TYRO3 plays a role in platelet aggregation and is involved in vascular injury responses [58]. Gas6 activates TYRO3, promoting the activation of pro-inflammatory endothelial cells, adhesion molecule expression, platelet adhesion to endothelial cells [40], and tissue factor release, which triggers exogenous coagulation and thrombus formation [59]. Studies in mice with TYRO3 deficiency have shown reduced platelet granule secretion, impaired thrombus formation, and decreased platelet aggregation stability [34, 60, 61]. TYRO3 also inhibits inflammation by enhancing the phagocytosis of apoptotic tumor cells by dendritic cells and macrophages [62–65]. Activated T cells contribute to this process by producing PROS1, which forms a PROS1-PtdSer complex with exposed PtdSer on their surface, stimulating TYRO3 on dendritic cells [51].

TYRO3 has dual roles, regulating platelet aggregation, immune responses, and cell growth while also exhibiting oncogenic potential [60, 66]. It interacts with the PI3K pathway and induce transformations of NIH3T3 cells via the EGFR/TYRO3 chimeric receptor. The PI3K pathway mediates part of TYRO3's oncogenic capacity [67]. Additionally, the synthesis and secretion of anticoagulant protein S, along with co-expression of the TYRO3 receptor, may contribute to lung carcinogenesis [19] (Fig. 2).

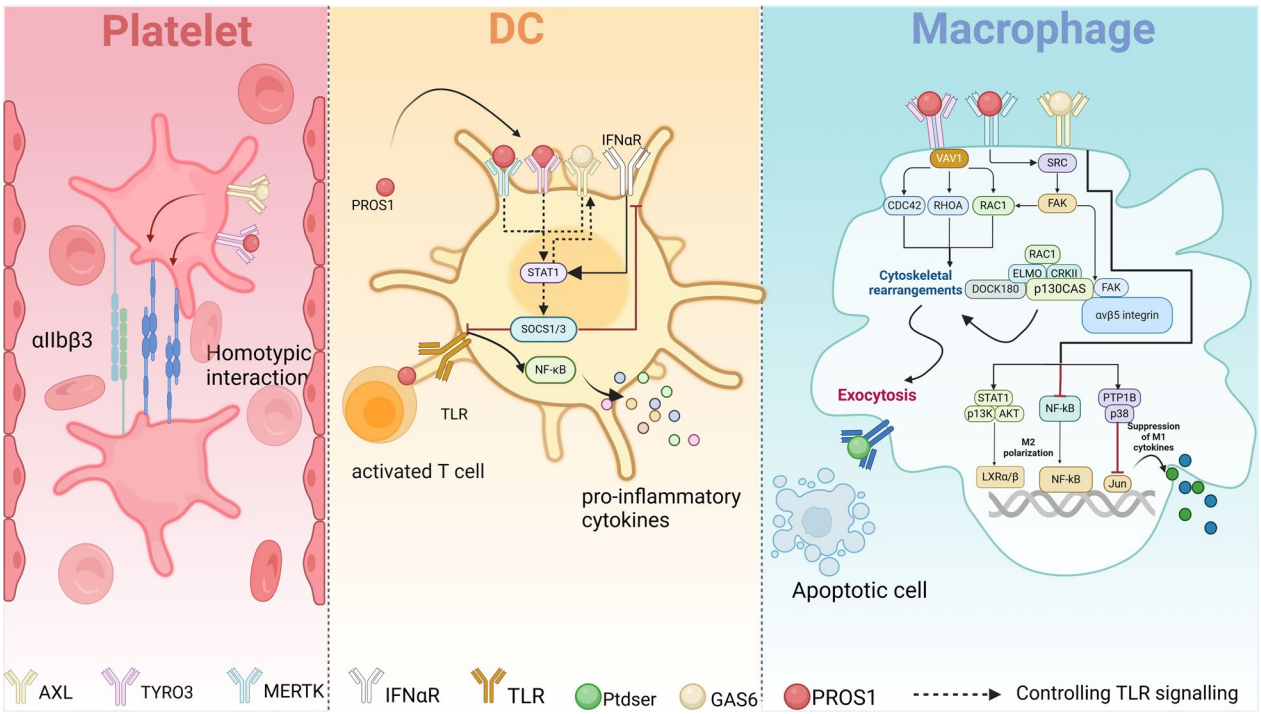

Fig. 2 Four main mechanisms of action exist for TAM. First, TAM facilitates platelet aggregation by activating integrin αIIbβ3 through AXL or TYRO3, enabling sustained platelet contact to promote thrombosis. Second, TAM modulates the inflammatory response by inhibiting TLR signaling and inflammatory cytokine production through STAT1-induced AXL-IFNαR interactions, which co-drive SOCS1 and SOCS3 feedback. Third, TAM mediates cytosolic burial by binding to PtdSer on apoptotic cells, activating downstream signaling via the VAV1-RHOA, p130cas-CRKII-DOCK180-ELMO, and related pathways to induce cytoskeletal reorganization. Finally, TAM promotes M2 polarization during wound healing by inhibiting NF-κB and activating the PI3K-AKT-STAT1-dependent LXRα/β pathway, while reducing M1 cytokine expression by disrupting the Jun transcription factor complex (Jun proto-oncogene is a member of AP-1 (activator protein-1) transcription factor family) through MERTK-PTP1B-p38α signalling

