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Review Article

Key Roles of Axl in Systemic Lupus Erythematosus

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Abstract

Axl is a member of the Receptor Tyrosine Kinase (RTK) family and, together, Tyro3, Axl, and Mer (TAM) constitute the TAM receptors. Growth arrest-specific protein 6 (Gas6) is a necessary ligand for Axl. The Gas6-Axl pathway is reported to have notable effects on cell stages change (including cell survival, proliferation, migration, and adhesion), phagocytosis, and immune homeostasis. Systemic Lupus Erythematosus (SLE) is an autoimmune disorder characterized by high titers of auto-antibodies and multiple organ damages. Recent studies have revealed that the abnormal expression of Axl receptors in different cells may contribute to autoimmune disorders such as SLE and Rheumatoid Arthritis (RA). In this review, we focus on the important role of Axl in systemic lupus erythematosus.

Keywords: Axl; Growth Arrest-Specific Protein 6; Mechanism; Systemic Lupus Erythematosus

Introduction

Systemic Lupus Erythematosus (SLE) is a chronic inflammatory disease with high prevalence, ranging from 0.02% to 15% [1]. SLE has multiple clinical manifestations such as skin damage, joint inflammation, nephritis, neurological disorder and other symptoms. Disorders in the immune system including over-production of inflammatory cytokines, hyperactive T and B lymphocytes and auto-antibodies play important roles in the progression of SLE [2]. Axl (also called Ufo or Ark [3]) was first identified in leukaemia [4]. As a Tyro3, Axl, and Mer (TAM) receptor, Axl belongs to the Receptor Tyrosine Kinase (RTK) family. Growth arrest-specific protein (Gas6), and protein S are two primary Vitamin-K dependent ligands of TAM receptors, but only Gas6 activates and has the greatest affinity for Axl (Axl > Tyro3 > Mer) [5]. The Gas6-Axl pathway is reported to play a significant role in clearing apoptotic debris [6], regulating innate immune responses [7] and mediating cell stage changes [8,9]. Axl is abnormally expressed in different cells in some autoimmune diseases, such as SLE [10], Rheumatoid Arthritis (RA) [11] and Sjogren's disease [12]. Currently, more attention is being paid to the function of TAM receptors in different autoimmune diseases. In this review, we aim to summarize the expression of Axl and its possible role in the pathogenesis of SLE.

Structure of Axl and Its Ligand

As a transmembrane receptor, Axl is expressed ubiquitously in a variety of cells [13]. In the extracellular ligand binding region, the Axl receptor has two repeated Immunoglobulins (Ig)-like domains and two repeated fibronectins type III (FNIII) motifs and the following region is a single-pass transmembrane domain. In the intracellular catalytic region, Axl has a conserved protein tyrosine kinase domain, which initiates the following cytoplasmic cascades (Figure 1) [14].

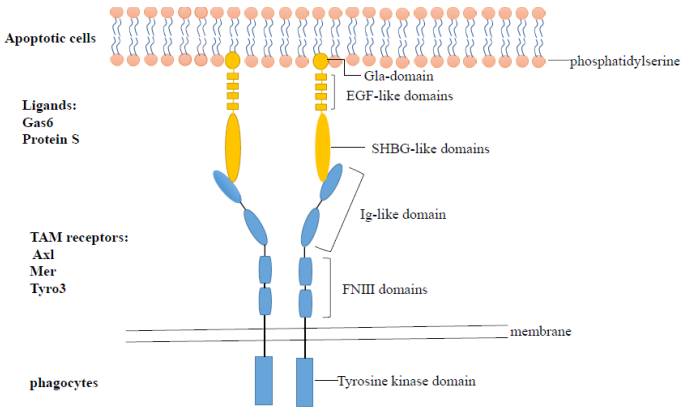

Figure 1: Structure of Axl and its ligand, growth arrest-specific protein 6 (Gas6). The extracellular structure of Axl has two tandem Ig-like domains

(blue ovals) and two FNIII domains (blue cylinders). The intracellular domain of Axl is a tyrosine kinase domain (blue rectangle). The Gla domain (yellow circle) of Gas6 links the phosphatidylserine expressed in apoptotic cells. The SHBG-like domain (yellow ovals) bind to Axl on phagocytes. Between Gla domain and SHBG-like domain in the structure of Gas6, there are four EGF-like molecules (yellow rectangles). Two complexes of 1:1 ligand-receptor dimerization are dispensable for signal transduction. FNIII, fibronectin type III; Ig, immunoglobulin; SHBG, sex hormone binding globulin; Gla, glutamic acid residues.

