AXL Receptor in Breast Cancer

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Breast cancer was one of the first malignancies to benefit from targeted therapy, i.e., treatments directed against specific markers. Inhibitors against HER2 are a significant example and they improved the life expectancy of a large cohort of patients. Research on new biomarkers, therefore, is always current and important. AXL, a member of the TYRO-3, AXL and MER (TAM) subfamily, is, today, considered a predictive and prognostic biomarker in many tumor contexts, primarily breast cancer. Its oncogenic implications make it an ideal target for the development of new pharmacological agents; moreover, its recent role as immune-modulator makes AXL particularly attractive to researchers involved in the study of interactions between cancer and the tumor microenvironment (TME). All these peculiarities characterize AXL as compared to other members of the TAM family.

AXL breast cancer biomarker

1. Introduction

In the oncological field, therapeutic scenarios are multiple and have evolved considerably in recent years. Unspecific treatments, such as chemotherapy, have given way to the new pharmacological frontiers of targeted therapy and immunotherapy. The discovery of new molecular targets and the well-established evidence of the tight interconnection between tumor cells and the microenvironment have revolutionized the clinical management of patients. Human epidermal growth factor receptor 2 (HER2) or estrogen receptor and (ER)/PROGESTERONE RECEPTOR (PR)-positive tumors have benefited from targeted treatments, but particularly aggressive forms have yet to find the optimal therapeutic approach. For example, for triple-negative breast cancer (TNBC), the research for new biomarkers is always open. AXL, especially in this molecular background, performs many oncogenic functions and is considered a potential marker in which to invest. However, although a great amount of evidence confirms that AXL is a key element of breast cell tumorigenesis, its clinical implications are still limited. Many inhibitors currently in use are multi-targets, and AXL's selective inhibitors are still in pre-clinical trials. Therefore, the necessity to better explore the molecular implications of AXL and its involvement in the immune response becomes even more important in order to develop its selective and effective molecules.

Currently, breast cancer is the second leading cause of oncological death in the female population globally and represents about 30% of invasive tumors in women [1][2]. Although significant advances have been made in the treatment of this pathology, phenomena such as metastasis and drug resistance still remain unresolved. Indeed, even if targeted therapy and immunotherapy have greatly improved the life expectancy of many patients, they have

not bypassed these problems at the basis of many cancer deaths. The use of high performance “omics” technologies, in recent years, has accelerated the identification of new molecular targets able to perform the dual function of predictive and/or prognostic factors [3]. Moreover, an extensive study of the biomarkers’ action mechanisms is desirable to allow the development of new inhibitors.

In recent years, it has emerged that receptor and non-receptor tyrosine kinases (TKs) are often overexpressed/mutated in many tumor models, including breast cancer, representing a possible molecular target in clinical cancer therapy [4]. TKs are a big family of proteins that perform a mediator role between the inside and outside of cell. Their activation regulates cell differentiation, proliferation, apoptosis and metabolism [5][6][7]. Receptor TKs (RTKs) include 20 families classifiable according to amino acid sequence within the kinase domain and structural analogism within extracellular regions [8][9][10]. The ligand/receptor interaction triggers a biochemical reaction cascade that culminates in tyrosine residue phosphorylation on different substrates [9]. RTKs’ subfamily is composed of TYRO-3 (or Sky), AXL (or UFO) and MER (or Eyk, Nym and Tyro12) (TAM) receptors, essentially formed by an extracellular region and a cytoplasmic kinase domain. Growth arrest-specific 6 (GAS6), protein S1 (PROS1), Tubby, Tubby-like protein 1 (TULP-1) and Galectin-3 are the most important ligands of TAMs [11][12]. Despite its highest affinity to AXL, GAS6 recognizes and binds TYRO-3 and MER also, while PROS1 seems to interact only with TYRO-3 and MER [12][13]. Moreover, TULP-1 binds all three TAM receptors and Tubby and Galectin-3 only recognize MER [14][15][16]. TAM receptors are overexpressed in several human malignancies, including leukemia, melanoma, breast, lung, gastric and colon cancers, promoting upregulation of pro-survival pathways [17][18]. All members of the TAM family are involved in the development and progression of different forms of cancer, such as lung and colon tumors [19][20]; however, in the genesis of the breast cancers, AXL is particularly involved; indeed, in this tumor context, it results often dysregulated and its overexpression is associated to unfavorable outcomes for patients. In addition, AXL contributes to all stages of malignant breast cell transformation, especially by affecting the transition to a mesenchymal and invasive state [21]. Therefore, several inhibitors for this receptor are developed, although its high structural affinity with other RTKs makes it difficult to produce specific drugs. BGB324 (Bemcentinib or R428) is probably the most selective AXL inhibitor and, recently, in combination with pembrolizumab, was implicated in clinical trials for triple-negative breast cancer (TNBC) and adenocarcinoma [22].

