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GPR124 a novel regulator of lipid metabolism involved in lineage commitment during leukemogenesis

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GPR124, a member of the Adhesion G Protein-Coupled Receptor family, has an established role in the embryonic development of central nervous system vasculature. However, its function in the context of Acute Myeloid Leukemia (AML) remains unexplored. Our transcriptome and proteome studies revealed upregulation of GPR124 in AML CD34+ blasts compared to healthy counterparts. Additionally, transcriptomic analysis of pediatric AML compared to Acute Lymphoid Leukemia (ALL), both harboring MLL-AF9 translocation, revealed exclusive expression of GPR124 in the AML cases. To study the role of GPR124 in leukemogenesis a cord blood CD34+ MLL-AF9 transduction model was employed. GPR124 overexpression skewed transformation towards the myeloid lineage with no subpopulation of the overexpression condition showing signs of lymphoid differentiation. To explore the underlying mechanisms and to identify potential ligands for this orphan receptor, we performed various LC-MS/MS-based interactome and bioID studies using lentiviral overexpression models in AML cell lines. Multiple lipid droplet (LD) formation related interacting proteins were identified. Supporting these findings, LD size was largely affected upon CRISPR KO in AML cell lines, as well as in bone marrow stromal cells stimulated towards adipocytic differentiation. Furthermore, GPR124 KO affected sensitivity to metabolic drugs and more specifically to RSL3 ferroptosis inducer indicating disturbed cellular lipid homeostasis. Currently, we are evaluating the metabolic state of GPR124 KO and overexpression cells using Seahorse and other metabolic assays. Our ultimate aim is to unravel the role of GPR124 in AML pathogenesis and to shed more light into the potential effects of metabolism in lineage determination.