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Structural insights into the regulation of human serine palmitoyltransferase complexes

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Abstract

Sphingolipids are essential lipids in eukaryotic membranes. In humans, the first and rate-limiting step of sphingolipid synthesis is catalyzed by the serine palmitoyltransferase (SPT) complex. The SPT complex consists of SPTLC1 and SPTLC2 as catalytic components, and ssSPTa and ORMDL3 as regulatory components. To understand the assembly, substrate processing and regulation of the complex, we determined cryo-electron microscopy structures of the human SPT complex in various functional states at resolutions of 2.6–3.4 Å. The structures elucidate how catalytic components recognize the substrate, as well as how regulatory components modulate the substrate-binding tunnel to control enzyme activity. These findings reveal the molecular mechanism of sphingolipid biogenesis governed by the serine palmitoyltransferase complex.