LPA-induced increase in triple-negative breast cancer stem cells via IL-8 production.

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Triple-negative breast cancer (TNBC) is a highly aggressive cancer with fewer effective targeted therapy. Since growing evidence suggests that TNBC is originated from breast cancer stem cells (BCSCs), it is required to elucidate the molecular mechanism of BCSC proliferation for new drug development. We have previously reported that a lipid mediator lysophosphatidic acid (LPA) increased BCSCs via Ca^{2+} signaling pathway. In this study, we examined whether calcineurin/NFAT pathway is involved in the LPA-induced increase in BCSCs. We found that LPA stimulation increased the transcriptional activation of NFAT. The calcineurin inhibitor cyclosporine A inhibited both LPA-increased NFAT activation and increase in BCSCs. We next examined the downstream signaling pathway. To identify NFAT target gene which is involved in the LPA-induced increase in BCSCs, we performed RNA-sequencing using MDA-MB-231 cells. We identified that 428 transcripts were upregulated by LPA by two fold or more. Among them, we focused on proinflammatory cytokine IL-8 which promoter contains NFAT consensus sequence. We found that LPA increased IL-8 production in MDA-MB-231 cells. In addition, a selective IL-8 receptor antagonist inhibited the LPA-induced increase in BCSCs. These results suggested that LPA increases BCSC through the NFAT-mediated IL-8 production.