2. AXL Inhibition in Breast Cancer Treatment

AXL inhibitors are classified, according to their action mechanisms, into three categories: (1) drugs that modulate and inhibit the kinase activity of the receptor; (2) specific antibodies that prevent the AXL dimerization and activation; (3) drugs that recognize and bind GAS6 [13].

The most important AXL inhibitors are summarized and described in Table 1.

Table 1. AXL inhibitors. Several AXL inhibitors (selective or not) are involved in the treatment of breast cancer. Many of them, however, are still in preclinical development.

Selective Inhibitors				
	Target(s)	**Function(s)**	**Field(s)**	**Reference(s)**
BGB324 (Bemcentinib or R428)	AXL	ATP-competitive AXL inhibitor that promotes apoptosis and reduces cell growth and metastasis	Preclinical and clinical	[23][24][25][26][27][28]
NA80X-1	AXL	Selective AXL inhibitor that decreases cell motility and invasion	Preclinical	[29]
YW327.6S2	AXL	Monoclonal antibody that inhibits GAS6/AXL interaction	Preclinical	[30]
GL21-T	AXL	RNA-based aptamer that blocks AXL's catalytic activity and inhibits mobility and metastasis	Preclinical	[31][32]
DN10764 (AZD7762)	AXL ChKs	Selective AXL inhibitor that decreases cell proliferation, invasion and migration and induces apoptosis	Preclinical	[33][34]
SGI-7079	AXL	Selective AXL inhibitor that decreases cell proliferation and metastasis	Preclinical	[35]
Non-Selective Inhibitors				
Rebastinib (DCC-2036)	MET VEGFR2 SRC AXL	Multi-target inhibitor that decreases cell proliferation, invasion, migration and EMT	Preclinical and Clinical	[36][37]
Cabozantinib (XL184)	RET VEGFR2 Flt 1-3-4 Tie2 MET AXL	Multi-target inhibitor that decreases cellular invasion and promotes immune system activation	Preclinical and clinical	[38][39][40][41][42][43]
Foretinib (XL880 or GSK-1363089)	MET RET VEGFR2 AXL	Multi-target inhibitor that restores the response to lapatinib in HER2+ context	Preclinical and clinical	[44]
Merestinib (LY2801653)	MET MST1R MKNK1/2 AXL	Multi-target agent that inhibits angiogenesis and mitosis	Preclinical and clinical	[45][46]
Bosutinib (SKI-606)	SRC Abl MEK	Multi-target inhibitors that decreases invasion, metastasis and tumor differentiation	Preclinical and clinical	[47][48][49]

Selective Inhibitors				
	Target(s)	Function(s)	Field(s)	Reference(s)
	BMX AXL			
Crizotinib (PF-02341066)	MET ALK ROS1 AXL	ATP-competitive agent that inhibits cell proliferation	Preclinical and clinical	[50][51]

2.1. AXL Selective Inhibitors

BGB324 (Bemcentinib or R428) is the more selective ATP-competitive inhibitor of AXL (IC_{50} = 14 nM) and was the first to enter clinical trials to treat several cancer forms, such as TNBC tumors, metastatic melanoma and NSCLC. By blocking AXL autophosphorylation on tyrosine residue Y821, in vitro, it induces apoptosis, inhibits cancer cell invasion and reverts erlotinib resistance in TNBC cells; in vivo, BGB324 reduces cancer metastasis [23][24][25][26]. In a recent preclinical study, BGB324 was tested in combination with auranofin, a gold phosphine derivative, initially used for the treatment of rheumatoid arthritis and also studied for the treatment of the other diseases, such as breast cancer. It is a thioredoxin reductase inhibitor and appears to induce apoptosis through PI3K pathway inhibition [27]. The authors of this study have observed that in different breast cancer settings (MDA-MB231 and MCF7), the combination of BGB234 and auranofin reduced cell growth by inducing apoptosis, mediated by increased levels of Bcl-2-associated X-protein (BAX) [28]. Recently, BGB324 was implicated in a phase II clinical trial (NCT03184558) for TNBC and inflammatory breast cancers, in combination with pembrolizumab; however, the results have not yet been released [22]. Other selective AXL inhibitors have been recently developed and have validated their efficacy in the preclinical field. NA80X-1 determines a decrease in cell motility and invasion in MDA-MB435 cells [29]. YW327.6S2 represents a potent anti-AXL monoclonal antibody that recognizes and binds AXL with high affinity. This antibody, by preventing the GAS6 interaction with the receptor, inhibits AXL activation and its downstream signaling [30]. GL21-T is an RNA-based aptamer which blocks AXL catalytic activity through interaction with the receptor extracellular domain [31]. In a recent preclinical study, the inhibitory action of this drug was evaluated in combination with the anti-metastatic miRNA148b. The authors have created a conjugate (AXL-148b) able to work only in positive AXL contexts. In vitro, by increasing the expression levels of miRNA148b, the conjugate has reduced the formation and mobility of mammospheres; in vivo, AXL-148b has blocked metastasis formation [32]. DN10764 (or AZD7762), developed as selective inhibitor of checkpoint kinases (ChKs) 1 and 2, is also involved in AXL downregulation. In a preclinical field study, DN10764 inhibited, in both vitro and in vivo experiments, AXL-dependent cell proliferation, invasion and migration and also induces apoptosis through caspases 3/7 activation [33][34]. SGI-7079 is another selective AXL inhibitor which, however, also targets the other members of the TAM family; in vitro experiments showed that it decreased cell proliferation and metastasis [35].

