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Molecular Pathways: AXL, a Membrane Receptor Mediator of Resistance to Therapy

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Abstract

AXL is a tyrosine kinase membrane receptor that signals via PI3K, MAPK, and protein kinase C (PKC), among other pathways. AXL has oncogenic potential and interacts with other membrane receptors, depending on their relative abundance and availability. The increased expression of AXL in cancer is often the result of pharmacologic selective pressure to a number of chemotherapies and targeted therapies and acts as a mechanism of acquired drug resistance. This resistance phenotype, frequently accompanied by epithelial-to-mesenchymal transition, can be reversed by AXL inhibition. In tumors with high levels of EGFR, including lung, head and neck, and triple-negative breast cancer, AXL dimerizes with this receptor and initiates signaling that circumvents the antitumor effects of anti-EGFR therapies. Likewise, AXL overexpression and dimerization with EGFR can overcome PI3K inhibition by activating the phospholipase C-γ-PKC cascade that, in turn, sustains mTORC1 activity. The causative role of AXL in inducing drug resistance is underscored by the fact that the suppression of AXL restores sensitivity to these agents. Hence, these observations indicate that AXL is selectively expressed in tumor cells refractory to therapy and that cotargeting AXL in this setting would potentially overcome drug resistance. The use of AXL inhibitors should be considered in the clinic.

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Background

The gene *AXL*, a name derived from the Greek word *anexelekto* ("uncontrolled") was first isolated from chronic myelogenous leukemia, and its overexpression was found to induce fibroblast transformation with simultaneous appearance of a 140-kDa tyrosine-phosphorylated protein (1). AXL is also known as adhesion-related kinase (2), Tyro7 (3), or unknown function (4). AXL belongs to the TAM family of receptor tyrosine kinases (RTK), which also includes Tyro3 and MERTK. TAM receptors have pleiotropic functions in many biologic processes, such as coagulation, immune response, and cancer progression (5). They share among their members 16% to 31% of their extracellular amino acid sequence and 54% to 59% of their intracellular domain (6). Autophosphorylation of the intracellular tyrosine kinase domain of AXL occurs following receptor activation and is mediated either by ligand-dependent or ligand-independent receptor dimerization. Growth arrest–specific protein 6 (Gas6) has been identified as the only ligand that binds the extracellular domain of AXL (7–9). Receptor homodimerization or heterodimerization with other RTKs, such as EGFR (10), results in rapid phosphorylation of AXL and the activation of a number of downstream effectors (see "AXL signaling pathway").

AXL is ubiquitously expressed in a wide variety of tissues, such as brain (hippocampus and cerebellum), heart, liver, and bone marrow (monocytes and macrophages; reviewed in refs. 5, 11). Increased expression of AXL has been reported in several human cancers, including colon, esophageal, thyroid, breast, lung, liver, and astrocytoma–glioblastoma (reviewed in refs. 12, 13).

The AXL receptor regulates fundamental cellular processes, including proliferation, survival, and migration (13). Moreover, AXL was shown to play a pivotal role in enhancing motility and invasiveness of breast (14) and lung cancer cells (15).

AXL signaling pathway

AXL activation initiates the signaling of a number of downstream pathways such as PI3K, MAPK, and PKC (Fig. 1; ref. 16). The phosphorylation of three specific tyrosine residues (Tyr) within the intracellular domain of AXL promotes the recruitment of p85 (the regulatory subunit of PI3K), phospholipase C-γ (PLCγ, the initiator of the PKC cascade), and growth factor receptor–bound protein 2 [Grb2, an adaptor molecule that allows the activation of the MAPK pathway (17)]. Although Grb2 binding seems to be specific for Tyr821, p85 can interact with both Tyr821 and Tyr779, whereas PLCγ can anchor to both Tyr821 and Tyr886 (Fig. 1; ref. 17).

Both ligand-dependent and -independent activation of AXL initiates downstream signaling in several cancer types, including prostate (18), ovarian (19), lung (mesothelioma; ref. 20), and head and neck (21). In turn, these signaling cascades can activate transcription factors regulating cell proliferation and survival. One example is the AKT-mediated destabilization of the IkBα–NF-κB complex, resulting in nuclear shuttling of NF-κB (18) and consequent transcription of antiapoptotic proteins such as cyclin D1, survivin, and focal adhesion kinase (22).

