Function of Axl receptor tyrosine kinase in non-small cell lung cancer (Review)

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Abstract. Axl receptor tyrosine kinase (hereafter Axl) is a member of the tyrosine-protein kinase receptor Tyro3, Axl and proto-oncogene tyrosine-protein kinase Mer family of receptor tyrosine kinases, possessing multiple different functions in normal cells. Axl is overexpressed and activated in numerous different human cancer types, triggering several signaling pathways and enhancing tumor progression. The present review assesses previous studies on the function of Axl in non-small cell lung cancer (NSCLC). Axl is overexpressed in the tumor tissues of a number of patients with NSCLC and is associated with poorer clinical outcomes; it promotes NSCLC tumor growth, invasion/metastasis, drug resistance and the epithelial-mesenchymal transition, thus providing a survival advantage to tumor cells. Therefore, Axl may be a promising target in NSCLC treatment.

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1. Introduction

Axl receptor tyrosine kinase (hereafter Axl) is a member of the tyrosine-protein kinase receptor Tyro3 (hereafter Tyro3), Axl and proto-oncogene tyrosine-protein kinase Mer (hereafter Mer) (TAM) family of receptor tyrosine kinases (RTKs) (1). The TAM family is distinguished from other RTKs by a conserved sequence, KW(I/L)A(I/L)ES, within the kinase domain and two immunoglobulin (Ig)-like domains plus two fibronectin type III domains, which comprise nearly the entire ectodomain of each family member (1,2). In adult tissues, Tyro3, Axl and Mer are widely distributed (1), and have notable functions in tissue repair, clearance of apoptotic material and immune regulation (1,3-5). TAM receptors were initially considered to be orphan receptors (6); however, it has since been revealed that there are diverse ligands for this family of receptors (6-10). Growth arrest-specific 6 (Gas6) and protein S were identified to be ligands for TAMs in the 1990s (6,7). These proteins are members of the vitamin K-dependent protein family, and demonstrated significant homology with each other (8). Gas6 binds to all three TAM RTKs (Axl>Tyro3>Mer), whereas protein S interacts with Mer and Tyro3, but not Axl. Previously, tubby, tubby-like protein 1 (Tulp-1) and galectin-3 have been revealed to be ligands for TAM receptors, and Tulp-1 binds to all three RTKs with differing levels of affinity, whereas tubby only binds to Mer (9,10).

The name Axl is derived from the Greek word anexelektos, which means 'uncontrolled'. The human Axl gene is located on chromosome 19q13.2 and has 20 exons (11). It was originally identified as a transforming gene in the cells of patients with chronic myelogenous leukemia (12) and had transforming potential when overexpressed in NIH/3T3 fibroblasts (13,14). As with other RTKs, Axl is composed of an extracellular domain, a transmembrane domain and an intracellular domain. A soluble Axl has also been reported (15), which may possess a diagnostic value for early-stage hepatocellular carcinoma (16). Axl is ubiquitously expressed in human tissues (1,17), with notable levels identified in the kidney (1,18), brain (19), heart (1), testis (1), skeletal muscle (1), liver (1,20), endothelial cells (21,22), monocytes/macrophages (23) and platelets (24). This wide expression pattern of Axl indicates that this protein exerts a notable function in normal cell function, including cell survival, proliferation, migration and adhesion (17). However, usually, more than one TAM receptor is expressed in a given cell type simultaneously that may be activated by one common ligand; for example, all three TAM members may be activated...
by Gas6 (25), thus making it difficult to elucidate the function of Axl on its own in one cell type.

2. Axl activation and signaling

Axl is activated by Gas6. The activation of RTKs involves ligand binding to the extracellular domain, which induces receptor dimerization and subsequent trans-autophosphorylation of the tyrosine residues within the cytoplasmic domain (2). Axl is activated by the binding of its ligand Gas6, which was identified as the ligand for Axl in 1995 by two separate studies (6,7). Prior to that, the Gas6 gene was first identified as one of several genes to be upregulated in NIH/3T3 fibroblasts under serum starvation-induced growth arrest (26). Gas6 was later revealed to be a common ligand for Axl, Tyro3 and Mer, with Axl possessing the highest affinity for Gas6 (3). Gas6 is widely expressed and has been identified in the lung, heart, kidney, intestine, endothelial cells, bone marrow, vascular smooth muscle cells and monocytes and at low levels in the liver and human blood plasma (27). It has cell-type-specific functions, including platelet aggregation and hematopoiesis, proliferation, survival and phagocytosis.

