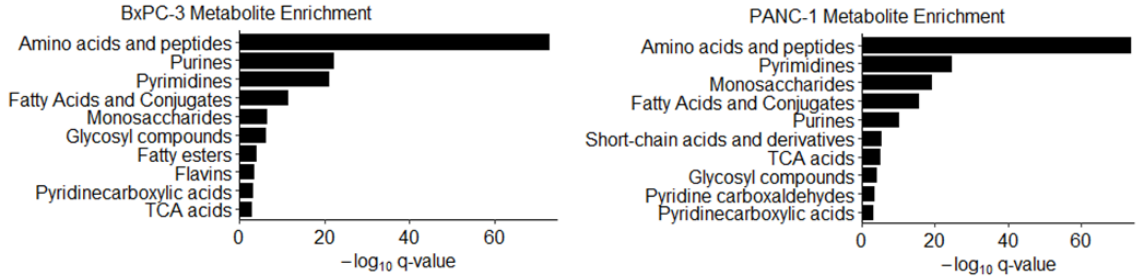
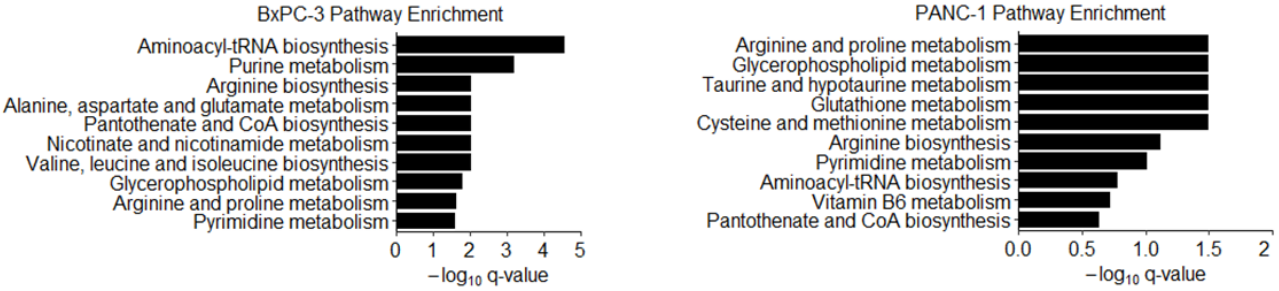
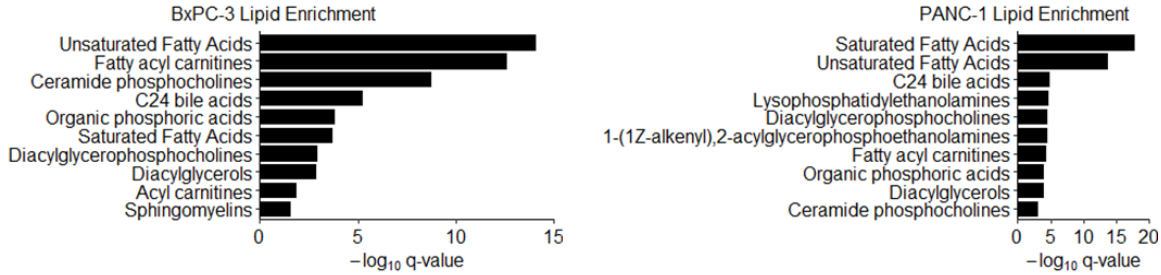


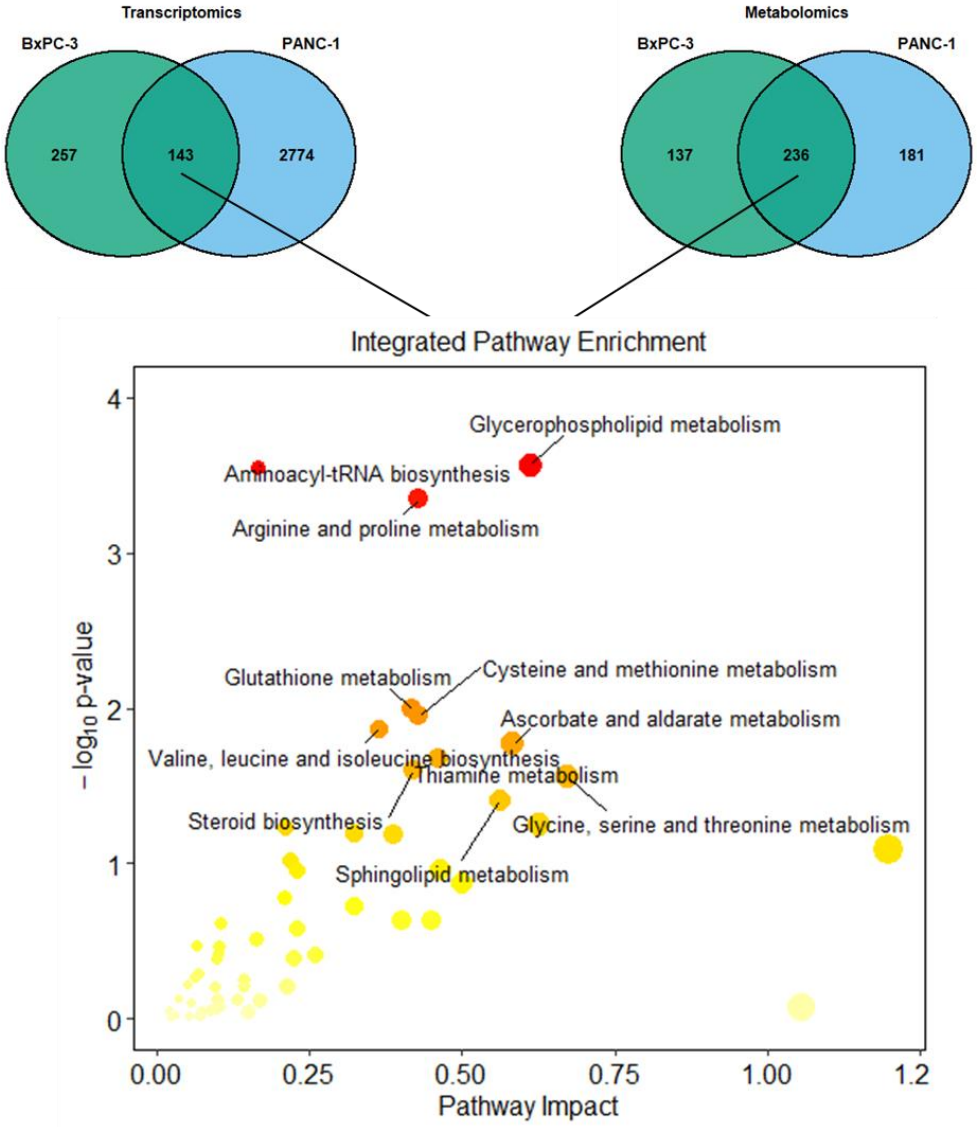
Supplementary Figure S1. Metabolite class enrichment of total DDMs is associated with amino acids and