

Lipid-mediated activation of ABC transporters

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Although ABC transporters are involved in membrane transport, little is known about the interaction between ABC transporters and lipids. We have reported that several transporters are activated by a specific lipid.

The multidrug transporter MDR1 (ABCB1) requires cholesterol for fully active transport. Cholesterol increases the affinity for drugs by 2-3 times or accelerates the turnover rate for several drugs (Kimura, *Biochem J*, 2007). Similarly, sphingomyelin (SM) increases the affinity of ABCG1 for cholesterol (Hirayama, *JLR*, 2014). We also found that the HDL-generating cholesterol transporter ABCA1 is completely dependent on phosphatidylserine (PS) which is rich in the plasma membrane (Sakata, *J Biochem*, 2024). PS enhanced the basal (without cholesterol) activity of ABCA1 and, importantly, cholesterol stimulated ATPase activity only in the presence of PS. This suggests that ABCA1 is a PS-dependent cholesterol transporter.

Why are some ABC transporters activated by specific lipids? The requirement for specific lipids is also found in different membrane proteins. Half of the GPCRs require cholesterol for their activity. Despite having the same ancestors, the plasma membrane P-type pump, Na-K ATPase, requires cholesterol, whereas the ER P-type pump, SERCA, does not. It is speculated that membrane proteins, including transporters, have evolved into the surrounding lipid where they function. I will discuss the methods to characterize the interaction between lipid and ABC transporters.