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## EDITED AND REVIEWED BY

Olivier Feron, Université catholique de Louvain, Belgium

## \*CORRESPONDENCE

Kyoung-Ho Pyo

✉ pkhpsh@gmail.com

<sup>†</sup>These authors have contributed equally to this work and share senior authorship

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# Editorial: Development of small molecule inhibitors and antibodies targeting AXL for tumor therapy and infectious disease control

Kyoung-Ho Pyo<sup>1,2,\*†</sup>, S. M. Mazidur Rahman<sup>3†</sup> and Diana Boraschi<sup>4,5,6,7†</sup>

<sup>1</sup>Severance Biomedical Science Institute, Yonsei University College of Medicine, Seoul, South Korea, <sup>2</sup>Yonsei New Il Han Institute for Integrative Lung Cancer Research, Yonsei University College of Medicine, Seoul, South Korea, <sup>3</sup>International Centre for Diarrhoeal Disease Research (icddr), Dhaka, Bangladesh, <sup>4</sup>Shenzhen Institute of Advanced Technology (SIAT), Chinese Academy of Sciences (CAS), Shenzhen, China, <sup>5</sup>Institute of Biochemistry and Cell Biology, National Research Council (CNR), Napoli, Italy, <sup>6</sup>Stazione Zoologica Anton Dohrn (SZN), Napoli, Italy, <sup>7</sup>China-Italy Joint Laboratory of Pharmacobiotechnology for Medical Immunomodulation, Shenzhen, China

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## Editorial on the Research Topic

### Development of small molecule inhibitors and antibodies targeting AXL for tumor therapy and infectious disease control

For a long time, anti-cancer therapeutic strategies have mainly addressed the tumor, in the attempt to subvert the altered signaling pathways leading to oncogenesis (1, 2). It is however evident that the tumor microenvironment plays a major role in determining tumor survival and growth. In particular, the role of immunity in eliminating or promoting tumor growth has been now clearly recognized (3–5).

The complex nature of tumorigenesis requires the identification of different therapeutic targets and the implementation of different therapeutic approaches, including drugs/strategies that could overcome resistance after treatment. The immunotherapeutic approaches with immune checkpoint inhibitors are an example of treatment that does not induce resistance, as its target is not the tumor but the re-activation of specific tumoricidal immune cells (6, 7). Thus, the development of anti-PD-1 and anti-PD-L1 immune checkpoint inhibitors has opened the way to novel anti-tumor approaches that go beyond inhibiting oncogenic signals and address the tumor microenvironment as a whole. In this context, AXL is an attractive target for designing future treatment targets.

AXL is a receptor tyrosine kinase of the TAM (TYRO3-AXL-MER) family (8–10). High AXL expression in tumor cells promotes aggressiveness, metastatic capacity and refractoriness to drug treatment (11, 12). In parallel, it was observed that the expression of AXL and other TAM receptors is higher in macrophages polarized towards the M2

anti-inflammatory pro-tumoral functional phenotype and that activation of AXL can induce M2 macrophages polarization (13–16). Since the M2 phenotype is typical of pro-tumoral tumor-associated macrophages, this points to AXL inhibition as a double target to reduce the aggressiveness of tumor cells and the tumor-promoting activity of the innate immune cells (macrophages). Importantly, AXL has been identified as a receptor used by several viruses (Zika, Dengue, RSV, JEV, SARS-CoV-2) for entry into host cells and spreading infections (17–20). Thus, inhibition of AXL in infectious diseases could have the double advantage of blocking virus entry and allowing protective macrophage activation (M1 polarization), by inhibiting M2 development. For these reasons, new drugs targeting AXL are being developed. An overview of AXL role in tumor and immune cells and the potential benefits of its inhibition are presented in Figure 1.

New technologies to suppress AXL functions include inhibition of downstream signaling with antibodies or blockade of GAS6, the ligand of AXL, and the use of small molecules that can inhibit AXL phosphorylation. The state-of-the-art of the use of AXL inhibitors in cancer therapy is reported by Tanaka et al., who have extensively described the AXL signaling pathway and listed the most promising AXL inhibitors that have been developed clinically or preclinically (21). The review presents the anti-tumor mechanisms of AXL inhibitors, and the improvement of therapeutic efficacy and immunoactivity of chemotherapy currently use in clinical practice (21).

