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602.MYELOID ONCOGENESIS: BASIC

The Role of G0S2 in Lipid Metabolism Regulation in Chronic Myeloid Leukemia

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Introduction: Chronic myeloid leukemia (CML) can be effectively treated with tyrosine kinase inhibitors (TKIs) targeting BCR::ABL1, but resistance remains a clinical problem. TKIs do not target the quiescent CML leukemic stem cell (LSC), and many patients are treated for life at a high economic burden and sometimes with significant side effects. We recently published a tumor suppressor role for G0/G1 switch gene 2 (G0S2) in CML. Our data showed that loss of G0S2 expression in CML promoted disease progression and drug resistance by disrupting glycerophospholipid metabolism (Gonzalezet al. *Clin Transl Med, 2022*). Interestingly, G0S2 is an estrogen-response gene that demonstrated anti-estrogenic and pro-migratory effects in ER+ versus ER- breast cancer. Additionally, deletion of G0S2 prevented obesity and insulin resistance in mouse models. Since sex-based differences in lipid metabolism and obesity are well documented, we hypothesized that the tumor suppressor role of *G0S2* in CML would differ based on sex.
Methods: We used peripheral blood from wild-type and *G0s2* knockout ($G0s2^{-/-}$) mice (both male and female) who were fed with a normal versus a high-fat diet. Resulting lineage-negative (Lin-) cells were cultured in recombinant murine cytokines ± granulocyte-colony stimulating factor (mG-CSF, 25 ng/ml, 7-10 days) in *in vitro* differentiation assays. Flow cytometry analysis was performed to measure CD11b+ neutrophils. Additionally, we transduced Lin- cells from wild-type or *G0s2* knockout mice with BCR::ABL1, and assessed their ability to form a leukemia-like disease process in male versus female recipient mice. We also performed G0S2 ectopic expression and knockdown experiments in the K562 CML cell line and assessed the resulting cells by liquid chromatography (LC)/mass spectrometry (MS)-based lipidomics and proteomics analyses. Immunoblots were performed to assess the resulting cells for changes in the autophagy markers, LC3A/B I-II.
Results: For the experiments conducted with mouse peripheral blood, RT-qPCR data showed high *G0S2* mRNA expression upon neutrophil differentiation in wild-type male mice (n=5), but not in the wild-type female mice (n=5). Flow cytometry measuring CD11b markers showed that a high-fat diet-induced neutrophil production in wild-type male mice, but not in wild-type female mice or $G0s2^{-/-}$ mice, suggesting hormonal regulation involving *G0S2* and female mice. Consistent with this observation, forced BCR::ABL1 expression in $G0s2^{-/-}$ bone marrow reduced overall survival in female (n=4/group) but not male (n=5/group) mice compared with wild-type controls. In mass spectrometry-based lipidomics analyses, G0S2 knockdown resulted in a substantial decrease of di- and triglycerides. G0S2 knockdown also resulted in substantial changes in phosphatidylethanolamine and phosphatidylcholine expression, implicating G0S2 in the production of lipid bilayer components. Conversely, ectopic *G0S2* expression promoted the accumulation of long- and very long-chain triglycerides and species of phosphatidylcholine and phosphatidylethanolamine in K562 cells. Proteomics analyses showed autophagy as one of the top pathways affected by altered G0S2 expression. When we measured LC3A/B I-II by immunoblot, we observed opposing effects comparing G0S2 ectopic expression versus knockdown.
Conclusion: Altogether, these findings suggest sex-based differences in the role of G0S2 and lipid metabolism in CML stem and progenitor cell differentiation, survival, and autophagy, both *in vitro* and *in vivo*. Restoring G0S2 expression combined with BCR::ABL1 inhibition may be a novel clinical strategy to induce treatment-free remission in CML. However, further studies should assess whether this strategy will have similar effects in male versus female patients.

Disclosures No relevant conflicts of interest to declare.

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