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ARTICLES

Biosynthesis and Biodegradation

Characterization of the role of COP9 signalosome in regulating cullin E3 ubiquitin ligase activity

Cullin RING E3 ligases require covalent modification with Nedd8 for activity. Neddylation is reversed by the COP9 signalosome (CSN). We characterize the role of CSN-dependent de neddylation in vivo and propose a model in which CSN binds to cullin ligases in their active conformation and functions to recruit important regulatory factors.

4706–4715

c-Fos activates and physically interacts with specific enzymes of the pathway of synthesis of polyphosphoinositides
A. R. A. Pecchio, A. M. C. Gizzi, M. L. Renner, M. Molina-Calavita, and B. L. Caputto

c-Fos increases the overall synthesis of polyphosphoinositides by an AP-1–independent mechanism involving activation of CDP-diacylglycerol synthase and phosphatidylinositol (PtdIns) 4-kinase II α but not of PtdIns synthase or PtdIns 4-kinase II β. Coimmunoprecipitation and FRET experiments show that c-Fos physically associates only with the enzymes it activates.

4716–4725

Exposure of bipartite hydrophobic signal triggers nuclear quality control of Ndc10 at the endoplasmic reticulum/nuclear envelope

Degradation of mutant Ndc10 is mediated by the E3 ligase Doa10 at the endoplasmic reticulum/nuclear envelope membrane. An autonomous degradation motif was localized to the C-terminal region of Ndc10. The motif is composed of two indispensable elements: a hydrophobic surface of an amphipathic helix and a loosely structured, hydrophobic C-terminal tail.

4726–4739

Cell Biology of Disease

Dynamic actin remodeling during epithelial–mesenchymal transition depends on increased moesin expression

LifeAct-GFP, a fluorescent reporter for actin filaments, is used to uncover the dynamics of actin cytoskeleton remodeling in real time during TGF-β–induced EMT. Efficient actin filament remodeling and complete transition to a mesenchymal phenotype depend on an increase in expression of the ERM protein moesin.

4750–4764

Compromised mutant EFEMP1 secretion associated with macular dystrophy remedied by proteostasis network alteration
J. D. Hulleman, S. Kaushal, W. E. Balch, and J. W. Kelly

R345W EFEMP1 is secreted poorly, causing the macular dystrophy malattia leventinese. A novel assay shows that other substitutions (F, Y, P) at residue 345 impair secretion, partly by reducing native disulfide bonds. EFEMP1 secretion is rescued by reduced growth temperature and translational attenuation—potential strategies to delay disease.

4765–4775
The Cx26-G45E mutation displays increased hemichannel activity in a mouse model of the lethal form of keratitis-ichthyosis-deafness syndrome


Dominant Cx26 mutations that cause keratitis-ichthyosis-deafness syndrome (KIDS) show increased hemichannel activity. Transgenic expression of these mutations recapitulates human skin disease in mice. Excess hemichannel activity persists in diseased epidermis from the transgenic mice. Thus hemichannel activity may be a novel therapeutic target in the treatment of KIDS.

Cell Interaction

RaIA and RaIB differentially regulate development of epithelial tight junctions

C. C. Hazelett, D. Sheff, and C. Yeaman

The closely related GTPases RaIA and RaIB are required for assembly of tight junction gate, but not fence, function. These activities depend on direct binding to the exocyst complex. Whereas RaIA–exocyst complexes are required for exocytosis of junction proteins, RaIB–exocyst complexes are required for endocytosis of these components.

Cell Motility

Functional states of kinetochores revealed by laser microsurgery and fluorescent speckle microscopy

J. R. LaFountain, Jr., C. S. Cohan, and R. Oldenbourg

The impact of mechanical forces on kinetochore motility was investigated using laser microsurgery and fluorescent speckle microscopy on kinetochores and associated microtubules during anaphase in crane fly spermatocytes. Kinetochores detached from their chromosomes moved at twice their normal speed, entering a motile state identified as “park.”

Cell Physiology

Low oxygen levels induce the expression of the embryonic morphogen Nodal


This study demonstrates that low oxygen (O$_2$) levels induce the embryonic protein Nodal. This finding is significant, as low O$_2$ levels characterize the microenvironments associated with both early development and tumor progression, and Nodal has been shown to promote tumorigenicity and to govern stem cell fate.

