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Cellular and Molecular Life Sciences

Announcement of the Editor-in-Chief

As decided in July 2005 we continue to publish once a year (in July) the names of the authors and the titles of the two most read (by Internet) Research Papers and Reviews published in Cell. Mol. Life Sci. the previous year. Thus we have the pleasure to provide you with the results of 2005.

Research Articles

1) Rescue of heterochromatin organization in Hutchinson-Gilford progeria by drug treatment

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Abstract. Hutchinson-Gilford progeria (HGPS) is a premature aging syndrome associated with LMNA mutations. Progeria cells bearing the G608G LMNA mutation are characterized by accumulation of a mutated lamin A precursor (progerin), nuclear dysmorphism and chromatin disorganization. In cultured HGPS fibroblasts, we found worsening of the cellular phenotype with patient age, mainly consisting of increased nuclear-shape abnormalities, progerin accumulation and heterochromatin loss. Moreover, transcript distribution was altered in HGPS nuclei, as determined by different techniques. In the attempt to improve the cellular phenotype, we applied treatment with drugs either affecting protein farnesylation or chromatin arrangement. Our results show that the combined treatment with mevinolin and the histone deacetylase inhibitor trichostatin A dramatically lowers progerin levels, leading to rescue of heterochromatin organization and reorganization of transcripts in HGPS fibroblasts. These results suggest that morpho-functional defects of HGPS nuclei are directly related to progerin accumulation and can be rectified by drug treatment.

November 2005, Volume 62, Number 22, pp. 2669–2678

2) A relevant in vitro rat model for the evaluation of blood-brain barrier translocation of nanoparticles

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Abstract. Poly(MePEG$_{2000}$cyanoacrylate-co-hexadecylcyanoacrylate) (PEG-PHDCA) nanoparticles have demonstrated their capacity to reach the rat central nervous system after intravenous injection. For insight into the transport of colloidal systems across the blood-brain barrier (BBB), we developed a relevant in vitro rat BBB model consisting of a coculture of rat brain endothelial cells (RBECs) and rat astrocytes. The RBECs used in our model displayed and retained structural characteristics of brain endothelial cells, such as expression of P-glycoprotein, occludin and ZO-1, and immunofluorescence studies showed the specific localization of occludin and ZO1. The high values of transendothelial electrical resistance and low permeability coefficients of marker molecules demonstrated the functionality of this model. The comparative passage of polyhexadecylcyanoacrylate and PEG-PHDCA nanoparticles through this model was investigated, showing a higher passage of PEGylated nanoparticles, presumably by endocytosis. This result was confirmed by confocal microscopy. Thanks to a good in vitro/in vivo correlation, this rat BBB model will help in understanding the mechanisms of nanoparticle translocation and in designing new types of colloidal carriers as brain delivery systems.

June 2005, Volume 62, Number 12, pp. 1400–1408

Reviews

1) G-protein signaling: back to the future

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Abstract. Heterotrimeric G-proteins are intracellular partners of G-protein-coupled receptors (GPCRs). GPCRs act on inactive Gα·GDP/G$\beta\gamma$ heterotrimers to promote GDP release and GTP binding, resulting in liberation of Gα from G$\beta\gamma$. Gα·GTP and G$\beta\gamma$ target effectors including adenylyl cyclases, phospholipases and ion channels. Signaling is terminated by intrinsic GTPase activity of Gα and heterotrimer reformation – a cycle accelerated by 'regulators of G-protein signaling' (RGS proteins). Recent studies have identified several unconventional G-protein signaling pathways that diverge from this standard model. Whereas phospholipase C (PLC) β is activated by Gα_q and G$\beta\gamma$, novel PLC isoforms are regulated by both heterotrimeric and Ras-superfamily G-proteins. An *Arabidopsis* protein has been discovered containing both GPCR and RGS domains within the same protein. Most surprisingly, a receptor-independent Gα nucleotide cycle that regulates cell division has been delineated in both *Caenorhabditis elegans* and *Drosophila melanogaster*. Here, we revisit classical heterotrimeric G-protein signaling and explore these new, non-canonical G-protein signaling pathways.

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2) Hsp70 chaperones: Cellular functions and molecular mechanism

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Abstract. Hsp70 proteins are central components of the cellular network of molecular chaperones and folding catalysts. They assist a large variety of protein folding processes in the cell by transient association of their substrate binding domain with short hydrophobic peptide segments within their substrate proteins. The substrate binding and release cycle is driven by the switching of Hsp70 between the low-affinity ATP bound state and the high-affinity ADP bound state. Thus, ATP binding and hydrolysis are essential in vitro and in vivo for the chaperone activity of Hsp70 proteins. This ATPase cycle is controlled by co-chaperones of the family of J-domain proteins, which target Hsp70s to their substrates, and by nucleotide exchange factors, which determine the lifetime of the Hsp70-substrate complex. Additional co-chaperones fine-tune this chaperone cycle. For specific tasks the Hsp70 cycle is coupled to the action of other chaperones, such as Hsp90 and Hsp100.

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