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BACTERIAL PHYSIOLOGY

Bacterial lipid rafts discovered

> functional lipid rafts that coordinate cellular signalling pathways exist in bacterial as well as eukaryotic membranes.

In eukaryotic cells, membrane proteins involved in signal transduction are often localized into microdomains that are enriched in particular lipid species. Commonly referred to as lipid rafts, these microdomains are important for cellular function, and their disruption can cause defects in signal transduction processes. In bacteria, the heterogeneous distribution of several proteins in the cytoplasmic membrane has hinted at the existence of functional membrane microdomains, but whether these foci are true lipid rafts has remained unclear. Now, writing in *Genes & Development*, López and Kolter describe the identification and characterization of bacterial lipid rafts that are important for the signalling pathways that regulate biofilm formation in *Bacillus subtilis*.

López and Kolter had previously discovered that the antifungal agent nystatin can trigger *B. subtilis* biofilm formation by activating a signalling pathway involving the membrane histidine kinase KinC and the transcription factor Spo0A. This observation was somewhat curious, given that nystatin inhibits fungal growth by binding to ergosterol in the membrane, but ergosterol is not produced by bacteria. Therefore, the authors used bioinformatics to identify known or putative *B. subtilis* genes that might be involved in the synthesis of ergosterol-like lipids. They identified *yisP*, which encodes a functional squalene synthase; the deletion of *yisP* blocked nystatin-dependent biofilm formation. Liquid chromatography–mass spectrometry analysis of lipid extracts from wild-type and Δ*yisP* strains revealed two peaks that were absent in the deletion mutant. Furthermore, addition of exogenous squalene-derived molecules rescued nystatin-dependent biofilm formation in the Δ*yisP* mutant.

To investigate whether the lipid species produced by YisP might organize KinC into membrane microdomains, the authors compared the constituents of the detergent-resistant membrane (DRM) and detergent-sensitive membrane (DSM) fractions from *B. subtilis* extracts. Using SDS-PAGE, they observed substantially different protein profiles in the two fractions, with KinC only present in the DRM fraction. Importantly, the number and intensity of the protein bands in the DRM fraction was greatly decreased in extracts from the Δ*yisP* mutant.

In eukaryotes, the protein flotillin 1 is a common constituent of lipid rafts and is thought to have roles in raft formation and enhancing signal transduction. Interestingly, flotillin-like proteins are encoded by most bacteria. Accordingly, López and Kolter observed that the *yuaG* gene product (which has 39% sequence identity with flotillin 1) was heterogeneously distributed into approximately six distinct foci in the *B. subtilis* membrane, leading them to rename the encoded protein FloT. Furthermore, they found that KinC colocalized with FloT in these foci and that treatment of the cells with zaragozic acid — a squalene synthase inhibitor that inhibits the activity of YisP, thereby blocking the formation of the membrane microdomains — led to a gradual loss of the foci as FloT diffused throughout the membrane. Finally, the authors observed distinct membrane foci formed by FloT homologues in the membranes of *Staphylococcus aureus* and *Escherichia coli*.

Taken together, these findings suggest that functional lipid rafts that coordinate cellular signalling pathways exist in bacterial as well as eukaryotic membranes. Furthermore, these findings might explain the remarkable reduction in the incidence of post-operative bacterial infections in patients receiving statins to decrease high cholesterol levels. Therefore, disrupting lipid rafts might prove to be an effective approach to antibacterial therapy.

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ORIGINAL RESEARCH PAPER López, D. & Kolter, R. Functional microdomains in bacterial membranes. *Genes Dev.* **24**, 1893–1902 (2010)