Gas6, as an indispensable ligand for Axl, contains N- and C-terminal regions. The N-terminal region contains a Glutamic acid residue (Gla) domain, which binds to phosphatidylserine or other specific molecules in target cells. The Gla region can be specifically γ-carboxylate in a vitamin K-dependent reaction [15]. Subsequently, four epidermal growth factor (EGF)-like molecules can be observed after the Gla domain. The C-terminal region is the sex hormone-binding globulin (SHBG)-like domain, which comprises two tandem laminin G motifs (Figure 1) [16,17]. The Axl is activated by Gas6 is a ligand-dependent manner, but ligand-independent activation also occurs. The overexpression of Axl receptor leads to homophilic dimerization of the extracellular domain in neighboring cells, which induces the auto phosphorylation of Axl [18]. Konishi et al [19]. revealed that reactive oxygen species also promoted the activation of Axl receptor in a Gas6-independent manner in vascular smooth muscle cells.

Axl Expression

Axl in the Immune System

A previous study reported that Axl was expressed in most cells, including epithelial, mesenchymal, hematopoietic origin, and normal non-transformed cells [19]. Under normal physiological conditions, Axl is reported to be expressed in the following immune cells, dendritic, macrophage, and immature nature killer cells [7,20]. However, T and resting B cells do not express Axl 21. There are two types of Axl receptors in the body; one is the membrane Axl (mAxl), which can be detected in the surface of immune cells [14], whereas the other is the soluble Axl (sAxl) found in the serum-ectodomain of the Axl membrane.

The matrix metalloprotease, A Dis-Integrin and Metalloproteinase 10 (ADAM10), and tumor necrosis factor [TNF]-α converting enzyme (TACE, ADAM17) have been reported to shed the extracellular domain of TAM receptors into the plasma [21]. Under pathological conditions, the serum levels of sAxl in numerous lupus-prone mice (including MRL-lpr, BWF1, B6·Sle1, B6·Sle1.Sle2. Sle3, B6·Sle3, B6·Sle1.Sle3, B6·Sle1.Yaa, and B6. Lyn-/-) were elevated compared with those in healthy C57BL/6J (B6) controls.

Moreover, mAxl and active Phosphorylated Axl (p-Axl) expression levels in MRL-lpr mouse splenocytes were lower than those in healthy B6 controls [22]. These changes in Axl expression in the immune system of lupus-prone mice were similar to those observed in patients with SLE. The sAxl levels of patients with active SLE were higher than those of patients with inactive SLE and healthy controls [23]. A similar finding was also reported by another study, showing that the level of sAxl was upregulated, whereas that of mAxl on the surface of CD14+ monocytes or macrophages was downregulated in patients with SLE [10].

Axl in kidney

In mice and humans, Axl has not been detected in the normal kidney, but it was expressed in glomerular mesangial and renal tubule epithelial cells in nephritis [24,25]. Several studies have indicated that the levels of Axl expression and activation were elevated in nephritis in mice and rats [24,26]. In patients with lupus nephritis, the expression of Axl in glomeruli mesangial cells was higher than that in patients with primary nephrotic syndrome [27].

Correlation between serum sAxl and SLE disease activity

Serum concentrations of sAxl in patients with SLE have been reported to be higher than concentrations in healthy subjects [28,29]. Furthermore, the serum concentration of sAxl in patients with active SLE was more elevated than that in patients with inactive SLE and healthy controls [22,30]. Importantly, an antibody-array-based proteomic screening showed that serum sAxl was correlated with estimated glomerular filtration (eGFR) in patients with lupus nephritis [31]. Moreover, a cross-sectional study found that serum sAxl was a promising biomarker with higher specificity than conventional markers in SLE [30]. Many clinical studies have shown that serum sAxl concentrations are correlated with SLE disease activity index (SLEDAI) [10,29,32]. However, some research studies have reported that the level of sAxl was indeed increased in patients with lupus, whereas the level of sMer was significantly correlated with SLEDAI rather than sAxl [33,34]. In addition, sMer and not sAxl was shown to be positively associated with lupus-specific auto-antibodies such as anti-double strand DNA (dsDNA), and inversely associated with complement C3 and C4 [34]. This discrepancy can be attributed to three phenomena. First, a difference in sample numbers between studies might affect the statistical power and results. Second, the use of different methods and reagent kits for measuring serum TAM receptors may lead to varying results. Third, distinct inclusion criteria also have an impact on the conclusions.

