Phosphatidylinositol 4-kinasesare evolutionarily conserved enzymes that catalyze the formation of phosphatidylinositol 4-phosphate and ADP from phosphatidylinositoland ATP, the first step in the synthesis of phosphatidylinositol phosphates. Two types of PtdIns 4-kinaseshave been identified based on their biochemical properties. Type III PtdIns 4-kinases all contain a common catalytic kinase domain, which is also found in type I PtdIns 3-kinases. There are two type III PtdIns 4-kinases in S. cerevisiae, encoded by PIK1 and STT4. LSB6 encodes the single type II PtdIns 4-kinase in yeast.Pik1p is a soluble 125-kDa enzyme, and Stt4p is a plasma membrane-associated 215-kDa enzyme. Together, Pik1p and Stt4p account for the vast majority of PtdIns 4-kinase activity in wild-type yeast cells. The two different type III PtdIns 4-kinases synthesize discrete pools of PtdIns 4-phosphate with essential roles in cell physiology. Overproduction of one of these type III PtdIns 4-kinases cannot compensate for a gene disruption in the other. Stt4p is homologous to mammalian PtdIns 4-kinase alpha, and Pik1p to mammalian PtdIns 4-kinase beta.Stt4p is required for the maintenance of vacuole morphology, cell wall integrity, and actin cytoskeleton organization, as well as 30148>sphingolipid biosynthesis. Stt4p also plays a role in the regulation of the intracellular transport of the aminophospholipid phosphatidylserine from the ER to the Golgi. Stt4p binds to the plasma membrane via the protein Sfk1p, where it promotes cell-wall synthesis, actin cytoskeleton organization, and the Rho1/Pkc1-mediated mitogen-activated protein kinase cascade. STT4 is an essential gene in some backgrounds, but not in others. Conditional stt4 mutants are temperature-sensitive and can be rescued by sorbitol. stt4 deletion mutants lack most of the PtdIns 4-kinase activity that is detected in the wild-type, and arrest in the G2/M phase of the cell cycle. Inactivation of Stt4p results in mislocalization of the Rho-GTPase guanine nucleotide exchange factor Rom2p, and also in the rapid attenuation of translation initiation. Synthetic genetic arrayanalysis using a temperature-sensitive allele of STT4 indicates that stt4cells can not tolerate perturbations in long chain fatty acid elongation.About Phosphatidylinositol Phosphate Biosynthesis The phosphorylated products of phosphatidylinositol, collectively referred to as phosphoinositides or phosphatidylinositol phosphates, are membrane-bound lipids that function as structural components of membranes, as well as regulators of many cellular processes in eukaryotes, including vesicle-mediated membrane trafficking, cell wall integrity, and actin cytoskeleton organization. PtdInsPs are also precursors of the water-soluble inositol phosphates, an important class of intracellular signaling molecules. The inositol ring of the membrane phospholipids and the water-soluble IPs are readily phosphorylated and dephosphorylated at a number of positions making them well suited as key regulators. PtdIns can be phosphorylated at one or a combination of positionson the inositol headgroup, generating a set of unique stereoisomers that have specific biological functions. These stereoisomers have been shown to be restricted to certain membranes. Phosphatidylinositol 4-phosphateis the major PtdInsP species of the Golgi apparatus, where it plays a role in the vesicular trafficking of secretory proteins from the Golgi to the plasma membrane. Phosphatidylinositol 4,5-bisphosphateis the major species found at the plasma membrane and is involved in the regulation of actin cytoskeleton organization, as well as cell wall integrity, and heat shock response pathways. Phosphatidylinositol 3-phosphateis found predominantly at endosomal membranes and in multivesicular bodies, where it plays a role in endosomal and vacuolar membrane trafficking. Phosphatidylinositol 3,5-bisphosphateis found on vacuolar membranes where it plays an important role in the MVB sorting pathway. Phosphorylation and dephosphorylation of the inositol headgroups of PtdInsPs at specific membrane locations signals the recruitment of certain proteins essential for vesicular transport. PtdInsPs recruit proteins that contain PtdInsP-specific binding domains, such as the well-studied pleckstrin homologydomain that recognizes the phosphorylation pattern of specific PtdInsP inositol headgroups. A number of kinases and phosphatases are involved in the generation and interconversions of PtdInsPs, the majority of which have been well conserved during evolution. The PtdInsP kinases, in contrast to the lipid phosphatases, have a higher degree of specificity. While each kinase appears to phosphorylate only one substrate, many of the lipid phosphatases can dephosphorylate a number of substrates.