Phosphatidylinositol transfer proteins and their role in eukaryotic cell: study in yeast.

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An important part of the mechanisms providing for the proper lipid composition of individual cell membranes are lipid transfer proteins. Phosphatidylinositol transfer proteins (PITPs) were found in all eukaryotic organisms from the lower unicellular organisms like yeasts to mammals, including humans. In mammals as well as in the model organisms individual PITPs play specific roles in many essential biological processes including neutrite outgrowth, membrane traffic, cytokinesis, and sensory transduction (1). These PITPs functions are connected to the roles of phosphorylated derivatives of phosphatidylinositol, phosphoinositides, which regulate fundamental biological processes. From numerous studies a model emerges in which PITPs promote the synthesis of phosphorylated derivatives of PI either by delivery of PI to the target membranes from the ER or by presentation of PI to PI modifying enzymes, PI kinases. It is generally accepted that PITPs extract a PI molecule from a donor membrane and transfer it in the hydrophobic pocket to an acceptor membrane. Such an efficient lipid exchange can be accomplished when transport occurs at membrane contact sites.

In the yeast *S. cerevisiae*, 6 PITPs were identified. These yeast PITPs reside in different cellular compartments and fulfill variable roles in the yeast cell physiology (2). Two homologous yeast PITPs, Pdr16p and Pdr17p, play a role in maintaining the proper membrane lipid composition. Pdr16p is considered one of the determinants of azole resistance in *S. cerevisiae* and also in pathogenic yeasts. Our study was aimed at a better understanding of Pdr16p function, especially in relation to azole resistance in yeast. We have identified changes in ergosterol biosynthesis in the pdr16 delta strain when the yeast cells were challenged with azoles. However, these changes were not caused by the increased accumulation of azoles. Based on complementation studies of the azole-susceptibility phenomenon, we propose a hypothesis that Pdr16p could assist in intracellular shuttling of sterols or their intermediates between membranes or, alternatively, between biosynthetic enzymes or complexes. Being a PITP protein, Pdr16p facilitates transfer of phosphatidylinositol (PI) between membrane compartments in *in vitro* systems. To understand the role of PI binding for Pdr16p function we generated Pdr16p$^{E235A,\ K267A}$ mutant defective in PI binding. This PI binding deficient mutant was not able to fulfill the role of Pdr16p in protection against azole and morpholine antifungals, providing evidence that PI binding is critical for Pdr16 function in modulation of sterol metabolism in response to these two types of antifungal drugs. A novel feature of Pdr16p, and especially of Pdr16p$^{E235A,\ K267A}$ mutant, to bind sterol molecules, was observed.

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(2) Griac P. 2007. Biochim Biophys Acta 1771: 737-45.