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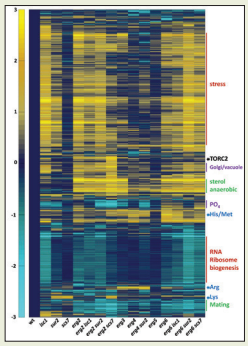
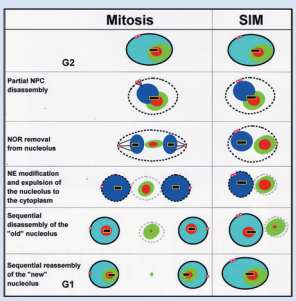
Functional Interactions between Sphingolipids and Sterols in Biological Membranes Regulating Cell Physiology



Xue Li Guan, Cleiton M. Souza, Harald Pichler, Gisèle Dewhurst, Olivier Schaad, Kentaro Kajiwara, Hirotomo Wakabayashi, Tanya Ivanova, Guillaume A. Castillon, Manuele Piccolis, Fumiyoshi Abe, Robbie Loewith, Kouichi Funato, Markus R. Wenk, and Howard Riezman

Even the simplest eukaryotic cells contain hundreds of different lipid species in their membranes. Astoundingly little is known about the functions of these lipids and the reasons for their diversity. Using a systematic, unbiased approach to study the function of sterols in yeast cells, the authors discovered that alterations in the sterol composition of membranes have profound and preferential effects on the sphingolipid composition. This prompted a genetic analysis of sterol-sphingolipid double mutants, which proved that the two pathways interact functionally. This study provides convincing evidence that sterols and sphingolipids function together in cells to carry out a wide variety of functions, including regulating how cells respond to drugs, suggesting that the interactions between sterols and sphingolipids that were described by biophysical experiments in vitro are relevant in cells. The authors provide insights into how sterols and sphingolipid structures may have remained compatible during evolution.

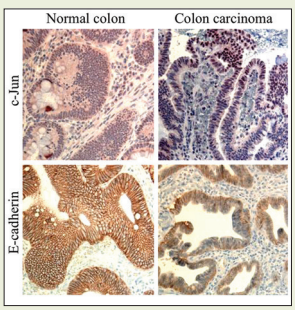


Nucleolar Separation from Chromosomes During *Aspergillus nidulans* Mitosis Can Occur without Spindle Forces

Leena Ukil, Colin P. De Souza, Hui-Lin Liu, and Stephen A. Osmani

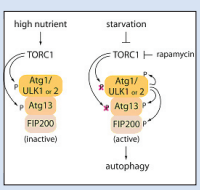
The nucleolus is the most prominent nuclear subcompartment and the site of ribosomal RNA (rRNA) transcription, pre-rRNA processing, and ribosome subunit assembly. During open mitosis, nucleoli are disassembled and then reassembled around segregated DNA containing the nucleolar organizing regions (NORs). The authors define a new mitotic mechanism of nucleolar segregation during the partially open mitosis of *Aspergillus nidulans.* In this process the nuclear envelope becomes constricted in two places, generating three structures: two daughter nuclei containing the segregated NORs and a cytoplasmic nuclear remnant containing the nucleolus. At G1 the cytoplasmic nucleolus undergoes stepwise disassembly and the cytoplasmic nucleolar proteins are transported into the daughter nuclei where they reassemble into new nucleoli. The authors also demonstrate that, surprisingly, nucleolar segregation, which is normally integrated with spindle function, can occur without mitotic spindle forces or DNA segregation, thus adding a further new twist to mitotic mechanisms.

Loss of E-Cadherin–Mediated Cell–Cell Contacts Activates a Novel Mechanism for Upregulation of the Proto-oncogene c-Jun



Revital Knirsh, Iris Ben-Dror, Barbara Spangler, Gideon D. Matthews, Silke Kuphal, Anja K. Bosserhoff, and Lily Vardimon

Loss of E-cadherin–mediated cell–cell contacts can elicit a signaling pathway that leads to acquisition of an invasive phenotype. The authors show that at the receiving end of this pathway is the proto-oncogene c-Jun, a member of the AP-1 family of transcription factors that play a key role in stimulation of cell proliferation and tumor promotion. They demonstrate that cell separation or abrogation of E-cadherin–mediated cell–cell contacts both cause a dramatic increase in accumulation of the c-Jun protein and that, unexpectedly, this increase is controlled translationally and not transcriptionally. Consistently, the increase in c-Jun accumulation is not dependent on activation of the β-catenin or MAPK pathways, but is mediated by signals triggered by the restructured cytoskeleton. This novel mechanism of c-Jun regulation appears to underlie the robust overexpression of c-Jun in tumor cells of patients with colon carcinoma.



Nutrient-dependent mTORC1 Association with the ULK1-Atg13-FIP200 Complex Required for Autophagy

Nao Hosokawa, Taichi Hara, Takeshi Kaizuka, Chieko Kishi, Akito Takamura, Yutaka Miura, Shun-ichiro Iemura, Tohru Natsume, Kenji Takehana, Naoyuki Yamada, Jun-Lin Guan, Noriko Oshiro, and Noboru Mizushima

ULK-Atg13-FIP200 Complexes Mediate mTOR Signaling to the Autophagy Machinery

Chang Hwa Jung, Chang Bong Jun, Seung-Hyun Ro, Young-Mi Kim, Neil Michael Otto, Jing Cao, Mondira Kundu, and Do-Hyung Kim

An Atg1/Atg13 Complex with Multiple Roles in TOR-mediated Autophagy Regulation

Yu-Yun Chang and Thomas P. Neufeld

In response to nutrient withdrawal, activation of the self-digestive process known as autophagy generates an intracellular source of nutrients, allowing cell survival during periods of starvation and other stresses. In yeast, the nutrient-sensitive **t**arget **o**f **r**apamycin kinase **c**omplex TORC1 inhibits formation of an autophagy-promoting protein complex containing Atg13, Atg17, and the protein kinase Atg1, through phosphorylation of Atg13. These articles now address this signaling mechanism in *Drosophila* and mammalian cells. The authors show that Atg13 is required for autophagy in these systems, and that it localizes to autophagic membranes and forms a stable ~3-MDa protein complex with Atg1/ULK1 and FIP200, a likely counterpart of Atg17. Upon nutrient stimulation, TORC1 is incorporated into this complex and promotes phosphorylation of Atg1/ULK1 and Atg13. Unlike in yeast, phosphorylation of Atg13 is observed under both autophagic and growth conditions, is dependent on both TOR and Atg1/ULK1 kinase activity, and does not preclude interaction of Atg13 with Atg1/ULK1. Thus, although the autophagic functions of Atg1 and Atg13 are broadly conserved, the mechanisms of TOR-mediated regulation of these proteins have significantly diverged from yeast to metazoans. ■