INP51, INP52, INP53, and INP54 encode members of a conserved family of phosphoinositde phosphatases that contain an inositol polyphosphate 5-phosphatase domain. This domain in these enzymes specifically hydrolyzes phosphates at position 5 of inositol rings, PtdIns[4,5]P2 being the preferred substrate. Inp52p is partially redundant in function with both Inp51p and Inp53p, but these latter two proteins have cellular functions that are independent of each other. None of the genes is essential for growth, however a triple deletion of inp51 inp52 inp53 is lethal. The inviability of the triple-null strain can be rescued by expressing mouse Inpp5b. Inp51p, Inp52p, and Inp53p also possess a second catalytic domain known as the Sac1-like domain, which is highly conserved and also found in the IP phosphatases Sac1p, Fig4p, and mammalian synaptojanin-1and synaptojanin-2. The Sac1-like domain of Inp52p and Inp53p enables these proteins to recognize and dephosphorylate a broader range of substrates including PtdIns[3]P, PtdIns[4]P, and PtdIns[3,5]P2. Although Inp51p contains a Sac1-like domain, this domain is non-functional due to mutations of key residues in the highly conserved CX5Rdomain.Inp54p tightly associates with the cytoplasmic side of the ER membrane via a hydrophobic region in its C-terminus. inp54 null mutants display increased levels of protein secretion.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.