The role of TAM in lung diseases

TAM and pulmonary inflammation

Lung inflammation can be either non-infectious or infectious in nature [68]. Pneumonia, a lung infection affecting susceptible individuals, often arises from chronic conditions (e.g., age, smoking, COPD, diabetes) or acute events (e.g., poisoning, air pollution, trauma) [69]. These factors lead to exudate accumulation in the lung parenchyma, impairing respiratory function [70]. The development of pneumonia, or pneumogenesis, is influenced by host biology, including immune resistance and tissue resilience [1]. Adaptive immunity significantly impacts pneumonia outcomes, particularly through recurrent respiratory infections and lung-resident memory cells triggered by atypical recall responses [71, 72]. Tissue resilience supports anti-inflammatory, pro-resolving, and reparative-regenerative pathways. The severity of pneumonia ultimately depends on the strength of the host's immune resistance and tissue elasticity [73].

Gas6 significantly impacts haemostasis and reduces inflammation by interacting with TAM [10]. The Gas6/TAM axis regulates inflammatory responses and fibrosis progression [8]. Physiologically, this axis plays a dual role, either promoting tissue repair or causing organ damage and dysfunction. Its activation can exhibit anti-inflammatory effects in certain cells and tissues, such as upregulating AXL phosphorylation in the alveolar epithelium during ischemia–reperfusion-induced acute lung injury (IR-ALI), where Gas6/AXL signalling activates the SOCS3-mediated pathway to reduce IR-related inflammation and injury [74]. However, it can also maintain pro-inflammatory responses in other contexts, depending on its anti-inflammatory or pro-fibrotic properties.

The anti-inflammatory effects of the Gas6/TAM system primarily stem from its regulation of macrophage activity [9]. When overexpressed in damaged tissues, Gas6 inhibits pro-inflammatory cytokine production, mediates apoptotic body cytotoxicity, and limits antigen presentation to antigen-presenting cells (APCs) by attenuating Toll-like receptors (TLRs) and type I IFN signalling. Additionally, it suppresses NLRP3 inflammasome activation through autophagy [22].

Studies have shown that MERTK and AXL specialize in coordinating apoptotic cell clearance across different contexts and play critical roles in inflammatory regulation [75]. MERTK facilitates the phagocytosis of microparticles by alveolar macrophages during acute lung injury, thereby reducing the pro-inflammatory effects on alveolar epithelial cells [76]. endothelial MERTK supports endothelial barrier function and mitigates inflammation by regulating neutrophil transmigration and endothelial permeability [77]. Dexmedetomidine (DEX) has been shown to alleviate sepsis-associated acute lung injury by inhibiting the ROS/ADAM10/AXL signalling pathway, reducing macrophage cytotoxicity, upregulating AXL expression in mouse alveolar macrophages, and enhancing apoptotic cell clearance [78]. If lung inflammation persists and worsens, it can progress to pulmonary fibrosis.

TAM and pulmonary fibrosis

Pulmonary fibrosis is a chronic and progressive lung disease marked by thickening of the alveolar walls, impaired gas exchange, and eventual respiratory failure [79, 80]. Based on pathomorphological characteristics, interstitial pneumonias are categorized into three groups: major idiopathic interstitial pneumonia, rare idiopathic interstitial pneumonia, and unclassifiable idiopathic interstitial pneumonia. Among these, idiopathic pulmonary fibrosis (IPF), a subset of major idiopathic interstitial pneumonia, is the most severe and irreversible form, characterized by progressive fibrosis of the lung parenchyma [81]. Fibrosis arises from dysfunctional wound healing [82], with chronic lung inflammation being a key contributing factor [83]. The primary effector cells in pulmonary fibrosis are fibroblasts and myofibroblasts. The disease is characterized by excessive ECM deposition and structural remodelling of the lung, which disrupts the dynamic equilibrium between ECM synthesis and degradation [3]. Two major regulatory mechanisms are involved: the proliferation and apoptosis of fibroblasts and myofibroblasts, and the synthesis and degradation of ECM components [4]. The main cause of pulmonary fibrosis is an imbalance in ECM homeostasis and a disruption in the physiological functions of fibroblasts and myofibroblasts.

IPF is a rare and heterogeneous disease with a complex etiology that remains poorly understood. Multiple factors contribute to its development, including genetic mutation [84–87], age, sex [88, 89], and environmental factors (smoking [90], Indoor pollutants [91]). However, recurrent epithelial injury from various aetiologies emphasize the IPF initiation [92]. For instance, mutations in surfactant-related genes, which are essential for normal epithelial function, can promote pulmonary fibrosis [93]. Additionally, dysfunction in pro-inflammatory cytokines, such as transforming growth factor-β (TGF-β), plays a significant role in the disease process [94, 95]. Elevated levels of connective tissue growth factor (CTGF), platelet-derived growth factor (PDGF), and fibroblast growth factors (FGFs) are known to exacerbate lung fibrosis. Inhibitors targeting these growth factors [96–99], such as TGF-β inhibitors [100], have shown potential

in halting fibrotic progression and improving outcomes for patients. The TAM receptor tyrosine kinase family, including AXL, TYRO3, and MERTK, plays a pivotal role in IPF. AXL forms a complex with Gas6, regulating Gas6-mediated signalling and modulating ligand availability [101]. This interaction negatively regulates the alveolar epithelial phenotypes, leading to a loss of epithelial integrity [102]. Interestingly, Gas6 exhibits antifibrotic effects, as demonstrated by studies where recombinant Gas6 (rGas6) reduced pulmonary fibrosis in mice by inhibiting EMT, apoptosis, and fibroblast activation in alveolar epithelial type II (ATII) cells [103].

