Cytosolic phospholipase A$_2$alpha (cPLA$_2$alpha) is a rate-limiting key enzyme that releases arachidonic acid (AA) from membrane phospholipid. This study shows a novel role of cPLA$_2$alpha for activation of peroxisome proliferator-activated receptor-delta (PPARdelta) and STAT3 in the nuclei. Overexpression of cPLA$_2$alpha in human hepatocellular carcinoma cells (Hep3B) induced the binding of PPARdelta to STAT3 response element through the release of transcriptional repressor Bcl-6 and increased STAT3 reporter activity as determined by luciferase reporter activity assay. These effects are significantly inhibited by the cPLA$_2$alpha siRNA and specific inhibitors (AACOCF3 and Pyrrolidine) as well as by siRNA knockdown of PPARdelta. Overexpression of PPARdelta or treatment with the selective PPARdelta ligand, GW501516, also increased PPARdelta binding to STAT3 response element and increased STAT3 reporter activity. Addition of GW501516 to nuclear extracts induced a comparable degree of PPARdelta binding to STAT3 response element. Moreover, overexpression of PPARdelta or treatment with GW501516 upregulated the expression of STAT3 and its downstream anti-apoptotic molecules including Mcl-1, Survivin and Bcl-XL. These results reveal a novel interaction linking cPLA$_2$alpha, PPARdelta and STAT3 signaling pathways in human hepatocellular carcinoma cells.

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