ABSTRACT

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Grant Title: The role of glucosylated phospholipid/GPR55 signaling axis in neutrophil homeostasis

Purpose:

Phosphatidyl-β-d-glucoside (PtdGlc) is a glycerophospholipid consisting of a glucose molecule bound to phosphatidic acid (1). PtdGlc is highly expressed on human neutrophils, where it induces spontaneous apoptosis. PtdGlc is deacylated by secretory phospholipase A2, which releases its lyso form (lysoPtdGlc) into the extracellular space. LysoPtdGlc acts as a spatial axon guidance molecule by interacting with the G protein-coupled receptor GPR55. Recent studies have demonstrated that lysoPtdGlc functions as a GPR55-mediated chemotactic molecule for human monocytes and macrophages (2). These findings suggest that the PtdGlc/lysoPtdGlc/GPR55 axis may regulate neutrophil homeostasis. To elucidate the role of PtdGlc in the apoptosis of neutrophilic lineage cells, this study examined three acute myeloid leukemia (AML) cell lines: HL-60 (AML-M2/M3), KG1 (AML-M1), and KG1a (AML-M0) (3).

Methods:

We compared PtdGlc expression and the apoptotic effects of the anti-PtdGlc monoclonal antibody DIM21 in the three AML cell lines: HL-60, KG1, and KG1a.

Results and Discussion:

PtdGlc was highly expressed in HL-60 and KG1 cells but not in KG1a cells. HL-60 and KG1 cells underwent early apoptosis when treated with DIM21; however, KG1a cells remained resistant, regardless of their differentiation status. Interestingly, DIM21 induced late-stage apoptosis in KG1 cells specifically after all-trans retinoic acid (ATRA)-mediated differentiation. Co-treatment with ATRA and DIM21 significantly enhanced this apoptotic response. Mechanistic analysis revealed that this apoptosis was independent of NADPH oxidase and Fas signaling; neither a reactive oxygen species inhibitor nor a neutralizing anti-Fas antibody affected the outcome. Instead, DIM21 activated caspase-3 and caspase-8, indicating that PtdGlc mediates apoptosis through a caspase-dependent but NADPH oxidase- and Fas-independent pathway. Taken together, these findings shed new light on the apoptotic signaling function of PtdGlc in neutrophilic lineage cells lineage cells and their homeostasis, and underscore its potential as a novel therapeutic target in AML.

References:

1. Hanafusa, K., Hotta, T., andIwabuchi, K. (2020) Glycolipids: Linchpins in the Organization and Function of Membrane Microdomains Front Cell Dev Biol 8, 589799 10.3389/fcell.2020.589799
2. Li, X., Hanafusa, K., Kage, M., Yokoyama, N., Nakayama, H., Hotta, T. et al. (2021) Lysophosphatidylglucoside is a GPR55 -mediated chemotactic molecule for human monocytes and macrophages Biochem Biophys Res Commun 569, 86-92 10.1016/j.bbrc.2021.06.090
3. Yokoyama N, Ekyalongo RC, Kage M, Hanafusa k, Nakayama H, Hirabayashi Y, et al. (2025) Phosphatidylglucoside regulates apoptosis of human neutrophilic lineage cells. Front. Immunol 16:1597423. 10.3389/fimmu.2025.1597423