Cytoskeleton

Splice variant–specific cellular function of the formin INF2 in maintenance of Golgi architecture

V. Ramabhadran, F. Korobova, G. J. Rahme, and H. N. Higgs

INF2 is a unique formin that can both polymerize and depolymerize actin. One INF2 splice variant localizes in an actin-dependent, web-like network in cytoplasm, whereas a second isoform is ER bound. Suppression of the first isoform causes Golgi dispersion. These findings denote isoform-specific cellular functions for INF2.

Effects of dynein on microtubule mechanics and centrosome positioning


When microtubules are severed by laser ablation, newly created minus ends increase in curvature, but they straighten when dynein is inhibited. It is found that cytoplasmic dynein generates tension and friction along microtubule lengths and that these forces govern the dynamics of centrosome centering.

Membrane Trafficking

Recruitment of cellular prion protein to mitochondrial raft-like microdomains contributes to apoptosis execution


PrP$^\text{C}$ is identified as a new component of mitochondrial raft-like microdomains in T cells undergoing CD95/Fas–mediated apoptosis, and microtubular network integrity and function could play a role in the redistribution of PrP$^\text{C}$ from the plasma membrane to the mitochondria.
A Highlights from MBoC Selection

The schizophrenia susceptibility factor dysbindin and its associated complex sort cargoes from cell bodies to the synapse
J. Larimore, K. Tornieri, P. V. Ryder, A. Gokhale, S. A. Zlatic, B. Craige, J. D. Lee, K. Talbot, J.-F. Pare, Y. Smith, and V. Faundez

A novel vesicle transport mechanism is described that requires dysbindin-associated complexes for cargo targeting from neuronal cell bodies to neurites and nerve terminals. The results suggest that mistargeting of specific vesicular cargoes may underlie, in part, the molecular pathogenesis of schizophrenia.

Nuclear Functions

The SUMO-specific isopeptidase SENP2 associates dynamically with nuclear pore complexes through interactions with karyopherins and the Nup107-160 nucleoporin subcomplex
J. Goeres, P.-K. Chan, D. Mukhopadhyay, H. Zhang, B. Raught, and M. J. Matunis

We determined that the small, ubiquitin-related modifier–specific isopeptidase, SENP2, is dynamically associated with nuclear pore complexes (NPCs). This association is determined by the activities of three N-terminal signals in SENP2: a high-affinity nuclear localization sequence, an Nup107-160–binding element, and a nuclear export signal. NPC association, and its potential regulation, affects SENP2 accessibility to substrates.

Signaling

RPTPμ tyrosine phosphatase promotes adipogenic differentiation via modulation of p120 catenin phosphorylation

Protein tyrosine phosphatases act as key regulators in differentiation-associated signaling pathways. It is proposed that RPTPμ acts as a positive regulator of adipogenesis by modulating the cytoplasmic p120 catenin level.

Cbk1 kinase and Bck2 control MAP kinase activation and inactivation during heat shock
V. K. Kuravi, C. Kurischko, M. Pun, and F. C. Luca

Cbk1 kinase was previously implicated in regulating polarized morphogenesis, gene expression, and cell integrity. This study reveals that Cbk1 regulates heat shock signaling and stress adaptation by modulating Mpk1 activity and MAPK phosphatase localization. A model for Cbk1 and its putative substrate for these functions is presented.

Sequestration of phosphoinositides by mutated MARCKS effector domain inhibits stimulated Ca\(^{2+}\) mobilization and degranulation in mast cells
D. Gadi, A. Wagenknecht-Wiesner, D. Holowka, and B. Baird

A new strategy for interfering with phosphoinositide-dependent processes at the plasma membrane uses high-avidity association of the polybasic MARCKS effector domain with negatively charged phospholipids to provide new insights into roles for phosphoinositides in IgE receptor signaling leading to exocytosis.

Defining pheromone-receptor signaling in *Candida albicans* and related asexual *Candida* species
C.-H. Lin, A. Choi, and R. J. Bennett

The pheromone response in *Candida albicans* is mediated by the Ste2 receptor. Intracellular (IC) loop 3 and C-terminal tail regions of Ste2 are required for signaling, whereas the large IC1 region is dispensable. Heterologous expression of receptors from asexual species can also drive signaling in *C. albicans*, allowing functional pheromone-receptor couples to be analyzed.