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"Gas6 and Pros1 Family Ligands in TAM Activation: Dual Function for Phosphatidylserine Binding and Protein Disulfide Isomerase Redox Regulation"

By

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Thursday, July 30th, 2026
10:00 AM
Cancer Center, G 1196

Join Zoom Meeting:

https://rutgers.zoom.us/j/98272787408?pwd=2MbZ9LX8bqh2Vkk8XnQS4birFaMu13.1

Meeting ID: 982 7278 7408
Password: 418857

Abstract

Growth arrest-specific protein 6 (Gas6) and Protein S (Pros1) are ligands for the TAM family receptors Tyro3, Axl, and MerTK, where receptor activation plays important roles in immune regulation and apoptotic cell clearance. Gas6 and Pros1 share common domain architecture, including an N-terminal γ-carboxyglutamic acid (Gla) domain, 4 repeat EGF-like domains, and carboxyl-terminal laminin G (LG) domains. Despite their sequence similarity, the molecular mechanisms by which these domains regulate TAM receptor activation remain incompletely understood. Here, we systematically compared the functional contributions of individual domains in Gas6 and Pros1 during TAM receptor activation. We found that vitamin K–dependent γ-carboxylation of the Gla domain is essential for phosphatidylserine (PS) binding and TAM receptor activation, and PS-positive apoptotic cells further promote hyperactivation of TAM signaling. Mutation of PS-binding residues within the Gla domain abolished TAM receptor activation. We next examined the role of LG domain–binding ligands and found that C4BPβ, soluble Axl (sAxl), and soluble Mer (sMer) differentially regulate Gas6- and Pros1-mediated TAM activation. Because the LG domains of Gas6 and Pros1 also serve as TAM receptor binding site, these LG-binding ligands likely inhibit TAM signaling through competitive interactions at the receptor-binding interface. Furthermore, progressive deletion of EGF-like domains gradually reduced TAM receptor activation, and conserved cysteine residues within these domains were required for TAM activation. Finally, we found that extracellular protein disulfide isomerase (PDI) enhances Gas6- and Pros1-induced TAM activation, whereas inhibition of PDI with PACMA31 significantly suppresses TAM signaling. Together, these findings define the domain-specific mechanisms that regulate Gas6- and Pros1-mediated TAM receptor activation and dual Function for Phosphatidylserine Binding and Protein Disulfide Isomerase Redox Regulation.