Gas6 possesses an N-terminal region containing a modified γ-carboxyglutamic acid (Gla) residue, which has the ability to interact with negatively charged membrane phospholipids to mediate the binding of Gas6 to apoptotic cells. The Gla domain is followed by a loop region, four epidermal growth factor (EGF)-like repeats and a C-terminal sex-hormone-binding globulin (SHBG)-like structure that is composed of two globular laminin G-like domains (28). The SHBG domain binds directly to the Ig domains of Axl, which results in the formation of a Gas6/Axl complex with a 1:1 ratio (29). The lateral diffusion of these complexes would then result in the formation of a minimal 2:2 Gas6/Axl signaling complex, which induces activation of Axl (29). Additionally, the γ-carboxylation of Gas6 and anionic phospholipids, including the externalized phosphatidylserine on apoptotic cells and enveloped viruses, possesses vital functions for the activation of Axl (3,30,31).

Atypical activation of Axl. In addition to conventional activation, atypical activation of Axl has been reported, including activation by crosstalk between receptors (1). Meyer et al (32) revealed that EGF receptor (EGFR) activation associated with Axl and EGF stimulation may activate Axl through EGFR in triple-negative breast cancer cells. In non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC) (33,34) and esophageal squamous cell carcinomas (ESCC) cells (34), this physical association between Axl and EGFR was also observed. This interaction has the potential to activate EGFR (33,34) and Axl (32,33). The ability of Axl to form complexes with other RTKs may make certain cancer types resistant to tyrosine kinase inhibitors (TKIs), as will be discussed further in the present review.

Three tyrosine residues, Y-779, Y-821 and Y-866, within the C-terminal domain of Axl have been proposed as potential autophosphorylation sites and putative docking sites for a variety of signaling proteins (1), including the p85α and p85β subunits of phosphatidylinositol 3-kinase (PI3K) (35,36), growth factor receptor-bound protein 2 (25,26), phospholipase Cγ (PLCγ) (36), c-src and lck (36) (Fig. 1). Additionally, the engulfment and cell motility (Elmo) scaffold protein has been reported to directly interact with Axl, and serves vital functions in Axl-induced breast cancer invasion (37). Notably, mutation of the three tyrosine residues did not abrogate the Axl-Elmo2 association, indicating that other docking sites may exist (37).