fatty acids. Total statistically significant ($P < 0.05$) DDMs were used.



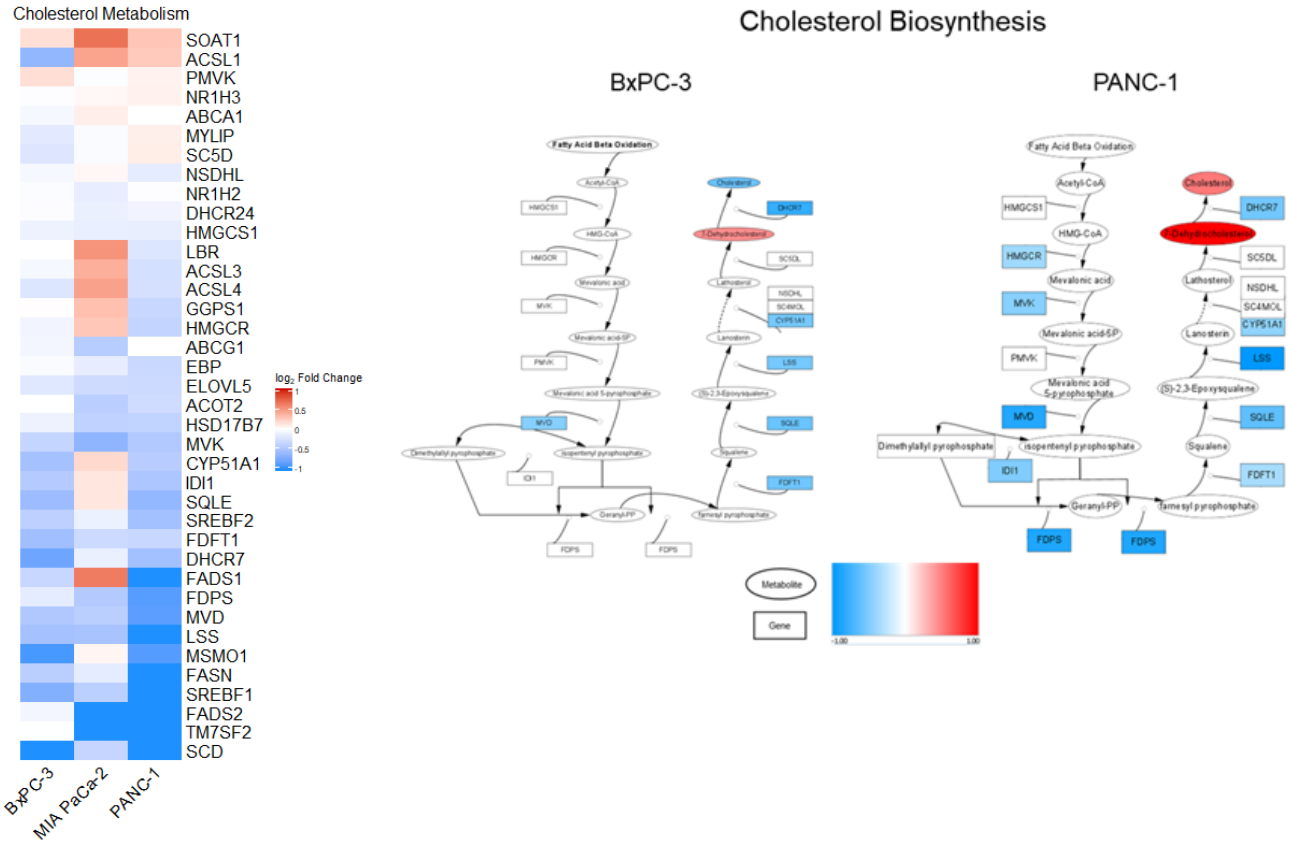
Supplementary Figure S2. Metabolite pathway enrichment of total DDMs is associated with amino acid and glycerophospholipid metabolism. Total statistically