Breast cancer is the second leading cause of cancer related deaths in women in the United States, with most mortalities associated with recurrent metastasis. Interestingly, high cholesterol levels are associated with an increased risk of breast cancer recurrence and poor prognosis, while therapies that lower cholesterol concentrations are associated with a good prognosis. Previous work has identified a metabolite of cholesterol, 27-Hydroxycholesterol (27HC), as being able to promote the progression and metastasis of breast cancer. 27HC does so by acting on myeloid immune cells. Within the tumor microenvironment, macrophages are abundant cells in the myeloid lineage. When macrophages were treated with 27HC, their ability to activate T cells was impaired. Those T cells that were activated, had a decreased anti-cancer cytotoxic response. Subsequent work has identified the LiverxReceptor (LXR) as mediating the immune-suppressive effects of 27HC. However, the mechanism by which LXR activity within myeloid cells inhibits subsequent T cell activity is unknown. ABCA1 is a classic target gene of LXR and is known to facilitate cholesterol efflux from the cell. Our analysis of publicly available transcriptome indicates that ABCA1 expression within breast tumors is associated
with good prognosis. These somewhat paradoxical observations suggest that ABCA1 exhibits a pro-immune and anti-cancer effect – opposite to what we would expect for LXR activation. Therefore, the goal of the current work is to determine the effect of manipulation of ABCA1 within macrophages and its consequent effect on T cells in vitro and in context to breast cancer metastasis. Our results to date indicate that knocking down ABCA1 using siRNA by targeting the 3’ UTR decreased the expression of genes associated with macrophage function and interaction with T cells. Importantly, many of those effects were rescued by over-expression of ABCA1. In summary, our results indicate that although ABCA1 is a target gene of LXR, the induction of ABCA1 by LXR may be compensatory rather than driving the immunosuppressive effects of 27HC. Thus, we hypothesize that ABCA1 plays a pro-immune function and could be a potential therapeutic target to boost the immune system.

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