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Research Article

STAT1/SOCS1/3 Are Involved in the Inflammation-Regulating Effect of GAS6/AXL in Periodontal Ligament Cells Induced by Porphyromonas gingivalis Lipopolysaccharide In Vitro

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Periodontitis involves chronic inflammation of the tissues around the teeth caused by plaque and the corresponding immune response. Growth arrest-specific protein 6 (GAS6) and AXL receptor tyrosine kinase (AXL) are known to be involved in inflammatory diseases, while signal transducer and activator of transcription-1 (STAT1) and suppressor of cytokine signaling (SOCS) are related to inflammatory processes. Moreover, miRNA34a directly targets AXL to regulate the AXL expression. However, the specific roles of GAS6 and AXL in periodontitis remain unclear. This study was designed to explore the effect and mechanism of AXL on the expression of inflammatory cytokines induced by Porphyromonas gingivalis lipopolysaccharide (P. gingivalis LPS) in human periodontal ligament cells (hPDLCs). The effects of different concentrations of P. gingivalis LPS on the expression of GAS6/AXL in hPDLCs were observed. Additionally, the effect of LPS on AXL was investigated by transfection of the miRNA34a inhibitor. AXL was knocked down or overexpressed to observe the release of inflammatory cytokines interleukin- (IL-) 8 and IL-6. The results showed that the expression levels of GAS6 and AXL decreased after P. gingivalis LPS infection. Transfection of a miR-34a inhibitor to hPDLCs demonstrated a role of miR-34a in the downregulation of AXL expression induced by LPS. Moreover, AXL knockdown or overexpression influencing the expression of IL-8 and IL-6 was investigated under LPS stimulation. AXL knockdown decreased the expression of STAT1 and SOCS1/3. Overall, these results demonstrate that AXL inhibits the expression of LPS-induced inflammatory cytokines in hPDLCs and that STAT1 and SOCS1/3 are involved in the regulation of inflammation by GAS6/AXL.

1. Introduction

Periodontitis is a chronic infectious disease caused by dental plaque that results in the destruction of periodontal tissue. Porphyromonas gingivalis is prevalsent in adult periodontitis patients [1], which is detected in more than 80% of all patients [2]. P. gingivalis lipopolysaccharide (P. gingivalis LPS) stimulates a proinflammatory reaction and bone resorption in vivo [3, 4]. In vitro studies have shown that multiple cells produce diverse proinflammatory cytokines, including interleukin- (IL-) 1α, IL-1β, IL-6, IL-8, and tumor necrosis factor (TNF-α), following P. gingivalis LPS challenge [5, 6].

The TAM family of receptor tyrosine kinases has three members: TYRO3, AXL receptor tyrosine kinase (AXL), and MERTK. AXL was originally isolated and identified in chronic myelogenous leukemia cells in 1991 [7–9], which is a transmembrane protein that is dependent on interaction with its ligand for activation [7]. The activation of TAM receptors depends on the binding of two ligands: growth arrest-specific 6 protein (GAS6) and protein S1 (PROS1) [10]. Among TAM receptors, GAS6 has the highest affinity for binding to AXL; however, the affinity between PROS1 and AXL has not yet been demonstrated [11, 12].

GAS6/AXL activates multiple signaling pathways in a variety of cells; plays several roles, including cell survival,