Possible Mechanisms of Action of Axl in SLE

Regulation of Axl in phagocytosis

To date, the etiology of SLE remains unclear. However, the impaired clearance of apoptotic cells by phagocytes may play a vital role in SLE development [32]. The phagocytosis process can be divided into four steps: phagocytes accumulate in an area where apoptosis occurs, phagocytes interact with apoptotic cells through specific receptors or bridge molecules, uptake of the "Junk," and the "Meal" is ingested in phagocytes [35]. Axl expressed in dendritic cells or macrophages is considered a phagocyte receptor, and Gas6, as a universal bridge molecule, binds to Axl [36]. Importantly, the interaction of the Gas6-Axl complex is essential for the recognition process of phagocytosis. TAM triple-knockout mice were reported to develop severe lupus-like autoimmune

disorders [37]. Furthermore, phagocyte deficiency in Axl and Mer receptors was shown to impair phagocytosis [38,39]. These data suggest that aberrant Axl receptors in phagocytes may be a key factor in SLE development. The surface of apoptotic cells is known to be different from those of normal cells; for example, the phospholipid in apoptotic cells is oxidized [40]. A significant change in apoptotic cells is that the phosphatidylserine normally expressed in the inner leaflet of the membrane is translocated to the outer layer of the membrane, and there is a dysfunction of the proteinase "Flippase" [41].

The ligand Gas6 binds to phosphatidylserine on apoptotic cells through its Gla domain and links Axl receptors expressed in phagocytes through its SHBG domain. This interaction tethers apoptotic cells on the surface of phagocytes and then promotes downstream cascades to induce the engulfment and ingestion processes [42]. Other bridge molecules such as milk-fat globule epidermal growth factor 8 (MFG-E8), β2-glycoprotein I (β2-GPI), and phagocyte receptors such as the class A scavenger receptor are also involved in the removal of dead cells [43].

Roles of Axl in inflammation

Axl activation suppressed the expression of inflammatory cytokines in lipopolysaccharide (LPS)-treated mice, indicating that Axl may play an anti-inflammatory role in immune responses [44]. Toll-like receptors (TLRs) are pattern-recognition-receptors expressed in sentinel cells such as dendritic cells, which mediate the innate immune response [45]. In the Axl-mediated inflammatory cycle, TLRs (such as TLR4 and TLR9) are activated by bacterial particles (such as LPS and dsDNA), and then they deliver signals to downstream cascades to initiate the burst of pro-inflammatory cytokines (green pathway in Figure 2).

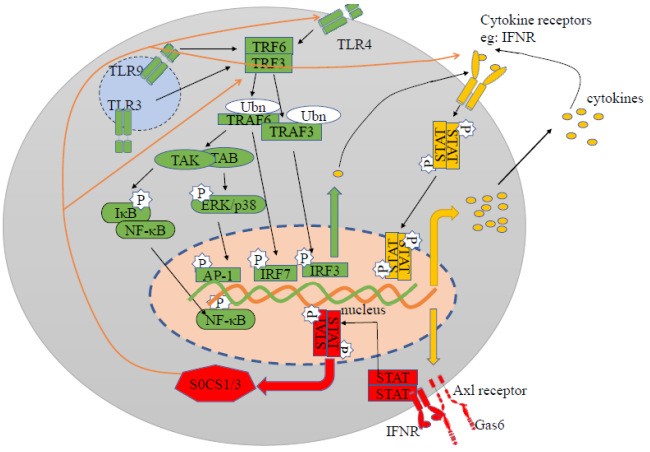

Figure 2: Inflammatory cycle mediated by Axl signal. Green pathway represents the first stage induced by TLR. Activation of TLR leads to the initial burst of pro-inflammatory cytokines. Then, the cytokines are amplified by the cytokine-cytokine receptor pathway in a positive feedback circle (yellow pathway). The final stage (red pathway) is mediated by Axl receptor, which is upregulated by IFNR-STAT1 pathway. Gas6-Axl complex and IFNR-STAT1 pathway induce the expression of SOCS1/3. As important negative regulators, SOCS1/3 are responsible for inhibiting TLR-pathway and cytokine-cytokine receptor signals.