Activation of Axl regulates a number of signal transduction pathways, depending on the cell types in question, primarily PI3K/protein kinase B (Akt) and mitogen-activated protein kinase (MEK)/extracellular-signal-regulated kinase (ERK), nuclear factor-κB (NF-κB), signal transducer and activator of transcription 3 (STAT3) (17,38,39) [references (1,3,17,40) contain further information on Axl signaling]. The activation of
Table I. Axl expression and clinical significance in NSCLC.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Tumor type (n)</th>
<th>Axl expression frequency</th>
<th>Clinical significance</th>
<th>Methods of evaluation of results</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shieh et al, 2005</td>
<td>AC (58)</td>
<td>48.3% (28/58)</td>
<td>Axl protein expression was significantly associated with lymph node involvement and clinical stage.</td>
<td>Staining results were classified into positive (&gt;25%) and negative (&lt;25%) categories.</td>
<td>(53)</td>
</tr>
<tr>
<td>Linger et al, 2013</td>
<td>NSCLC [88, including SCC (37), AC (39), LCUC (7), BAC (5)]</td>
<td>93.2% (82/88)</td>
<td>Axl expression was not associated with overall patient survival and did not differ significantly by stage or histology.</td>
<td>An H-score was calculated for each specimen by multiplying the percentage of positive tumor cells (0-100%) by the dominant staining intensity (scale 0-4). An H-score ≥5 was considered positive.</td>
<td>(41)</td>
</tr>
<tr>
<td>Ishikawa et al, 2013</td>
<td>AC (88)</td>
<td>33.0% (29/88)</td>
<td>Higher expression of Axl protein was significantly associated with worse clinicopathological features (lymph node metastasis) and prognosis (overall survival and disease-free survival).</td>
<td>Staining intensity was graded as 0 (no staining), 1 (weak), 2 (moderate), or 3 (strong), and percentage of positive cells was graded as 0 (negative), 1 (&lt;10%), 2 (11-50%), 3 (51-80%), or 4 (&gt;80%). The final IHC score was obtained by multiplication of the two grading results. A score &gt;7 was considered to be Axl IHC high.</td>
<td>(52)</td>
</tr>
<tr>
<td>Iida et al, 2014</td>
<td>AC (112)</td>
<td>59.8% (67/112)</td>
<td>Phosphorylated Axl expression is significantly associated with larger tumor size and with overall survival of the patients.</td>
<td>Status of immunoreactivity was classified into three groups: Negative, weakly positive and markedly positive.</td>
<td>(42)</td>
</tr>
<tr>
<td>Wu et al, 2015</td>
<td>AC (109)</td>
<td>55.0% (60/109)</td>
<td>Axl expression was significantly associated with lymph node metastasis.</td>
<td>Intensity was scored from 0 to 3+: 0, no staining; 1+, weak staining; 2+, moderate staining; 3+, strong staining. Scores representing the proportion of positively stained tumor cells were graded as follows: 0, no positive tumor cells; 1, &lt;10%; 2, 10-50%; and 3, &gt;50%. The staining index was scored by multiplying the percentage of positive cells by the intensity. A staining index score of ≥1 was considered positive staining. Proportion of positive cells (&lt;30%, 1 point; 30-60%, 2 point; &gt;60%, 3 points) and the color of staining (colorless or light yellow, 1 point; yellow, 2 points; brown, 3 points). The final scores were obtained by multiplying the two integrates and were used to determine the following classifications: 1-2, negative expression; 3-9, positive expression.</td>
<td>(54)</td>
</tr>
<tr>
<td>Qu et al, 2015</td>
<td>NSCLC (134)</td>
<td>54.5% (73/134)</td>
<td>Axl expression was significantly associated with differentiation and TNM stage of NSCLC. Axl expression was an independent risk factor for poor prognosis according to univariate Cox regression analysis.</td>
<td></td>
<td>(85)</td>
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NSCLC, non-small cell lung carcinoma; AC, adenocarcinoma; SCC, small cell carcinoma; LCUC, large-cell undifferentiated carcinoma; BAC, bronchioalveolar carcinoma; IHC, immunohistochemistry; TNM, tumor-node-metastasis.
these pathways elicits different responses in different cells, including cell proliferation, migration or survival (3,17) (Fig. 1).

3. Function of Axl in NSCLC

Axl is overexpressed in a subset of NSCLC, and is associated with poorer clinical outcomes. The expression of Axl and Gas6 in normal lung cells is not well documented. Studies aimed at detecting Axl expression in lung cancer cells demonstrated that Axl is not expressed in normal lung alveolar cells or the bronchial epithelium adjacent to a tumor (41,42). Axl is expressed in lung airway macrophages, but not interstitial macrophages and other lung leukocytes under homeostatic conditions and is constitutively ligated to Gas6 (43). Axl was believed to serve notable functions in mediating immune homeostasis through the clearance of apoptotic cells during inflammation (43) and promoting an antiviral response through maintaining the appropriate production of type I interferon (44). Axl and Gas6 are also expressed in the blood endothelial cells of lung (45), in which they maintain the integrity of the vasculature and vascular remodeling under pathological conditions (27).

Axl is expressed in NSCLC, with expression rates varying from ~33.0 to ~93.2% detected by different groups (Table I). This inconsistency may be caused by different Axl antibodies used, and different evaluation methods. The varying clinicopathological characteristics of patients with NSCLC studied may also contribute to this inconsistency. These studies suggest a number of patients with NSCLC express Axl, and it may be associated with a poorer prognosis. Consistently, patients with NSCLC that exhibit high Axl mRNA expression had a shorter disease-free survival time than patients exhibiting low Axl mRNA expression (46).