Furthermore, AXL, TYRO3, and their ligand Gas6 contribute to the activation of lung fibroblasts in IPF, while MERTK is not expressed in these cells [11]. However, MERTK expression is upregulated in certain macrophage subpopulations within IPF, where it is involved in myofibroblast activation and fibrosis [12, 104]. Gas6 has the highest affinity for AXL, suggesting that the Gas6/TAM system primarily exerts its effects through AXL in IPF. The roles of MERTK and TYRO3 in IPF require further investigation. Notably, AXL inhibition has shown differential effects depending on the disease stage: worsening inflammation and fibrosis in the acute phase, but alleviating pulmonary fibrosis in the fibrotic phase. These highlights need for staged and targeted therapeutic approaches in treating pulmonary fibrosis [105]. The Gas6/TAM system has been implicated in the pathogenesis of pulmonary fibrosis, particularly in IPF. Further exploration of its role in other fibrotic diseases may provide valuable insights into broader therapeutic applications.

TAM and lung tumor

Mechanisms of lung tumor

Lung cancer is one of the most common and deadly malignancies worldwide, with NSCLC being the most prevalent form [5]. Smoking remains the primary risk factor, and countries with high or rising smoking rates are expected to see increased lung cancer incidence [106, 107]. A key feature of lung cancer is the aberrant activation of the extracellular regulatory protein kinase signalling pathway. The zinc finger protein ZNF251, which is overexpressed in clinical lung cancer samples and promotes tumor cell growth, has emerged as a potential therapeutic target. ZNF251 inhibits the expression of dual specificity phosphatases 6 (DUSP6), a negative regulator of ERK activation, by directly binding to its promoter region [108]. Additionally, exosomes derived from lung cancer tumors have been shown to play a significant role in promoting cancer progression. These exosomes induce epithelial-mesenchymal transition, foster a favourable tumor microenvironment, enhance cell proliferations, inhibit apoptosis, regulate invasion and metastasis, mediate immunosuppression and immune evasion, promote angiogenesis, drive cancer-related fibroblast transformation, and contribute to resistance against radiotherapy and chemotherapy [109–114].

AXL and lung tumors

AXL is recognized for its carcinogenic potential, particularly in NSCLC, where it is co-expressed with its ligand Gas6 in specific cell lines [115, 116], contrasting with its absence in normal bronchial epithelial and small cell lung cancer cells. This expression pattern may relate to histochemical and adhesive phenotypes [117]. AXL promotes NSCLC progression by enhancing tumor growth, metastasis, invasion, drug resistance, and EMT, encouraging a conducive environment for tumorigenesis [13]. AXL also plays a role in immune regulation by clearing apoptotic cells [118], reducing inflammation, and creating an immune-tolerant microenvironment that influences lung cancer growth [117, 119]. Oxidative stress exacerbates AXL-mediated cell migration and invasion via the AKT1/Rac1 pathway [15]. Additionally, CD73 activates AXL by binding to its R55 site, independently of Gas6, promoting metastasis and EMT through the CD73/AXL axis [120].

AXL is closely linked to the epithelial-mesenchymal transition [121–123]. a process where polarized epithelial cells lose adhesion and gain migratory and invasive mesenchymal properties [124]. EMT plays a key role in the progression of NSCLC [124–127]. AXL expression is higher in NSCLC mesenchymal cancer cells than in epithelial cancer cells, and its abnormal expression promotes EMT-related phenotypes, enhancing cell migration and invasion [17], while maintaining the EMT state [128]. The AXL-MET axis represents a potential therapeutic target for NSCLC. Research indicates that Phosphofructokinase platelet (PFKP), a metabolic enzyme essential for cancer hyperglycolysis, binds to AXL, activating its signalling pathway and promoting MET phosphorylation to drive NSCLC progression. Nanoparticle system (NPs)-mediated PFKP silencing reduces cell proliferation, migration, invasion, and colony formation by inhibiting the AXL-MET axis. A nanoparticle system encapsulating PFKP siRNAs enhances the stability of siRNA and promotes its release into the cytoplasm, effectively inhibiting PFKP expression, enhancing the targeted inhibition of the PFKP-mediated AXL-MET axis in tumors, and ultimately hindering tumor growth in vivo [129].

Cancer stem cells (H1299-sdCSCs) are obtained from tumor spheres of the human NSCLC cell line H1299. AXL is highly expressed in H1299-sdCSCs and regulates

their biophysical properties, including low stiffness and soft elasticity. AXL knockdown significantly reduces tumor sphere formation [130, 131]. In addition, AXL may play a role in promoting pro-tumor macrophages. Studies have shown that targeted inhibition of AXL on M2 polarized tumor-associated macrophages (M2-TAMs) helps to polarize them towards the M1 type and activate macrophage anti-tumor immunity. Direct inhibition of AXL carried by macrophages and AXL on tumor cells can effectively interfere with M2 polarization and its pro-tumor activit [132].