The activation of AXL is negatively regulated by a soluble form of the receptor that directly interacts with Gas6 and reduces ligand availability (23). Mechanistically, soluble AXL acts as a decoy receptor blocking Gas6 binding to membrane-bound TAM receptors and thus preventing AXL activation. A positive correlation between the levels of soluble AXL and membrane-bound AXL was observed in hepatocellular carcinoma (24), suggesting that the detection of soluble AXL could potentially be used as a biomarker to monitor increased AXL expression and emergence of drug resistance overtime. In addition, C1 domain–containing phosphatase and tensin homolog(C1-TEN), a focal adhesion molecule with phosphatase properties and highly similar to PTEN, has been described to interact directly with AXL and negatively regulate the downstream activation of AKT (25, 26). AXL activation and downstream signaling propagation results in enhanced cell motility and invasion by increasing filopodia formation and cell-to-cell interactions (27). This phenotype is mechanistically explained, at least in part, by the AXL-mediated phosphorylation of engulfment and cell motility scaffold protein that, in turn, promotes Rac-mediated cytoskeleton changes, resulting in increased cancer cell migration (28). Accordingly, this is reversed by both AXL and Rac inhibition (29).

AXL expression regulation

Although the regulation of AXL expression remains to be fully elucidated, it is not mediated by genomic amplification (30, 31). Likewise, no hotspot-activating mutations have been reported (30, 31). Overexpression of AXL may occur via alternative mechanisms, including activation of transcription factors, regulation of miRNAs, and posttranslational modifications. Specifically, transcriptional activation mediated by Fos/cJun/AP1 (16, 32), Sp1/Sp3 (33), and YAP1 (34) transcription factors results in increased AXL mRNA expression. AXL is also a direct transcriptional target of the Fos family member transcription factor Fos-related antigen 1 (Fra-1). Fra-1 was described to bind to four different regulatory regions of *AXL*-promoting gene expression (35). This was also confirmed by exogenous expression of Fra-1, which results in AXL upregulation (35). In imatinib-resistant chronic myeloid leukemia cells, the transcription factor activator protein 1 (AP-1) seems to be required for AXL overexpression, as the promoter activity of AXL is almost completely abolished when carrying a mutation on its AP1-binding site (16). AXL expression may also be regulated by miR-34a and miR-199a/b, which target the 3′-UTR of the *AXL* gene (36–38). In non–small cell lung (NSCLC), breast, and colorectal cancers, for example, high levels of AXL can result from low expression of these miRNAs, which are suppressed by promoter methylation (36).

AXL protein levels can also depend on its stability. Receptor ubiquitination mediated by the Casitas B-lineage lymphoma (Cbl) E3 ubiquitin ligases can regulate the abundance of AXL in several cells (39, 40). Likewise, increased AXL half-life by impaired degradation of the receptor can occur in lung cancer cell lines, resulting in the net increase of AXL levels (41).

Clinical–Translational Advances

Targeted therapy frequently results in a rapid increase of RTK expression that can compensate for the acute inhibition of a specific signaling pathway. In breast cancer, for

example, HER3 is often overexpressed as a result of PI3K/AKT inhibition (42–44), whereas increased expression and activity of EGFR plays a pivotal role in limiting the efficacy of BRAF inhibition in colon cancer (45, 46). These occurrences do not require genomic amplification, are versatile (not specific for a tumor type or a treatment), and inevitably result in the activation of downstream effectors that can oppose the pharmacologic pressure. The net result is either activation of parallel signaling or reactivation of the suppressed pathway, both of which overcome the pharmacologic pressure.