The contribution of AXL to immune evasion underlines the importance of its inhibition in anti-tumor therapies. GAS6/AXL

signaling can participate to evasion from anti-tumor immune response within the tumor microenvironment in multiple ways (Son and Jeong). These include modulation of MHC-1 and PD-L1 expression, production of immunosuppressive cytokines, increased recruitment of myeloid derived suppressor cells and decreased infiltration of T cells, inhibition of apoptosis, promotion of CTLA4 and Foxp3 expression in Treg cells and of their immunosuppressive activity, and regulation of tumor associated innate immune cells. The use of AXL inhibitors, both in preclinical studies and in clinical trials, provides valuable information on the modulation of GAS6/AXL-mediated immune evasion (Son and Jeong). Not only AXL but also other receptors of the family, such as TYRO3, are strongly involved in the regulation of tumor cell apoptosis, as demonstrated in colon carcinoma *in vitro* and *in vivo* models by using a specific inhibitor (Kim et al.).

The potential application of AXL inhibitor as a single agent or in combination with immunotherapy in patients with lung cancer has been investigated based on clinical treatment results and treatment advantages (Sang et al.). AXL inhibitors have shown therapeutic benefits in combination with chemotherapy to increase survival rate through enhanced activation of immune cells (Lee et al.). However, detailed anti-tumor effects of AXL signaling pathway is yet to be understood.

While the current development of AXL inhibitors offers promising opportunities for effective therapeutic intervention against cancer, future research should aim at fully clarifying the effects of AXL and, more in general, TAM inhibitors. This should start from a complete understanding of the physiological role of these receptors and the assessment of

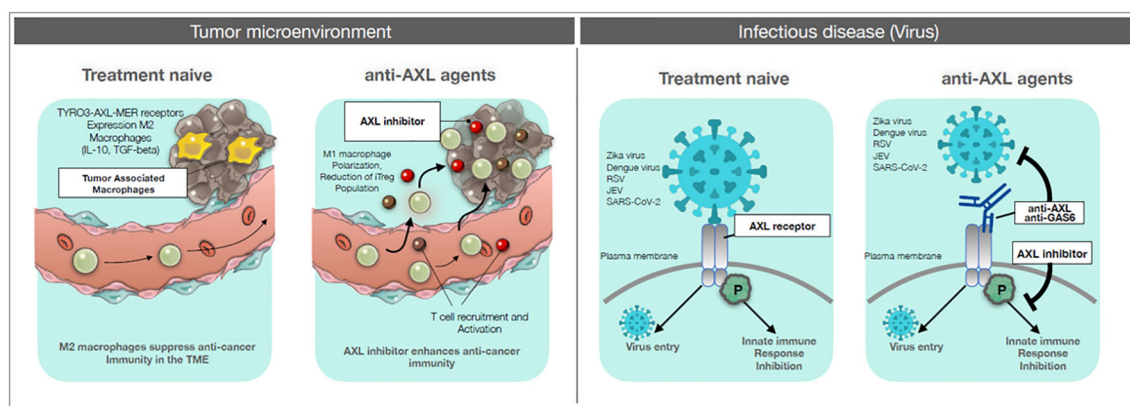


FIGURE 1

AXL targeting drugs on cancer and infectious diseases. Left panels: Tumor microenvironment. Left: treatment-naïve: circulating monocytes and tissue-resident macrophages are recruited to the tumor site. These tumor-associated macrophages are polarized towards an M2 functional phenotype, which can suppress anti-tumor response and promote tumor growth. Right: anti-AXL agents: by blocking the signaling pathway of AXL with anti-AXL agents, recruited monocytes and macrophages can be polarized towards the inflammatory, immunostimulatory and cytotoxic M1 phenotype, thereby allowing the development of anti-tumor immune responses and also acting as anti-tumor killer cells. Right panels: Infectious diseases. Left: treatment-naïve: viruses (Zika, Dengue, RSV, JEV, SARS-CoV-2) can gain entry into the host cell through interaction with an AXL receptor, thereby efficiently infecting the host. In addition, viral binding can induce an AXL-mediated inhibitory signaling for innate immune responses. Right: anti-AXL agents: anti-AXL agents that bind to the extracellular domain of AXL can block virus binding and subsequent infection. Also, anti-AXL agents that block the virus-induced AXL inhibitory signaling can restore efficient innate immunity against the viral infection.

their pathology-linked molecular and functional variations. On these grounds, AXL inhibition can be precisely targeted, to attain high therapeutic efficacy and limited side effects. The possibility of modulating AXL functions in macrophages and in virus-host interactions opens a large spectrum of therapeutic/preventive possibilities beyond cancer.

## Author contributions

KP wrote the editorial, RM and DB contributed to writing the manuscript and critically revised it. All authors approved the submitted version.

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## Conflict of interest

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