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Phosphoinositides play important roles as signaling molecules in different cell compartments by regulating the localization and activity of proteins through their interaction with specific domains. The activity of these lipids depends on which sites on the inositol ring are phosphorylated. Signaling pathways dependent on phosphoinositides phosphorylated at the D3 position of this ring (3-phosphoinositides) are negatively regulated by 3-phosphoinositide-specific phosphatases that include PTEN and myotubularin. Using the conserved PTEN catalytic core motif, we have identified a new protein in the Dictyostelium genome called phospholipid-inositol phosphatase (PLIP), which defines a new subfamily of phosphoinositide phosphatases clearly distinct from PTEN or other closely related proteins. We show that PLIP is able to dephosphorylate a broad spectrum of phosphoinositides, including 3-phosphoinositides. In contrast to previously characterized phosphoinositide phosphatases, PLIP has a preference for phosphatidylinositol 5-phosphate, a newly discovered phosphoinositide. We found that PLIP is localized in the Golgi, with its phosphatase domain facing the cytoplasmic compartment. PLIP null cells created via homologous recombination are unable to effectively aggregate to form multicellular organisms at low cell densities. The presence of PLIP in the Golgi suggests that it may be involved in membrane trafficking.