6. マイクロドメインとアミロイド前駆体蛋白質プロセッシング

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Summary

Lipid rafts and their component, cholesterol, modulate the processing of β-amyloid precursor protein (APP). However, the role of sphingolipids, another major component of lipid rafts, in APP processing remains undetermined. Here we report the effect of sphingolipid deficiency on APP processing in Chinese hamster ovary cells treated with a specific inhibitor of serine palmitoyltransferase (SPT), which catalyzes the first step of sphingolipid biosynthesis, and in a mutant LY-B strain defective in the LCB1 subunit of SPT. We found that in sphingolipid-deficient cells, the secretion of soluble APPα (sAPPα) and the generation of C-terminal fragment cleaved at α-site dramatically increased, while β-cleavage activity remained unchanged and the ε-cleavage activity decreased without alteration of total APP level. The secretion of amyloid β-protein 42 (Aβ42) increased in sphingolipid-deficient cells, while that of Aβ40 didn't. All these alterations were restored in sphingolipid-deficient cells by adding exogenous sphingosine, and in LY-B cells by transfection with c*LCB1*. Sphingolipid deficiency increased mitogen-activated protein kinase (MAPK/ERK) activity and a specific inhibitor of MAPK kinase, PD98059, restored sAPPα level, indicating that sphingolipid deficiency enhances sAPPα secretion via activation of MAPK/ERK pathway. These results suggest that not only the cellular level of cholesterol but also that of sphingolipids may be involved in the pathological process of Alzheimer's disease by modulating APP cleavage.

References

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