The activation and overexpression of MERTK and AXL are key factors promoting NSCLC, with complementary and overlapping roles. These receptors are aberrantly expressed in NSCLC but are absent or present at low levels in NHBE cells (Normal Human Bronchial Epithelial Cells) [133–136]. MERTK promotes tumor cell proliferation and anti-apoptotic signalling, while AXL reduces sensitivities to chemotherapy. Together, MERTK and AXL enhance tumor cell survival by inhibiting apoptosis, fostering growth, and decreasing chemosensitivity in NSCLC cells [56]. However, the precise mechanisms by which AXL contributes to drug resistance requires further investigation, potentially involving EMT status and interactions with other receptors in targeted signalling pathways. AXL expression is linked to aggressive tumor phenotypes, and its upregulation and hyperactivation influence the tumor microenvironment. Therefore, combining AXL inhibitors [137] with current chemoimmunotherapy regimens, such as immune checkpoint Inhibitors (ICIs) [138] and epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) [139–147] may benefit NSCLC patients.

Notably, AXL exhibits dual functionality, supporting normal cell growth while also possessing oncogenic properties. It can induce cancer cell apoptosis, inhibit tumor growth, and reduce drug resistance by preventing AXL overexpression or its co-expression with ligands, offering potential strategies for lung cancer treatment.

MERKT and lung tumor

MERTK's role in cancer is linked to the inappropriate expression of its ligands and alterations in chimeric receptor signalling pathways [18]. Unbiased gain-of-function retroviral insertion screens have also highlighted MERTK's oncogenic potential [148]. MERTK promotes tumorigenesis through its ligands, primarily Gas6 and PROS1, which activate the PI3K/AKT and mitogen-activated protein kinase (MAPK) signaling cascades, pathways also associated with the Epidermal Growth Factor Receptor (EGFR) [149]. Protein S, another ligand, requires modification to activate MERTK-mediated phagocytosis of apoptotic cells [150, 151]. Additionally, galectin-3, which is overexpressed in many cancers, may contribute to MERTK signalling [152].

MERTK also contributes to lung tumorigenesis via chimeric receptor signalling. For instance, human CSF-1 induces MERTK autophosphorylation, activating phospholipase Cg, PI3K, p70S6 kinases, MEK, and ERK [153]. Furthermore, a constitutively active MERTK chimera, formed by fusing the extracellular domain of CD8 with MERTK's intracellular region [154], activates MEK1, ERK, PI3K, and the p38 pathway, influencing the proliferation, migration, and survival of lung cancer cells [155].

In NSCLC, Gas6-induced phosphorylation of p38, ERK1/2, MEK1/2, AKT (Protein Kinase B), CREB, and FAK (Focal Adhesion Kinase) promotes tumor cell migration and invasion [56]. MERTK activation triggers multiple pro-oncogenic signalling pathways, including MAPK, p38, and PI3K, which drive lung carcinogenesis by enhancing cell proliferation and migration while reducing apoptosis and chemosensitivity [18]. Inhibiting MERTK in NSCLC increases apoptosis, reduces colony formation, enhances chemosensitivity, and decreases tumor formation.

Cancer progression is often linked to MERTK mutations, ligand overexpression, or altered chimeric receptor signalling. Targeting MERTK in tumor cells offers a promising therapeutic strategy, with potential inhibitors including ligand traps, monoclonal antibodies, and small molecule tyrosine kinase inhibitors. A novel macrocyclic dual MERTK/AXL inhibitor, lead compound 43, shows therapeutic potentials with low nanomolar potency against MERTK and AXL, demonstrating anti-tumor activity in lung cancer cell lines [156].

TYRO3 and lung tumor

Studies have shown that the co-expression of TYRO3 and protein S is a common feature in most lung cancer cell lines. Unlike Gas6, protein S does not stimulate TYRO3 kinase activity [157, 158]. However, as an active anticoagulant protein produced by cancer epithelial cells [159], protein S may contribute to lung carcinogenesis or progression through a receptor-ligand system that influences local anticoagulation, proliferation, or differentiation [19]. The interaction between protein S and TYRO3 may also promote cell survival or aid in tissue repair, suggesting a dual role in lung cancer development and progression, with mechanisms that require further investigation. Additionally, combining TYRO3-targeted inhibitors with checkpoint inhibitors may enhance antitumor activity and benefit NSCLC patients [160]. Furthermore research is needed to explore whether TYRO3 influences lung cancer through other

