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MS7-O2 Membrane Enzymes: the Structural basis of Phosphatidylinositol Mannosides Biosynthesis in Mycobacteria

Marcelo E. Guerin[1,2]

1. IKERBASQUE, Basque Foundation for Science, 48013, Bilbao, Spain
2. Structural Biology Unit, CIC bioGUNE, Bizkaia Technology Park, 48160 Derio, Spain

email: mrcguerin@gmail.com

Membrane enzymes constitute a large class of proteins with critical roles in a variety of cellular processes in all living organisms. They generate a significant amount of structural diversity in biological systems, which are particularly apparent in cell-pathogen interactions. Many of these enzymes are required to access a lipophilic substrate located in the membranes and to catalyze its reaction with a polar, water-soluble compound.[1] Here we focus on the membrane enzymes involved in the early steps of the phosphatidylinositol mannosides (PIMs) biosynthetic pathway, essential structural components of the cell envelope of *Mycobacterium tuberculosis*. Of particular relevance, we demonstrate the occurrence of a conformational switch during the catalytic cycle of the retaining glycosyltransferase PimA, the enzyme that start the pathway, involving both β-strand–to–α-helix and α-helix–to–β-strand transitions. [2, 3] These structural changes seem to modulate catalysis and are promoted by interactions of the protein with anionic phospholipids in the membrane surface. Our studies demonstrate that protein-membrane interactions might entail unanticipated structural changes in otherwise well conserved protein architectures, and suggests that similar changes may also play a functional role in other membrane-associated enzymes. Finally, we report the crystal structures of PatA, an essential membrane acyltransferase that transfers a palmitoyl moiety from palmitoyl–CoA to the 6-position of the mannose ring added by PimA, in the presence of its naturally occurring acyl donor palmitate and a nonhydrolyzable palmitoyl–CoA analog. The structures reveal an α/β architecture, with the acyl chain deeply buried into a hydrophobic pocket that runs perpendicular to a long groove where the active site is located. Enzyme catalysis is mediated by an unprecedented charge relay system, which markedly diverges from the canonical HX_4D motif. Our studies establish the mechanistic basis of substrate/membrane recognition and catalysis for an important family of acyltransferases, providing exciting possibilities for inhibitor design. [4]

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