Axl and tumor growth in NSCLC. Similar to other RTKs, Axl overexpression may provide survival and growth advantages to tumor cells (3). In NSCLC cell lines, the small interfering RNA (siRNA)-mediated downregulation of Axl results in decreased cell growth in vitro and in xenograft mouse models (41,47), in addition to the suppression of Akt and ERK activation (34). Similarly, the proliferation of H226 cells, which express moderate levels of Axl, may be suppressed by the anti-Axl monoclonal antibody MAb173 or the specific Axl inhibitor R428 (33). These studies indicate that Axl is involved in maintaining the proliferation of NSCLC cells.

Axl and the epithelial-mesenchymal transition (EMT) in NSCLC. EMT is a process by which epithelial cells lose their cell polarity and cell-cell adhesion, and gain mesenchymal cell-like migratory and invasive properties (48). Axl is recognized as having vital functions in NSCLC EMT. Firstly, Axl is a marker for the mesenchymal phenotype in NSCLC. From the RNA-sequencing data of 643 cancer cell lines, including NSCLC, Axl expression was markedly associated with a mesenchymal phenotype (49). It was further revealed that in 45 NSCLC cell lines, higher Axl protein expression tends to be associated with a higher protein expression of vimentin, a mesenchymal marker (49). Similarly, Axl expression was higher in NSCLC mesenchymal cancer cells than in epithelial cancer cells, based on the mRNA expression profile of 54 NSCLC cell lines and the protein expression data of 49 patients with NSCLC (50).

Furthermore, in the transforming growth factor β-induced EMT model, Axl is upregulated, similar to vimentin (49). In addition, Axl aids the maintenance of the EMT state in NSCLC cells. A549 and H460 are mesenchymal NSCLC cells (50); in these cell lines, Axl downregulation results in the increased expression of E-cadherin and decreased expression of vimentin and N-cadherin, which are features of the reverse of EMT (47).

Axl and NSCLC invasion and migration. Patients with cancer that have solid tumors primarily succumb to mortality due to metastatic lesions rather than from the primary tumors (51). Axl has been implicated in metastasis in multiple tumor types (3). In patients with NSCLC, Axl expression is associated with lymph node metastasis (52-54). Cisplatin- and gefitinib-resistant HCC4006 cells express high levels of Axl, and siRNA-mediated Axl downregulation suppressed the migratory capacity of these cells (55). Lay et al (56) established a series of cell lines with different invasive abilities by the selection of increasingly invasive cancer cell populations from a cell line of human lung adenocarcinoma (CL1-0) using a Transwell invasion chamber assay. It was revealed that Axl expression was highly associated with the migratory ability of these cell lines. NF-kB signaling was responsible for Axl-enhanced migration, with its suppression blunting Axl-induced migration. Huang et al (57) additionally reported that Axl mediates H2O2-induced migration by activating PI3K/Akt/Ras-related C3 botulinum toxin substrate 1 signaling. Furthermore, the first Ig-like domain and the intracellular domain were vital for the function of Axl in these two models. These studies indicated that Axl may not only activate migration-promoting signals itself, but additionally mediate the effect of other molecules to increase migration. Mechanistically, Axl increases the expression of matrix metalloproteinase-9 (MMP9) and MMP2, which promote tissue remodeling and cancer invasion (58-61). Additionally, as discussed above, Axl promotes the EMT of cancer cells (62,63), a process associated with migratory and invasive properties (48). Axl has also been associated with invasion through the modification of the cytoskeleton regulator Rac (37,57,64), leading to cytoskeletal reorganization and increased migration and invasion.

Axl and cancer drug resistance in NSCLC. Drug resistance is the main reason for the failure of cancer treatments. Axl serves a notable function in the drug resistance of a number of different cancer types (34,65-67); its function in NSCLC drug resistance has been studied intensively (68). Evidence is primarily derived from in vitro cell line studies (Table II), with limited data from mouse models (33,69) and the tumor tissues of patients with cancer (69,70) (Table III). Thus, these results may require further confirmation, particularly in human tumors in vivo.

