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Commentary

Lipids and Their Effects in Chronic Lymphocytic Leukemia

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Chronic lymphocytic leukemia (CLL) is an incurable common B-cell malignancy with a spectrum of clinical outcomes. Over the past decade, our increasing understanding of the drivers of CLL progression has led to the development and use of novel therapeutics. For example, B-cell receptor (BCR) signaling was shown to be overactive in CLL, and subsequently the kinase inhibitors ibrutinib (BTK inhibitor) and idelalisib (PI3K delta inhibitor) were found to have clinical efficacy in this malignancy (Byrd et al., 2013; Furman et al., 2014). Despite these new treatments, CLL remains incurable and there remains a need to identify new therapeutic targets.

The therapeutic target of interest for McCaw et al. (2017) in their *EBioMedicine* article is lipid metabolism. It has been appreciated for many years that lipids have importance in CLL progression and outcomes. Most notably, lipoprotein lipase is a well-known (although not routinely measured clinically) prognostic factor in CLL, with higher levels associated with inferior clinical outcomes. LPL is not expressed in normal lymphocytes, but its expression is increased in CLL cells, particularly in the IGHV unmutated subset (Heintel et al., 2005). LPL catalyzes hydrolysis of VLDL and chylomicrons, releasing fatty acids. LPL also has non-catalytic functions, for example co-localizing with lipoproteins at the cell surface. In CLL cells, the exact function of LPL and the reason for its overexpression compared to normal B-cells is not fully understood. However, recent work has demonstrated that inhibition of LPL with orlistat induces CLL apoptosis, and that LPL expression is increased by BCR cross-linking, by binding of STAT3 to the LPL promoter, and by certain CLL stimulants that induce demethylation of the LPL gene (Moreno et al., 2013; Pallasch et al., 2008; Rozovski et al., 2015). Together, this previous work has suggested that free fatty acids, liberated by LPL, may be a protective factor for CLL lymphocytes.

Within this context, McCaw et al. (2017) provide a compelling argument for the role of lipids in inducing second messenger signaling in CLL. The authors were intrigued by a recent case-control study in Canada that demonstrated that CLL patients have more dyslipidemia than age-matched controls, and that CLL patients who took HMG-CoA reductase inhibitors ("statins") had improved survival compared to CLL patients who did not take these medications, which confirmed similar results in smaller CLL cohorts (Chae et al., 2014; Friedman et al., 2010; Mozessohn et al., 2017). Together with the story regarding lipoprotein lipase, these clinical data beg the question of if and how LDLs affect CLL cells.

In their paper, McCaw et al. (2017) focus on LDL potentiation of cytokine-induced STAT3 phosphorylation. The authors demonstrate that LDLs are able to increase STAT3 phosphorylation within the context of cytokine stimulation, not BCR cross-linking. The induced STAT3 phosphorylation was suppressed by anti-IL10 antibodies and by small molecule JAK inhibition, suggesting overlapping pathways with IL10 and JAK mediated signaling. The authors evaluated which of the different components of LDL contributed to the effect on STAT3 phosphorylation, and they found that long-chain fatty acids and free cholesterol were the main actors. Lastly, the authors found a negative correlation between the extent of LDL-potentiated STAT3 phosphorylation and HMGCoA reductase expression. Since HMGCoA reductase is the rate limiting step in cholesterol synthesis, this suggests that the subset of CLL cells with lower intracellular cholesterol synthesis are affected more by LDL incubation, and that this mechanism may be important for disease progression amongst these patients.

McCaw et al.'s work (McCaw et al., 2017) adds important information to the growing knowledge regarding the effect of lipids on CLL cell biology, however numerous unknowns remain. For example, molecular prognostic markers in the CLL patients in these experiments are not fully detailed, LPL levels are unknown, and serum lipid levels are unknown. These could affect the *in vitro* findings observed. Second, the relevance of the results in this manuscript within the context of research related to LPL is not explored. Third, it would be helpful to investigate LDL-induced effects on a broader representation of relevant CLL signaling pathways including other chemokines, TNF family members (BAFF, APRIL), and TLR agonists. This would provide insight into the relative importance of lipoprotein metabolism in different aspects of CLL cell biology. Fourth, as more attention is paid to the CLL microenvironment, it would be interesting to learn if and how lipids and lipoproteins modulate the interaction between CLL cells and nurse-like cells. Lastly, from a therapeutic perspective, do lipid-lowering medications, such as statins, synergize with BTK or PI3K inhibitors in CLL?

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The key messages to take away from the work performed by McCaw et al. (2017) is that lipids and lipoproteins appear to contribute to intracellular second messenger signaling in CLL cells. As these findings occur in the context of stimulated CLL cells *in vitro*, it is not clear whether these results are important for CLL patients themselves. These concerns are addressed in part by the findings that CLL patients with dyslipidemia have inferior outcomes, but additional confirmatory studies are needed. The next logical areas to investigate are (1) the effect of lipids and lipoproteins on CLL cell viability, particularly in the context of supportive nurse-like cells, (2) the effect of lipids and lipoproteins in the Eμ-TCL1 CLL mouse model, and (3) the extent to which lipid lowering therapies can add to existing kinase inhibitors in their anti-CLL effect (either *in vitro* or *in vivo*). McCaw and colleagues' studies will be a key stepping stone in the future understanding of this important pathway in CLL.

Disclosure

The author declared no conflicts of interest.

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