significant ($P < 0.05$) DDMs were used.



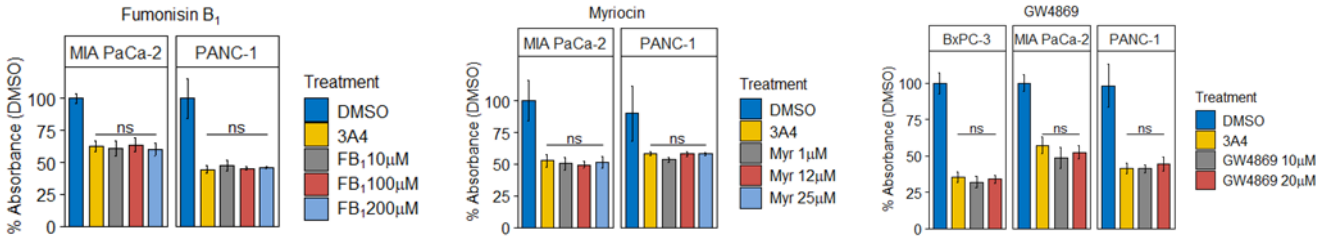
Supplementary Figure S3. Lipid metabolite enrichment of total DDMs is associated with fatty acids and phospholipids. Total statistically significant ($P < 0.05$) DDMs were used.