2.2. Multi-Targets Inhibitors

Rebastinib (or DCC-2036) is a multi-target inhibitor involved in the regulation of cell proliferation, invasion, migration and EMT processes by blocking the activity of several TKs, such as MET, vascular endothelial growth

factor receptor 2 (VEGFR2), SRC and AXL. A recent in vitro and in vivo study has shown that in TNBCs (little responsive to hormonal and anti-HER2 therapies), rebastinib inhibited cell proliferation, invasion and EMT more efficiently as compared to other drugs used for breast cancer treatment. In addition, its combination with lapatinib or cisplatin significantly decreased the growth of TNBC cells [36]. Although it does not have a single site of action, rebastinib seems to carry out its inhibitory function mainly on AXL and its downstream targets. Indeed, the drug decreases cell growth only in murine models inoculated with TNBC characterized by high levels of AXL [37].

Cabozantinib (or XL184) recognizes and blocks many RTKs, such as Rearranged during Transfection (RET), VEGFR2, Kit, fms-related tyrosine kinases (Flt) 1, 3 and 4, tyrosine kinase with immunoglobulin-like and EGF-like domains 2 (Tie2), MET and AXL [38]. It is implicated in the treatment of several solid malignancies, such as renal cell carcinoma, medullary thyroid, NSCLC and TNBC tumors, by decreasing the metastatic and invasive potential of cancer cells. In a recent phase II trial (NCT01738438) conducted on metastatic TNBC patients, cabozantinib administration led to a clinical benefit of 34%, determining a median PFS of 2.0 months; moreover, cabozantinib treatment has determined quite encouraging results in terms of immune system activation. Indeed, patients treated with this drug showed higher circulating levels of $CD8^+$ T lymphocytes and a greater activation of antitumor immunity. However, these results are still not very consistent and need further investigation [39][40][41][42][43].

Foretinib (XL880 or GSK-1363089) is another multi-kinase inhibitor which blocks AXL, MET, RET and VEGFR2 activity. In HER2-amplified breast tumors, it restores sensitivity to lapatinib and trastuzumab in resistant cells with high levels of AXL. AXL and HER3 interaction bypasses the lapatinib-mediated HER2 block, promoting PI3K/AKT pathway hyperactivation and drug resistance. AXL inhibition, mediated by foretinib, removes the AXL/HER3 interconnection and restores cell response to lapatinib [44]. In a phase II clinical trial (NCT01147484), 46% of enrolled TNBC patients benefited from foretinib treatment [22][52].

Merestinib (or LY2801653) is a small molecule kinase inhibitor which targets AXL, MET, macrophage-stimulating protein receptor (MST1R) and MAP kinase-interacting serine/threonine kinase 1 (MKNK1/2). In vitro and in vivo experiments have shown that merestinib inhibits angiogenesis and mitosis [45][46].

Bosutinib (or SKI-606), originally identified as an SRC and Abelson murine leukemia viral oncogene (Abl) kinase inhibitor, is also a powerful inhibitor of AXL, Mitogen-activated protein kinase kinase (MEK) and BMX [47]. In breast cancer, it regulates invasion, metastasis and tumor differentiation [48][49]. Bosutinib is implicated, for breast tumors, in several clinical trials [22].

Crizotinib (or PF-02341066) is an ATP-competitive small-molecule inhibitor which blocks MET, anaplastic lymphoma receptor tyrosine kinase (ALK), c-ros oncogene 1 receptor tyrosine kinase (ROS1) and AXL. In breast cancer cell lines, it inhibits cellular proliferation [50][51]. As described for the other non-selective inhibitors, crizotinib is also involved in several clinical trials as a modulator of other molecular targets [22].

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