The majority of cell line-based studies use drug-resistant cells, obtained by the long-term treatment of cancer cells with increasing doses of drugs, and such studies have revealed that Axl is upregulated in drug-resistant cancer cells (Table II). One study additionally revealed that suppression of Axl with genomic or pharmaceutical methods may restore the sensitivity of cancer cells to drugs, further informing on the function of Axl in these drug-resistant models (69). Other studies downregulated Axl expression in Axl-overexpressed NSCLC cancer
Table II. Cell line-based evidence on Axl upregulation being an independent mechanism of non-small cell lung carcinoma drug resistance.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Models used</th>
<th>Main results</th>
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<td></td>
<td>In vitro cell line models</td>
<td>In vivo models</td>
</tr>
<tr>
<td>Choi et al, 2015</td>
<td>HCC827</td>
<td>-</td>
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<tr>
<td>Bae et al, 2015</td>
<td>H292</td>
<td>-</td>
</tr>
<tr>
<td>Yoshida et al, 2014</td>
<td>PC9</td>
<td>-</td>
</tr>
<tr>
<td>Wu et al, 2014</td>
<td>H462, A549</td>
<td>-</td>
</tr>
<tr>
<td>Wang et al, 2014</td>
<td>HCC827</td>
<td>-</td>
</tr>
<tr>
<td>Brand et al, 2014</td>
<td>H226 Mouse models</td>
<td>Mouse models</td>
</tr>
<tr>
<td>Linger et al, 2013</td>
<td>A549</td>
<td>-</td>
</tr>
<tr>
<td>Kim et al, 2013</td>
<td>H2228</td>
<td>-</td>
</tr>
<tr>
<td>Zhang et al, 2012</td>
<td>HCC827, PC9 Mouse models</td>
<td>Erlotinib</td>
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siRNA, small interfering RNA.
cells, including A549 and H462, to survey the change of the half maximal inhibitory concentration of cancer cells to drugs, and it was observed that the silencing of Axl enhanced the sensitivity of cancer cells to drugs, including several chemotherapeutic drugs and erlotinib (41,47). Zhang et al (69) used a combination of strategies, including mouse models and matched NSCLC tumor tissues (tissues from the same patient prior to treatment and following the development of drug resistance), providing convincing evidence supporting the involvement of Axl in the mechanisms underlying NSCLC EGFR TKI resistance, and that targeting this molecule may restore the sensitivity of resistant cells. Similarly, Brand et al (33) used several differing strategies, including the ectopic overexpression of Axl, siRNA-mediated downregulation of Axl and mouse models, to demonstrate that Axl serves a notable function in NSCLC resistance to cetuximab, a chimeric monoclonal antibody targeting EGFR. In addition to the work of Zhang et al (69), Ji et al (70) provides further evidence using the tumor tissue of patients with NSCLC demonstrating that Axl upregulation is an independent mechanism of NSCLC resistance to EGFR-TKI (Table III).

A detailed mechanism for Axl-mediated drug resistance is yet to be elucidated. However, a number of studies have provided notable information. As previously discussed, the overexpression of Axl is linked to EMT status, which was associated with drug resistance (71,72). Additionally, Axl impedes therapeutically induced apoptosis by exerting anti-apoptotic effects by modulating the expression or activation of apoptosis regulators, including B-cell lymphoma extra large, survivin (41), B-cell lymphoma-2 (Bcl-2) associated agonist of cell death (73), Bh3 interacting-domain death agonist (74) and Bcl-2 (75). Additionally, a number of previous studies have suggested that the ability of Axl to form complexes with other RTKs may be one key aspect of this function. Cetuximab-resistant NSCLC cell line H226 cells exhibited upregulation of Axl signaling, which was further elucidated to form a physical complex with EGFR (33). Furthermore, treatment with EGFR or tumor necrosis factor resulted in H226 cells resistant to cetuximab, with the formation of a physical complex between Axl and EGFR, similar to that in resistant cells. This indicates that the Axl-EGFR complex serves a role in eliciting a drug-resistant phenotype of cancer cells. These studies further demonstrated that Axl and EGFR were involved in maintaining the growth of these resistant cells. Additionally, silencing the expression of either Axl or EGFR with siRNA decreased the growth of these cells. The Axl-EGFR complex was also observed in other drug resistant cancer models. For example, as mentioned above, HNSCC and ESCC cells induced to be resistant to PI3K inhibitor BYL719 additionally displayed this Axl-EGFR complex (34). In sensitive parental cells, EGFR activated the PI3K/Akt pathway, which maintained mechanistic target of rapamycin (mTOR) activity (76). In resistant cells, the Axl-EGFR complex activated PLCγ-protein kinase C (PKC) signaling, which in turn activated mTOR (76). Thus, tumor cells became less dependent on PI3K/Akt signaling and resistant to PI3K inhibitor BYL719. Combining BYL719 and R428 may reverse the resistant phenotype. This complex additionally formed in breast cancer cells, and Axl in this complex amplified and diversified EGFR signaling (32). Thus, it may be that this complex increased the resistance of cancer cells to EGFR inhibitors and that the suppression of Axl may enhance the efficacy of EGFR inhibitors. Further studies revealed that the suppression of Axl activation with R428 significantly increased the killing ability of erlotinib (32). Furthermore, Wu et al (54) revealed that Axl and EGFR are co-expressed in a subset of NSCLC tumor tissues. This may allow this complex to form readily, promoting drug resistance. Other receptors, including human epidermal growth factor receptor 2 (HER2), HER3, MET proto-oncogene and platelet-derived growth factor receptor-β have been reported to be associated with Axl (32). This association of Axl with other receptors may have implications for targeted therapies, as these complexes may change the response of RTKs to TKIs, or make cancer cells less dependent on the signaling pathways that were targeted (34), which may result in cancer cells resistant to TKIs.