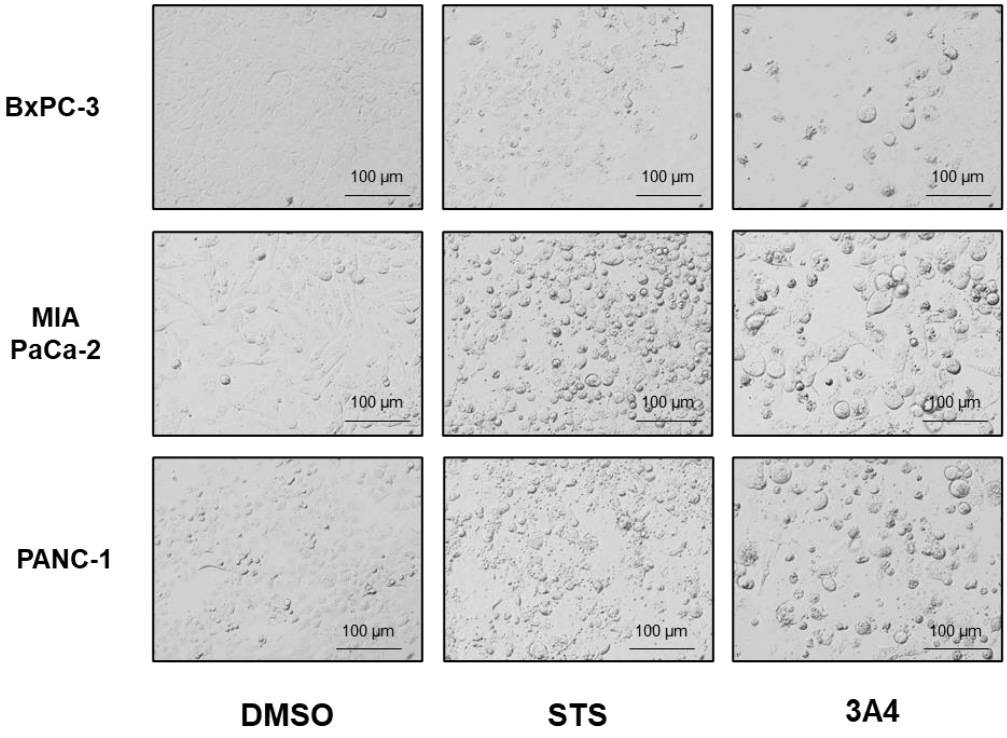
Supplementary Figure S4. Integration of transcriptomics and metabolomics indicates glycerophospholipid metabolism is highly enriched. Joint pathway enrichment analysis was performed with MetaboAnalyst 5.0 using the overlapping statistically significant DEGs and DDMs from BxPC-3 and PANC-1. Negative $\log_{10}$ p-values are shown on y-axis and pathway impact values from pathway topology analysis are shown on x-axis. Labels are shown for those with p-values < 0.05. Color corresponds to statistical significance and size to pathway impact value.



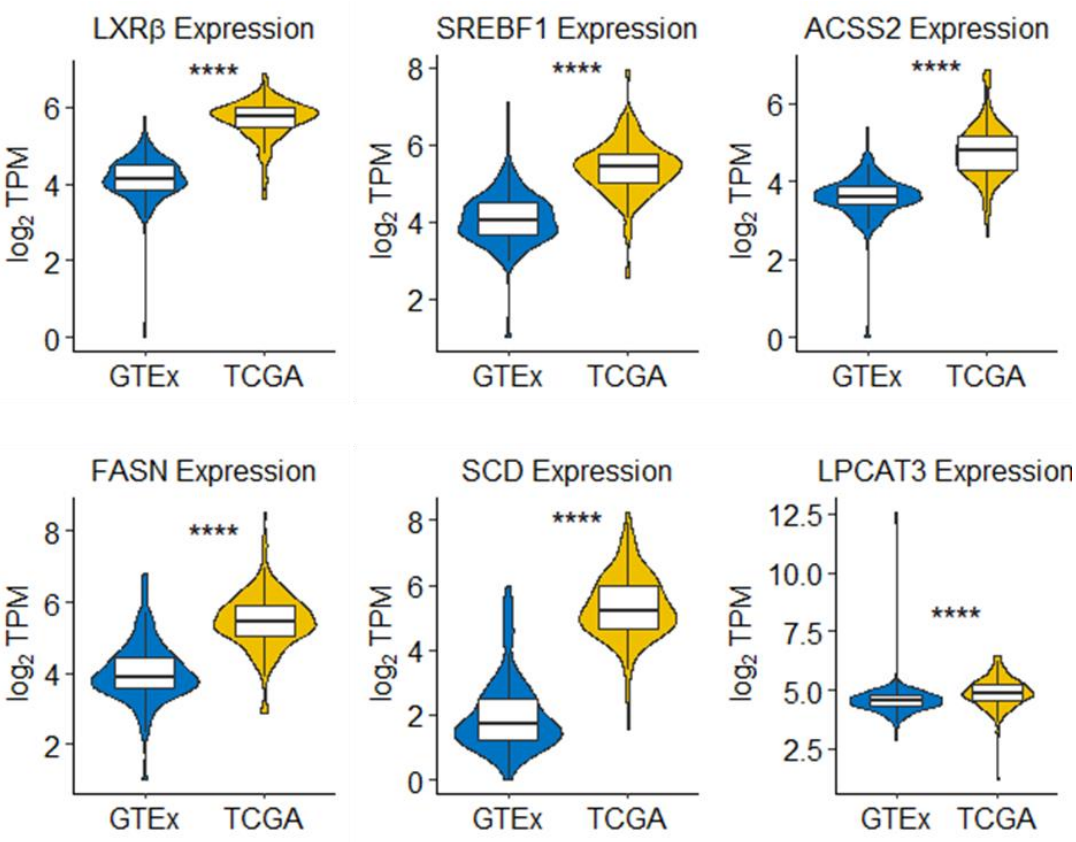
Supplementary Figure S5. 3A4 affects the expression of cholesterol biosynthesis genes. (Left) heatmap of $\log_2$ fold change (vs. DMSO) expression values of cholesterol metabolism genes. (Right) cholesterol biosynthesis pathway map of metabolites and genes. Log_2 fold change (vs. DMSO) reported for metabolites and genes. Metabolites are depicted as ellipses and genes as rectangles.



