論文内容の要旨

論文題目：

Regulation of signaling cross-talk among yeast MAP kinase pathways

（出芽酵母 MAPK 経路間のシグナル • クロストークを制御する分子機構）

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Mucins are a group of large, highly O-glycosylated proteins that are either secreted or membrane-associated. Until recently, functions of membrane-associated mucins were obscure, except for protection of cell surface by their viscosity. Increasingly, however, evidence is being emerged that some membrane-associated mucins regulate intracellular signaling, both in mammals and in yeast. Those are therefore termed signaling mucins.

Msb2 is a yeast signaling mucin, and is composed of a large, highly glycosylated (mucin-like) extracellular domain, a transmembrane segment, and a relatively short cytoplasmic domain. My previous study has demonstrated that Msb2 is a likely osmosensor for the osmoregulatory Hog1 MAPK pathway (*EMBO J* **26**: 3521-3533, 2007), and another group has reported that Msb2 is also involved in the filamentous growth/invasive growth (FG/IG) Kss1 MAPK pathway. Expression of Msb2 mutants

that lack a significant portion of the mucin-like Ser/Thr-rich domain activates the HOG and the FG/IG MAPK pathways, indicating that the mucin-like domain of Msb2 has an inhibitory function.

In this thesis, I will describe my recent findings about the regulatory mechanism of Msb2 in the HOG and the FG MAPK pathways. I found that the FG-specific Kss1 MAPK is activated by defective glycosylation of Msb2 resulting from a combination of an O-glycosylation defect caused by disruption of the gene encoding the protein O-mannosyltransferase Pmt4, and an N-glycosylation defect induced by tunicamycin. The O-glycosylated membrane proteins Msb2 and Opy2 are both essential for activating the FG MAPK pathway, but only defective glycosylation of Msb2 activates the FG MAPK pathway. Although the osmoregulatory HOG MAPK pathway and the FG MAPK pathway share almost the entire upstream signaling machinery, osmostress activates only the HOG-specific Hog1 MAPK. Conversely, now I show that glycosylation defects usually activate only Kss1. In the absence of Kss1, however, glycosylation defects do activate Hog1. Activated Kss1 inhibits Hog1 via the Ptp2 tyrosine phosphatase. (Figure A) When Hog1 is activated by glycosylation defects in *ptp2* mutant cells, Kss1 activation is suppressed by Hog1. (Figure B) Mutating *HOG1* gene in *ptp2* mutant cells relieves the suppression of Kss1 activity by Hog1. (Figure C) Thus, the reciprocal inhibitory loop between Kss1 and Hog1 allows only one or the other of these MAPKs to be stably activated under various stress conditions.

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