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Details of the Collaborative Activity

Name of the Collaborating Institute: School of Biomedical Sciences, Li Ka Shing Faculty of Medicine, the University of Hong Kong, Hong Kong.

Name of the Collaborating Department: Yenepoya Research Center and Dept of Surgical Oncology

Joint Research project and publications

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A pathway map of AXL receptor-mediated signaling network

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Introduction

AXL is a transmembrane protein that comes under TAM (TYRO3, AXL and MERTK) family of receptor tyrosine kinases (RTKs) (Myers et al. 2019). It is first identified as a transforming gene isolated from primary human myeloid leukemia cells (O'Bryan et al. 1991). The AXL gene is located in chromosome 19, at 19q13.1 (Linz et al. 1993), which encodes a protein of 894 amino acids (Korshunov 2012). AXL receptor has an extracellular, a transmembrane and an intracellular domains. The extracellular domain contains two immunoglobulin-like (IgL) and fibronectin type-III (FN III)-like domains with a single-pass transmembrane domain (Linger et al. 2008). The intracellular tyrosine kinase domain of AXL contains six phosphorylation sites. Among these three phosphorylation sites were in C-terminal domain (Tyr⁷⁷⁹, Tyr⁸²¹ and Tyr⁸⁶⁶) and others in N-terminal domain (Tyr⁶⁹⁸, Tyr⁷⁰², Tyr⁷⁰³). Autophosphorylation of C-terminal phosphorylation sites stimulated by GAS6 has a role in the kinase

activity of AXL (Linger et al. 2008, O'Bryan et al. 1991). Phosphorylation of the residues in the N-terminal domain induced by GAS6 has also been shown (Pao-Chun et al. 2009). In particular, phosphorylated Tyr⁷⁰² may stabilize the conformation of the activation loop of AXL, promoting AXL activity (PMID: 28,724,631). AXL is known to extensively express in various tissues such as brain, heart, liver, bone marrow, neurons and vascular tissues (Jin et al. 2015, Lemke 2013, Lemke and Rothlin 2008, Nielsen-Preiss et al. 2007).

AXL activation is mediated by a ligand called growth arrest-specific protein 6 (GAS6), which is the product of GAS6 gene. GAS6 is a vitamin-K dependent growth factor mainly express in multiple cells (Sasaki et al. 2006). GAS6 has the highest affinity for AXL among the TAM family members. The stimulation of AXL receptor by binding of GAS6 induces receptor dimerization and subsequently AXL activation, which transfers signals from the extracellular matrix into the cytoplasm and results in various signaling pathways through its downstream substrates. The activation of

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