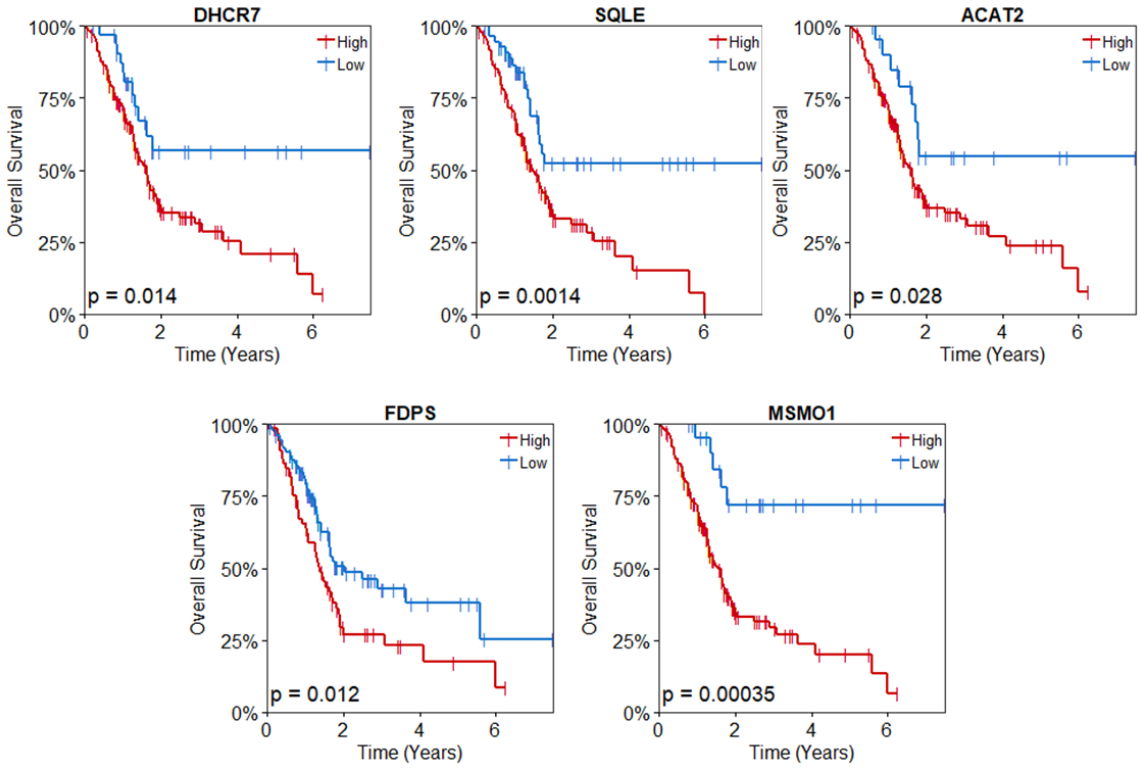
Supplementary Figure S6. Ceramide synthesis inhibition does not rescue the antiproliferative effects of 3A4. MTS viability assays of chemical ceramide synthesis inhibitors Fumonisin B1, Myriocin, and GW4869. Results are from three independent biological replicates and represent the mean ± SEM. Student's t-test, with $p < 0.05$ considered statistically significant.