Table III. Patient tumor tissue-based evidence to demonstrate that Axl upregulation is an independent mechanism of NSCLC drug resistance.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Tumor tissues description</th>
<th>Patients, n</th>
<th>Main results</th>
<th>(Refs.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang et al, 2012</td>
<td>Matched EGFR mutant NSCLC specimens obtained prior to treatment with EGFR TKIs erlotinib or gefitinib and following the development of resistance to these compounds.</td>
<td>35</td>
<td>Compared with the treatment-native tumor tissues, a higher expression level of Axl and Gas6 were detected in 7/35 (20%) and 7/28 (25%) of TKI-resistant tissues, respectively.</td>
<td>(69)</td>
</tr>
<tr>
<td>Ji et al, 2013</td>
<td>Matched EGFR mutant NSCLC specimens obtained prior to treatment with EGFR TKIs erlotinib or gefitinib and following the development of resistance to these compounds.</td>
<td>26</td>
<td>Increased Axl expression was observed in 5/26 (19.2%) of patients with TKI-resistant NSCLC.</td>
<td>(70)</td>
</tr>
</tbody>
</table>

NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor; EGFR, epidermal growth factor receptor; Gas6, growth arrest-specific 6.
4. Conclusion

Axl is a promising therapeutic target, considering that it serves notable functions in NSCLC tumor growth, EMT, invasion and drug resistance. A number of Axl inhibitors have been developed and a number are in clinical trials, including foretinib (XL880, GSK1363089), cabozantinib, crizotinib, ASLAN002 and BGB324 (R428) (3.78–81). It is important to note that although a wide range of Axl kinase inhibitors have been described, a majority of them are nonspecific multi-kinase inhibitors. BGB324 (R428) was the first selective Axl inhibitor to be developed (82). Oral treatment with BGB324 (R428) in mouse xenograft models revealed that it reduced breast cancer metastasis and prolonged survival. It entered phase 1 clinical trials in 2013 (83). At present, clinical trials including patients with melanoma, NSCLC and acute myeloid leukemia are ongoing to determine the safety and efficiency of BGB324 (https://clinicaltrials.gov/ct2/results?cond=&term=BGB324&ctry=1&state= &Search=Search). The identification of appropriate biomarkers for the selection of patients is another key issue for the development of Axl-targeted therapies. Immunohistochemistry appears to be the most feasible strategy for identifying appropriate biomarkers, with other strategies including the detection of Axl expression in vivo by single-photon emission computed tomography imaging using a 125I-labeled Axl antibody (84). With the development of AXL inhibitors, and an increase in the understanding of the underlying molecular mechanisms responsible for NSCLC, patients who are suitable for AXL-targeted therapies could be screened and treated with this form of therapy.

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References