TLR, Toll-like receptor; TRAF, tumor-necrosis-factor receptor-associated receptor; TAK, transforming-growth-factor-β-activated kinase; TAB, TAK1-binding protein; Ubn, ubiquitination; P, phosphorylation; NF-κB, nuclear factor-κB; IKK, inhibitor of NF-κB kinase; AP1, activator protein 1; IRF, interferon regulatory factor; STAT, signal transducers and activators of transcription; SOCS, suppressor of cytokine signaling; Gas6, growth arrest-specific protein 6; IFNR, interferon receptor.

The produced cytokines bind to membranous cytokine receptors such as the type-1 interferon (IFN) receptor (IFNR) and the complex drives the phosphorylation of signal transducers and activators of transcription 1 (STAT1) protein. This action subsequently stimulates STAT1 dimers, which are transported from the cytoplasm into the nucleus to amplify proinflammatory cytokines (yellow pathway in Figure 2). On the one hand, the IFNR/STAT1 pathway promotes the amplification of cytokines in a positive feedback loop while on the other, it inhibits inflammatory responses. The expression of Axl is upregulated in an IFNR-STAT1-dependent manner. The Gas6-Axl complex together with the IFNR-STAT1 pathway induces the production of protein suppressor of cytokine signaling 1 (SOCS-1) and SOCS3, which negatively regulated inflammatory responses [7,17] (red pathway in Figure 2). First, the protein sSOCS1/3 suppress inflammation by inhibiting the TLR4 pathway and ubiquitination of TNF receptor-associated factor 3/6 (TRAF3/6) [46,47]. Second, SOCS1/3 protein inhibits IFNR-STAT1-dependent cytokine amplification (red pathway in Figure 2). Furthermore, the activation of TAM receptors by agonists such as Gas6 has been reported to reduce the production of cytokines, which could be a potential treatment strategy for autoimmune disorders [21].

Lupus nephritis is a common and serious manifestation of SLE. The Gas6-Axl pathway has been reported to induce glomerular mesangial hypertrophy under inflammatory conditions [26,48]. In anti-Thy1.1-mediated glomerulonephritis rats, the expression of Axl in the kidney was strikingly elevated. Moreover, glomerular mesangial cell proliferation and renal injury were significantly alleviated in rats treated with warfarin or Axl-Fc [26]. Axl-knockout mice treated with nephrotoxic serum (NTS) showed better renal function and longer survival time than wild-type mice did [24]. Moreover, another study revealed that glomerular injury in Gas6-knockout mice treated with NTS was more alleviated than that in wild-type mice [48]. Gas6-Axl has been suggested to play a pro-inflammatory role in renal inflammation. R428 is an inhibitor of Axl that has been used clinically for cancer therapy, but it has not been applied in SLE. More investigations would be necessary to elucidate the effects of Axl antagonists in SLE. The regulatory mechanism of the Gas6-Axl pathway is complicated and whether Axl has a proinflammatory or anti-inflammatory role in SLE is still controversial. Moreover, Axl may play a proinflammatory role in the kidney and an anti-inflammatory role in the immune response.

Conclusions

In conclusion, the levels of sAxl and mAxl were found to increase and decrease in SLE, respectively. Moreover, sAxl may be a promising biomarker, which is correlated with SLEDAI in

patients with SLE. Aberrant expression of Axl in phagocytes may contribute to the inefficiency of phagocytosis, which could lead to an unbalanced immune system. In addition, Axl-deficiency in immune cells increases the production of pro-inflammatory cytokines, whereas the overexpression of Axl in inflammatory conditions promotes the proliferation of glomerular mesangial cells. However, the Gas6-Axl pathway has opposing roles in peripheral organs and the kidney, and basic and clinical research studies are needed to validate whether Axl has an anti-inflammatory or pro-inflammatory role or both in SLE.

Author Contributions

Mengyuan li wrote the manuscript. Tianfu Wu provided critical suggestions for the manuscript. Ling Qin designed the review and edited the manuscript.

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