Increased AXL expression has been correlated with resistance to both antimitotic drugs and targeted agents. In AML, AXL was the only RTK overexpressed in cells from 4 patients that progressed on chemotherapy. Consistently, cell lines intrinsically resistant to chemotherapy express higher levels of AXL, and the chemotherapy exposure is sufficient to induce the expression of AXL (47). A similar effect is observed in NSCLC cell lines, with acquired resistance to cisplatin *in vitro*. Refractoriness to cisplatin coincided with induction of AXL expression, transcriptional changes compatible with epithelial-to-mesenchymal transition (EMT), and partial resistance to the EGFR kinase inhibitor gefitinib (48). EMT is a conserved transdifferentiation process that many tumor cell types undergo during cancer evolution (49). It is caused by a complex transcription rewiring that results in the acquisition of mesenchymal properties and nonspecific drug resistance. A recent report confirmed the association between induction of EMT and increased AXL expression but concluded that EMT-associated drug resistance is independent of AXL function (50). Nonetheless, these data indicate that AXL inhibition sensitizes mesenchymal cells to antimitotic agents, such as docetaxel or aurora kinase and polo-like kinase 1 inhibitors, both *in vitro* and *in vivo*. This finding is in contrast with another report showing that the overexpression of AXL is sufficient to induce EMT directly in breast cancer cells and that AXL suppression can reverse this phenotype (51). Overall, there is consensus in ascribing to AXL a central role in leading to transcriptional changes related to EMT.

In terms of resistance to RTK inhibitors, although AXL can also interact with HER2 (52) and HER3 (53), EGFR seems to be the strongest dimerization partner of AXL in several tumor types. AXL interacts and dimerizes with EGFR in lung (54), triple-negative breast cancer (10), and head and neck squamous cell carcinomas (21, 32). In accordance, overexpression of AXL has been shown to be sufficient to limit the sensitivity to anti-EGFR therapy in several models, both *in vitro* and *in vivo* (10, 32, 38, 55, 56). In particular, AXL overexpression and activation, accompanied by EMT-associated transcriptional changes, was observed in EGFR-mutant lung cancer xenografts that acquired partial resistance to the EGFR kinase inhibitor erlotinib *in vivo* (54). The causative role of AXL in inducing this phenotype was demonstrated by the facts that exogenous expression of AXL was sufficient to induce partial resistance to erlotinib in parental erlotinib-sensitive cells and that AXL inhibition restored erlotinib sensitivity in the resistant xenografts. In head and neck cancer cells, overexpression of AXL and its dimerization with EGFR can maintain EGFR activation and signaling even in the presence of the EGFR blocking antibody cetuximab (32). In these cells, AXL overexpression and dimerization with EGFR also results in acquired resistance to α isoform–specific PI3K inhibition, both *in vitro* and in animal models (21). In this case, the mechanism of resistance involves the engagement of a parallel signaling cascade (PLCγ-

PKC) that compensates for PI3K/AKT inhibition via downstream parallel mTORC1 activation.

As mentioned, AXL can also interact with HER2 in $HER2^+$ breast cancer cells. In this context, AXL–HER3 dimerization bypassed HER2 signaling inhibition and provided the rationale to combine lapatinib, a small-molecule HER2 kinase inhibitor, with an AXL kinase inhibitor (53). Another plausible combinatorial strategy is the simultaneous suppression of AXL and the MAPK pathway in melanoma. In this case, AXL suppression seems to be important in cell lines/human tumors with low levels of microphthalmia-associated transcription factor and high levels of AXL, a cell state associated with acquired resistance to MAPK pathway inhibition (57, 58). These findings support the clinical development of AXL inhibitors in cancer in combination with targeted agents (EGFR, HER2, and PI3K inhibitors) at the time of acquired resistance and high AXL levels. Similarly, AXL inhibitors could be tested upfront if AXL overexpression is detected earlier in the course of the disease. In Table 1, we list the AXL inhibitors currently being developed in the laboratory, in animal models, and in the clinic.

In summary, the available data suggest that overexpression of AXL may be restricted to cells that are, or more frequently become, refractory to either chemotherapy or targeted therapy. Its suppression may revert the drug-resistant phenotype, either by reversing EMT or blunting the activation of a compensatory pathway that limits therapy effectiveness.