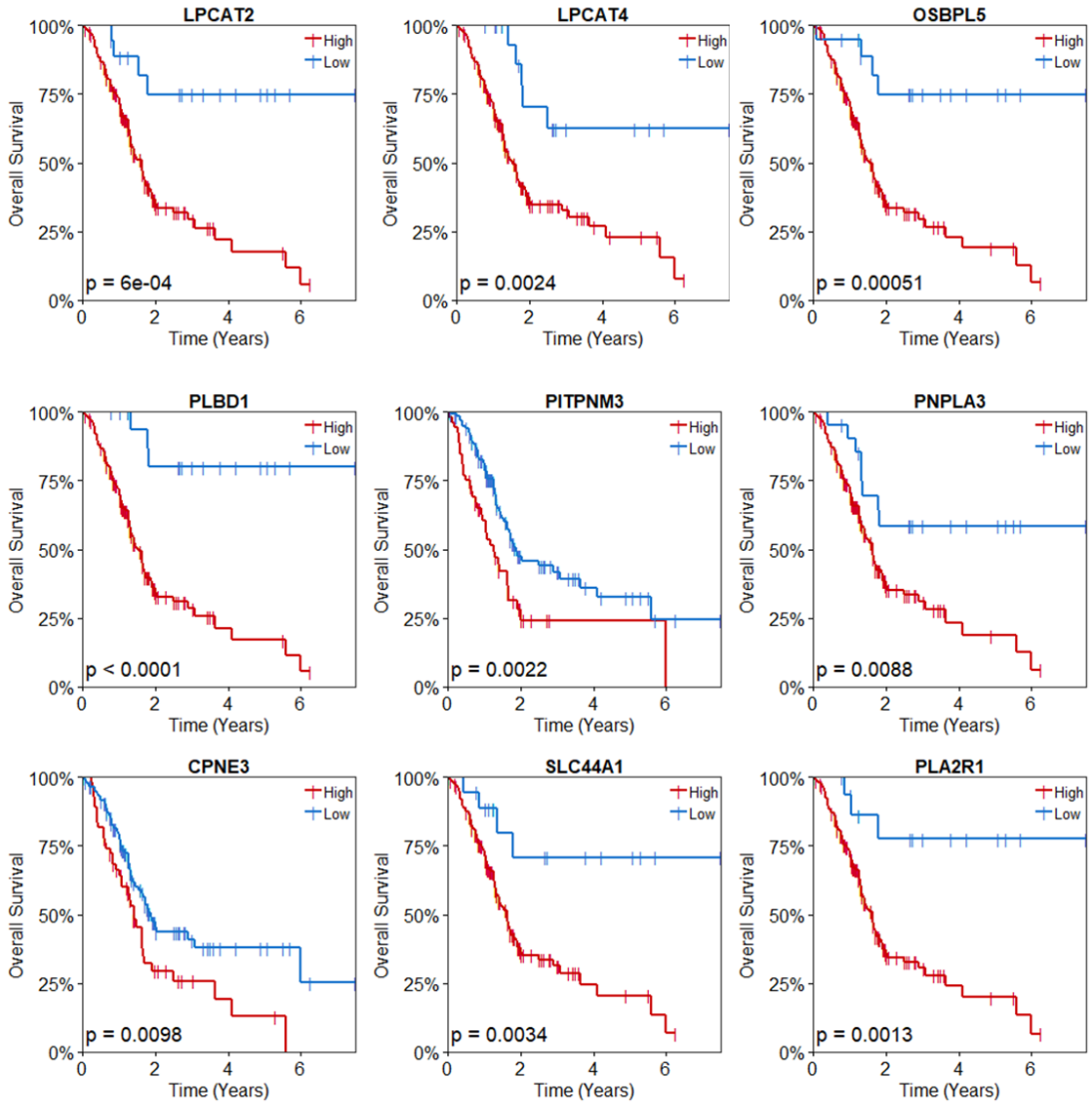
Supplementary Figure S7. Morphological changes induced by 3A4 differ from apoptosis. Cells were treated with DMSO, the apoptosis inducer staurosporine (STS), and 3A4 for 72 hours and imaged with brightfield microscopy at 400X total magnification.



Supplementary Figure S8. LXRβ and its target genes are overexpressed in pancreatic cancer. TPM values of LXRβ and associated genes in TCGA pancreatic cancer samples (PAAD) and GTEx normal pancreas samples. Statistical significance of differences in means determined by Welch's t-test (**** = $P < 0.0001$).



Supplementary Figure S9. Cholesterol synthesis genes are correlated with survival in PDAC patients. Kaplan-Meier plots of TCGA data from the PAAD cohort for genes involved in cholesterol synthesis that are downregulated by 3A4.



Supplementary Figure S10. Phospholipid synthesis and remodeling genes are correlated with survival in PDAC patients. Kaplan-Meier plots of TCGA data from the PAAD cohort for genes involved in phospholipid synthesis/remodeling that are downregulated by 3A4.