T cells are often absent from human cancer tissues during both spontaneously-raised immunity and therapeutic immunotherapy, even in the presence of a functional T cell-recruiting chemokine system, suggesting the existence T cell exclusion mechanisms that impair infiltration. Using a genome-wide *in vitro* screening platform, we identified a role for phospholipase A2 group 10 (PLA2G10) protein in T cell exclusion. PLA2G10 upregulation is widespread in human cancers and is associated with poor T cell infiltration in tumor tissues. PLA2G10 overexpression in immunogenic mouse tumors excluded T cells from infiltration, resulting in resistance to anti-PD-1 immunotherapy. PLA2G10 can hydrolyze phospholipids into small lipid metabolites thus inhibiting chemokine-mediated T cell mobility. Ablation of PLA2G10’s enzymatic activity enhanced T cell infiltration and sensitized PLA2G10-overexpressing tumors to immunotherapies. Our study implicates a role for PLA2G10 in T cell exclusion from tumors and suggests a potential target for cancer immunotherapy.