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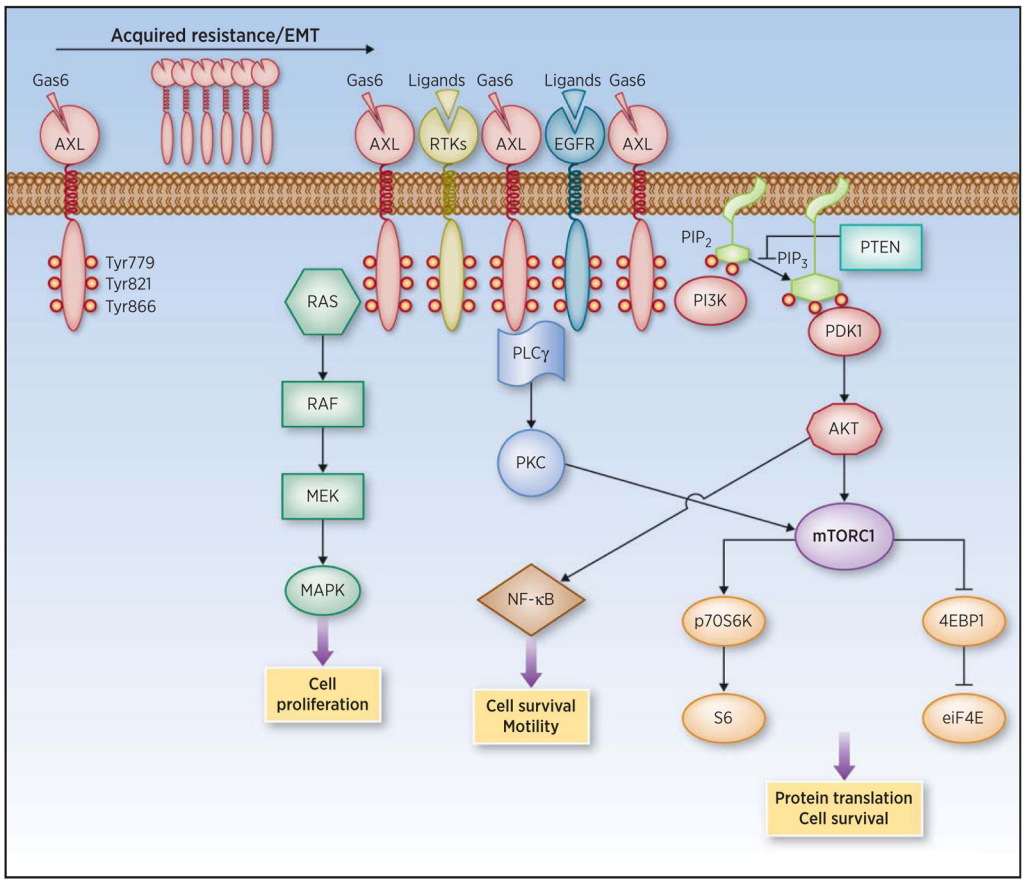

Figure 1.

AXL overexpression and activation of downstream signaling pathways. AXL is overexpressed upon acquisition of therapy resistance and can induce epithelial-to-mesenchymal transition (EMT). It dimerizes with RTKs present in the membrane of tumor cells to initiate signaling cascades that ultimately lead to increased cell motility and survival.

Table 1

Anti-AXL agents currently in preclinical or clinical development

Company	Compound	Target(s)	Indication	Clinical status
Servier	S49076 (kinase inhibitor)	MET, AXL, FGFR1/2/3	Advanced solid tumors	Phase I 2013-003079-37
Mirati Therapeutics Inc.	MGCD516 (kinase inhibitor)	MET, AXL, and members of the VEGFR, PDGFR, DDR2, TRK, and Eph families	Advanced solid tumors	Phase I NCT02219711
Mirati Therapeutics Inc.	MGCD265 (kinase inhibitor)	MET/AXL	Advanced malignancies	Phase I NTC00697632
Betta Pharmaceuticals Co., Ltd	BPI-9016M (kinase inhibitor)	MET/AXL	Advanced solid tumors	Phase I NCT02478866
BerGenBio AS	BGB324 (R428; kinase inhibitor)	AXL	NSCLC and AML	Phase I/II NCT02488408 NCT02424617
Tolero Pharmaceuticals and Astex Pharmaceuticals	TP-0903 (kinase inhibitor)	AXL	Pancreatic cancer, lung cancer	Preclinical

Abbreviations: AML, acute myelogenous leukemia; DDR, discoidin domain receptor; Eph, ephrin; FGFR, fibroblast growth factor receptor; PDGFR, platelet-derived growth factor receptor; TRK, tropomyosin receptor kinase.