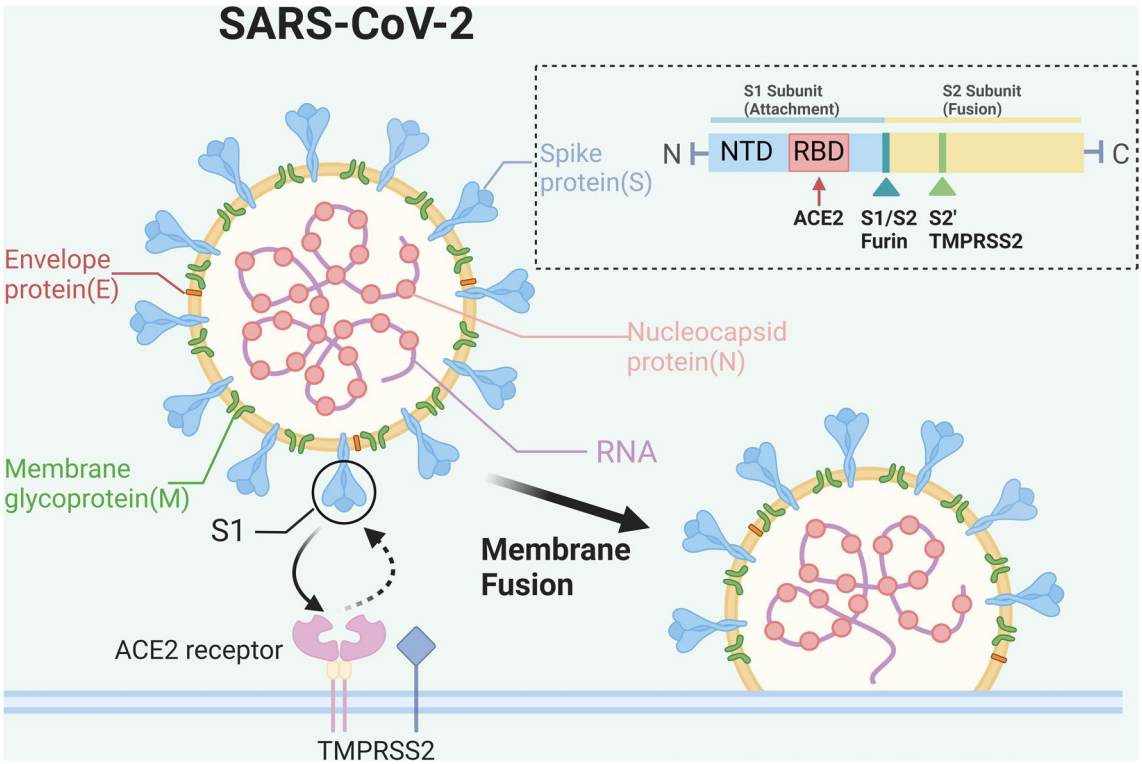

Fig. 3 SARS-CoV-2 utilizes its surface spike (S) protein for receptor recognition and membrane fusion. The viral genome encodes four structural proteins: S, membrane (M), nucleocapsid (N), and envelope (E). The S protein, a glycoprotein composed of S1 and S2 subunits, mediates viral entry. Specifically, the S1 receptor-binding domain (RBD) binds ACE2, while S2 facilitates membrane fusion

mechanisms or pathways, as current studies on its role remain limited.

Mechanisms of TAM in COVID-19-induced lung injury

SARS-CoV-2, the virus responsible for COVID-19, is a pathogen that causes an acute respiratory disease. It encodes four major structural proteins: spike protein (S), membrane protein (M), nucleocapsid protein (N), and envelope protein (E) [161]. The spike protein, a glycoprotein, consists of two functional subunits, S1 and S2. The S1 subunit, exposed on the surface, contains a receptor-binding domain (RBD) that specifically recognizes angiotensin-converting enzyme 2 (ACE2) on host cells, facilitating viral entry [162, 163]. The S2 subunit is primarily involved in membrane fusion [164] (Fig. 3).

Gas6 binds PtdSer on viral surfaces and interacts with TAM to connect viruses to macrophages and other phagocytes, facilitating either lattice protein-mediated endocytosis or viral megalocytosis [24], leading to viral internalization [165, 166]. Serum ACE2 and AXL levels are linked to the severity of COVID-19, particularly with pulmonary inflammation [167], and targeting these proteins provides an effective strategy to block viral entry into cells [168, 169]. AXL facilitates the entry of viruses into cells [20], while increased galectin-3, a ligand for MERTK and TYRO3 activation, correlates with fibrosis, inflammation, and tissue damage [170]. Plasma levels of Gas6 and soluble AXL (sAXL) correlate with COVID-19 severity, progressing with disease intensity and serving as potential biomarkers for prognosis [171]. TAM receptors may play a role in both adaptive and non-adaptive immunity [172]. The Gas6/TAM axis is a key regulator of the innate immune system, and under inflammatory conditions, elevated levels of sAXL, sMERTK, and sTYRO3 help modulate the inflammatory response and protect against tissue damage [21, 22].

The development of pulmonary fibrosis following viral infection can be attributed to two main mechanisms: virus-induced lung injury with abnormal wound healing and immune-mediated injury, which involves the activation of pro-inflammatory and pro-fibrotic signals [20]. Clinical studies in COVID-19 patients have demonstrated that SARS-CoV-2 disrupts normal re-epithelialization, leading to abnormal wound healing and subsequent lung injury [173]. This injury is often accompanied by thrombotic activation, as thrombosis

and disseminated intravascular coagulation are common in these patients [174–176]. PROS1, a critical regulator of the coagulation cascade, plays a key role in preventing coagulopathy [177]. However, its depletion due to SARS-CoV-2 infection of blood vessels can result in uncontrolled cytokine production, triggering cytokine storms and damaging lung vasculature. Coagulation dysfunction, vascular necrosis, and bleeding complications may also reduce TAM ligand levels, as thrombus exposure accelerates PROS1 consumption [178]. In contrast, the Gas6/TAM axis is essential for maintaining vascular homeostasis and regulating platelet activation, serving as a protective mechanism against vascular damage and endothelial repair [39, 179]. ADP-P2Y12 and Gas6 work synergistically to activate PI3K signalling, promoting sustained activation of αIIbβ3 and stabilizing thrombus [180]. However, moderate inhibition of the Gas6/TAM axis can reduce platelet activation and thrombosis while still allowing platelet plugs to form, thereby maintaining haemostatic function [181].

