LIPID METABOLISM

Orm SPOTS demand

> the SPOTS complex dynamically coordinates the localization and activity of sphingolipid metabolism enzymes

Strongly conserved but of unknown function, orosomucoid (Orm) family proteins (encoded by Orm and Ormdl genes) are implicated in the development of childhood asthma. For example, single nucleotide polymorphisms that are associated with increased expression of Ormdl genes confer a heightened risk of the disease. Now, a global approach to characterizing Orm gene function identifies Orm proteins as homeostatic regulators of sphingolipid biosynthesis, thus implicating sphingolipid metabolism in the pathogenesis of asthma.

Sphingolipids are a large family of lipids with complex signalling functions. Their synthesis begins in the endoplasmic reticulum (ER), where the rate-limiting step is catalysed by serine palmitoyltransferase. This enzyme is encoded in yeast by *Lcb1* and *Lcb2*, and joins the sphingolipid precursors fatty acids and L-serine.

Breslow *et al*. investigated Orm function in the yeast *Saccharomyces cerevisiae*, using a genetic analysis that compares the phenotypic profiles of double mutants to identify pathways in which the individual mutant genes function. As the Orm family are ER proteins, the authors used the profiles of mutants from a study of ER biology, and identified a link between Orm genes and *Lcb1* and *Lcb2*. The overexpression of *Orm1* or *Orm2* produced profiles that correlated with decreased *Lcb1* and *Lcb2* expression, whereas the profile from the deletion of *Orm2* was inverted by comparison. This suggests that Orm proteins negatively regulate sphingolipid biosynthesis, which was confirmed by global lipidomic analysis: deletion of *Orm1* and *Orm2* causes higher flux throughout the sphingolipid biosynthetic pathway.

But how might Orm proteins inhibit sphingolipid biosynthesis? A novel protein complex, the serine palmitoyltransferase, Orm1 and Orm2, Tsc3 and Sac1 (SPOTS) complex, was identified using binding assays. Whereas Tsc3 is an activator of serine palmitoyltransferase, Sac1 is a phosphoinositide phosphatase involved in ER and Golgi trafficking. Deletion of Sac1 increases levels of sphingolipid precursors, but, as the Orm proteins and Sac1 bind to serine palmitoyltransferase independently, the authors suggest that they negatively regulate its function by distinct mechanisms.

The identification of several phosphorylated Orm species, and the use of the serine palmitoyltransferase inhibitor myriocin, provided further mechanistic clues. Comparisons of growth rate and metabolite levels between *Orm1*- and *Orm2*-deleted and wild-type yeast, with or without myriocin, indicated that cells use progressive inactivation of Orm1 and Orm2 to maintain sphingolipid output as serine palmitoyltransferase activity is inhibited. Inactivation of Orm proteins correlates with their phosphorylation, which seems to alter the higher-order assembly of the SPOTS complex. Phosphomutant Orm1 and Orm2 were able to interact with each other and with serine palmitoyltransferase, but blocked the normal regulation of SPOTS oligomerization and disrupted sphingolipid homeostasis. In the presence of myriocin, the suborganellar localization of labelled Orm2 was also altered.

The authors suggest that the SPOTS complex dynamically coordinates the localization and activity of sphingolipid metabolism enzymes in response to cellular demand. Now the focus turns to whether misregulation of this axis can directly cause asthma.

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ORIGINAL RESEARCH PAPER Breslow, D. *et al.* Orm family proteins mediate sphingolipid homeostasis. *Nature*, **463**, 1048–1053 (2010)
FURTHER READING Hannun, Y. A. & Obeid, L. M. Principles of bioactive lipid signalling: lessons from sphingolipids. *Nature Rev. Mol. Cell Biol.* **9**, 139–150 (2008)