Viruses can trigger immune-mediated injury by activating pro-inflammatory and pro-fibrotic signals. In the case of SARS-CoV-2, the immune response can become overactive, leading to excessive cytokine production, recruitment of neutrophils, monocytes, and macrophages, which express phosphatidylinositol 3-kinase gamma (PI3Kγ) [182]. This exacerbates immune damage and contributes to pulmonary fibrosis [173]. Elevated levels of cytokines such as IL-6 and tumor necrosis factors (TNF) in COVID-19 patients have been linked to widespread lung damage [183, 184]. PROS1 plays a critical role in cytokine regulation by binding to the extracellular domain of MERTK, activating its kinase to suppress cytokine release during infections caused by viral, bacterial, and other pathogens [185]. In COVID-19 patients, reduced PROS1 expression impairs TAM signalling, resulting in chronic immune hyperactivation, ineffective clearance of apoptotic cells, and an increased risk of autoimmune diseases. Interestingly, PROS1 has dual functions, acting as both an anticoagulant and a potential inducer of excessive blood coagulation and immune responses, possibly linked to its role as a TAM ligand.

The Gas6/TAM system is implicated in the pathological processes of COVID-19, with receptors like AXL potentially mediating viral entry, inflammatory regulation, and the coagulation cascades. This suggests the system's significance in understanding COVID-19 pathogenesis. Exploring the role of Gas6/TAM in pulmonary inflammation and fibrosis could offer novel therapeutic strategies for COVID-19 patients (Table 1).

Summary and outlook

This review focuses on the role of TAM (TYRO3, AXL, and MERTK) in the haematopoietic, immune, fibrotic, and inflammatory systems of the lung. TAM exhibits dual roles in regulating lung cell biology, highlighting its complexity as a highly regulated system. To elucidate TAM's impact on lung disease progression, this review examines its function alongside its ligands, Gas6 and PROS1, in processes such as proliferation and differentiation. It provides a comprehensive analysis of TAM's involvement in four key areas: lung inflammation, fibrosis, tumour development, and COVID-19-related lung injury.

This review highlights that TAM receptors can exacerbate lung inflammation and fibrosis via the Gas6/TAM axis. While MERTK and AXL can collaborate to clear apoptotic cells and limit inflammatory progression, AXL plays a role in lung cancer by driving tumor growth, metastasis, invasion, drug resistance, and epithelial-mesenchymal transition. Mutations in MERTK, abnormal ligand expression, and altered chimeric receptor signalling can activate pro-cancer pathways, enhancing cell proliferation and migration while reducing apoptosis and chemotherapy sensitivity, thereby promoting lung cancer development. Additionally, the co-expression of TYRO3 and protein S is a common feature in most lung cancer cell lines and contributes to tumor progression.

A detailed review of the progress in understanding the mechanism of action of TAM in lung diseases can help identify new therapeutic targets for lung tumor treatment. Inhibition of the TAM signalling pathways has shown promise in lung tumor therapy by blocking the co-expression of AXL and its ligand Gas6, thereby reducing cell adhesion, mitotic activity, and proliferation, which inhibits tumor growth. The AXL-MET axis is a potential therapeutic target for NSCLC patients, as inhibiting AXL expression can reduce EMT-related phenotypic transformation and stabilize the cytoskeleton, thereby inhibiting metastasis, invasion, and drug resistance. Additionally, targeting MERTK, which is selectively demanded by tumor cells, offers a strategy for developing inhibitors, such as ligand traps, monoclonal antibodies, and small molecule tyrosine kinase inhibitors, to inhibit lung tumor occurrence and development. The co-expression of TYRO3 and protein S, a common feature in most lung cancer cell lines, also contributes to tumor development. Furthermore, targeting ACE2 and AXL provides an effective strategy to inhibit the entry of the COVID-19 virus into cells.

TAM inhibitors can restore drug sensitivity, inhibit angiogenesis, reduce lung tumorigenesis and prevent lung tumor formation. Current therapeutic candidates include the dual MERTK/AXL inhibitor compound

Table 1 Study on the mechanism of TAM receptor in various lung diseases

Diseases	TAM receptors	Study type	Subjects	Signal pathway	Main findings	Ref
lung inflammation	AXL	In vivo + In vitro	Rat alveolar epithelial MLE-12 cells	Gas6/Axl/SOCS3	Gas6/Axl signalling activates SOCS3-mediated pathways and attenuates IR-associated inflammation and injury	[74]
		In vivo + In vitro	C57BL/6 J mice, Mouse primary alveolar microparticles, Human T lymphocytes, PBMCs	ROS/ADAM10/AXL	DEX promotes macrophage proliferation through the ROS/ADAM10/AXL signalling pathway, thereby effectively attenuating septic lung injury	[78]
		In vivo + In vitro	Male C57BL/6 wild-type (WT) mice, $Axl^{-/-}$mice, $MerTk^{-/-}$ mice, Colonic macrophage isolation (cMPs), pMPs	–	MerTk and Axl specifically coordinate the clearance of apoptotic cells in different environments and play important roles in lung immune homeostasis, silicosis cell burial and inflammation regulation	[75]
	MERTK					
		In vivo + In vitro	C57BL/$MerTK^{-/-}$mice, B6.129 mice, primary alveolar microparticles	–	The resident alveolar macrophages effectively remove the microparticles released from lung injury through MerTK mediated phagocytosis	[76]
		In vivo + In vitro	C57BL/6 J mice, $Mertk^{-/-}$ mice, human endothelial cells	MERTK/VE—cadherin, MERTK/PECAM—1, MERTK/Rac1	The absence of MERTK in human pulmonary microvascular endothelial cells and all cells in vivo aggravated the inflammatory response. However, selective MERTK depletion of endothelial cells in vivo cannot replicate this response	[77]
lung fibrosis	AXL	In vitro	Multi-potent cells	–	Axl is activated during the proliferation of epithelial cells in idiopathic pulmonary fibrosis, and the integrity of the epithelial barrier is lost	[102]
		In vitro + In vivo	ATII cells treated with BLM, C57BL / 6 $Gas6^{-/-}$ mice treated with BLM	Gas6/AXL	Mouse recombinant Gas6 (rGas6) attenuates pulmonary fibrosis by inhibiting the EMT process and apoptosis of ATII and fibroblast activation	[103]
		In vivo + In vitro	SCID/Bg mice, $Gas6^{-/-}$mice, primary lung fibroblasts	Gas6/TAM/ RTK pathway	Gas6 / TAM receptor activity is involved in the activation of lung fibroblasts in IPF. Targeting the RTK signalling pathway may be an effective anti-fibrosis strategy for the treatment of IPF	[11]
	MERTK	Human body	IPF lung tissue	SPP1/MERTK	Macrophages expressing SPP 1 / MERTK proliferate and promote the activation of IPF myofibroblasts and pulmonary fibrosis	[12]
		In vitro + In vivo	lung macrophages, BLM-induced pulmonary fibrosis mouse model	–	Macrophages overexpressing MERTK have pro-fibrotic functions and eliminate pro-fibrotic effects by down-regulating MERTK through endocytosis	[104]
	TYRO3	In vitro + In vivo	SCID / Bg mice, $Gas6^{-/-}$mice, Primary lung fibroblasts	Gas6/TAM/ RTK pathway	Mediating the pro-fibrotic effects of Gas6 as a means of activating the Gas6/TAM receptor pathway to promote pulmonary fibrosis	[11]

Table 1 (continued)

Diseases	TAM receptors	Study type	Subjects	Signal pathway	Main findings	Ref
lung cancer	AXL	In vitro	SCLC and NSCLC cell lines	–	Axl was co-expressed with Gas6 and was expressed in NSCLC cell line but not in SCLC cell line. The histotypic and phenotypic expression of Axl determines the direction of differentiation of lung cancer cells	[117]
		In vitro	CL1 subline	–	Ectopic overexpression of AXL may lead to enhanced invasiveness and increased drug resistance of lung cancer cells	[17]
		In vitro	NSCLC cell lines with low metastatic (CL1-0) and high metastatic (CL1-5) potentials	Akt1/Rac1	Oxidative stress enhances Axl-mediated cell migration and invasion through an Akt1 / Rac1-dependent mechanism	[15]
		In vitro + In vivo	A549, H1299, H838 and H1975 cell lines, mouse xenograft model	AXL/MET	PFKP binds to AXL to activate the AXL signalling pathway and promotes MET phosphorylation to promote NSCLC progression. Nanoparticles-mediated PFKP silencing reduces cell proliferation, migration, invasion, and colony formation by inhibiting the AXL-MET axis	[129]
		In vitro + In vivo	CD73-silenced stable cell lines, overexpression CD73 cell lines, nude mouse models	CD73 / AXL	CD73 may activate AXL by directly binding to the R55 site of the AXL extracellular region without relying on GAS6 and promote NSCLC metastasis and invasion by regulating epithelial-mesenchymal transition (EMT) through the CD73 / AXL axis	[120]
		In vitro	Tumor samples from NSCLC patients treated with ICI monotherapy	–	AXL expression is associated with aggressive phenotypic traits, and its upregulation and hypermutation regulate the tumor microenvironment, so AXL inhibitors in combination with current chemo-immunotherapeutic regimens could benefit NSCLC patients	[138]
		In vitro	H1299-parental cells, cancer stem cells of human NSCLC cell line H1299 (H1299-sdCSCs)	AXL/ALDH/SLUG	EGCG Inhibits Stemness and Tumorigenicity of Human Lung Cancer Cells by Suppressing AXL	[130]
		In vitro + In vivo	BMDM BALB/c mice	–	Targeting and inhibiting AXL can help tumor-associated macrophages polarize to the M1 phenotype and activate the anti-tumor immunity of macrophages, which can effectively interfere with M2 polarization and its tumor-promoting activity.	[132]
		In vivo + In vitro	Subcutaneous transplantation of NSCLC, in vitro cloning of NSCLC in nude mice	–	Both MERTK and Axl have complementary and overlapping roles in NSCLC, and MERTK or AXL favours tumor cell survival by inhibiting NSCLC cell apoptosis, promoting their growth, and reducing chemosensitivity	[56]

Table 1 (continued)

Diseases	TAM receptors	Study type	Subjects	Signal pathway	Main findings	Ref
	MERTK					
		In vitro	NIH 3T3 cells	–	CSF-1 treatment induced MERTK autophosphorylation, transformed NIH 3T3 cells, and induced lung tumorigenesis	[153]
		In vitro	Human BL-41 lymphoma cells	–	Autooxidation and oligomerization of the apoptotic cell surface protein S are required for Mer tyrosine kinase mediated phagocytosis of apoptotic cells	[150]
	TYRO3	In vitro	NSCLC cell line, SCLC cell line, normal bronchial epithelial cells	–	Co-expression of TYRO3, and anticoagulant protein S, TYRO3 participates in the development or progression of lung cancer by affecting local anticoagulation by binding with anticoagulant protein S or local proliferation or differentiation process	[19]
COVID-19	AXL	In vitro	H1299 cell, BEAS-2B cell	–	AXL is a candidate receptor for SARS-CoV-2 that can mediate viral entry into cells and can promote infection of lung and bronchial epithelial cells	[20]
		Human body	COVID-19 Patient plasma samples	–	Plasma levels of Gas6 and sAXL were associated with COVID-19 severity, which gradually increased with increasing disease severity	[171]
		Human body	COVID-19 Patient plasma samples	–	Serum ACE2 and AXL Levels Correlate with COVID-19 Severity	[167]
	MERTK	Human body	COVID-19 Patient serum samples	–	Elevated Concentrations of Galactaglutinin-3, a Ligand Associated with MERTK and TYRO3 Activation, Promote Fibrosis and Positively Correlate with Markers of Inflammation and Tissue Damage	[170]
	TYRO3					
	TAM receptor	In vivo	$Pros1^{+/-}$ heterozygous mice, $Pros1^{-/-}$ mice	–	Depletion of PROS1 in the blood, which leads to dysfunctional coagulation and allows blood vessels to rupture and bleed due to necrosis, may also reduce TAM ligand levels	[177, 178]
		In vivo	A mouse model of thrombosis	Gas6/TAM	Gas6 enhances platelet degranulation and aggregation through TAM, promotes platelet activation and mediates thrombosis, thereby preventing thrombosis, preventing vascular injury, and repairing endothelium without increasing bleeding	[39]
		In vivo + In vitro	Mice deficient in Gas6, Tyro3, Axl or Mer, wild-type (WT) mice, platelets	Gas6/TAM	ADP-P2Y (12) and Gas6 synergistically activate PI3K and induce TAM receptor signalling to achieve sustained activation of allbb3 and thrombus stability	[38]

43, immune checkpoint inhibitors, EGFR-TKIs, TYRO3-targeted inhibitors combined with checkpoint inhibitors. However, the long-term effects of TAM signalling inhibition on lung disease development remain unexplored, and population-based trials are lacking. There is also a scarcity of research data and statistics needed to translate the theoretical framework into practical applications. Conducting relevant population trials to emphasize TAM's role and impact in lung diseases could lead to more rational treatment strategies, enabling targeted therapy for lung diseases without affecting other cells and tissues.

Abbreviations

ACE2	Angiotensin-converting enzyme 2
AKT	Protein kinase B
AP-1	Activator protein-1
APCs	Antigen-presenting cells
ATII	Alveolar epithelial type II
COPD	Chronic obstructive pulmonary disease
CSF-1	Colony-stimulating factor 1
CTGF	Connective tissue growth factor
DCs	Dendritic cells
DEX	Dexmedetomidine
DUSP6	Dual specificity phosphatases 6
ECM	Extracellular matrix
EGFR	Epidermal growth factor receptor
EGFR-TKI	Epidermal growth factor receptor tyrosine kinase inhibitor
EMT	Epithelial-mesenchymal transition
ERK	Extracellular regulatory protein kinase
FAK	Focal adhesion kinase
FGFs	Fibroblast growth factors
ICIs	Immune checkpoint inhibitors
IPF	Idiopathic pulmonary fibrosis
IR-ALI	Ischemia-reperfusion-induced acute lung injury
M2-TAMs	M2 polarized tumor-associated macrophages
MAPK	Mitogen-activated protein kinase
MDSCs	Myeloid-derived suppressor cells
MEK	Mitogen-activated extracellular signal-regulated kinase
NHBE cells	Normal human bronchial epithelial cells
NK	Natural killer
NKT	Natural killer T
NPs	Nanoparticle System
NSCLC	Non-small cell lung cancer
p38	P38 mitogen-activated protein kinase
PDGF	Platelet-derived growth factor
PFKP	Phosphofructokinase platelet
PI3K	Phosphatidylinositol 3-kinase
PI3Kγ	Phosphatidylinositol 3-kinase gamma
PROS1	Protein S
PtdSer	Phosphatidylserine
RBD	Receptor-binding domain
rGas6	Recombinant Gas6
RTKs	Receptor tyrosine kinases
sAXL	Soluble AXL
TGF-β	Transforming growth factor-β
TLRs	Toll-like receptors
TNF	Tumor necrosis factors
Tregs	Regulatory T cells

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Data availability
Not applicable.

Declarations

Competing interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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