

Receptor trafficking and signalling (p. 3075) *Signal Transduction and Cellular Organization*

Endocytosis of receptors is a well-established mechanism for attenuation of signalling. But it also allows receptors to interact with downstream molecules not available at the plasma membrane, which can potentially influence both signalling and receptor trafficking. Michael Clague and Sylvie Urbé discuss the roles of three proteins present in endocytic compartments - Rab5, Hrs and Cbl - that function at this 'interface' in EGF receptor (EGFR) trafficking and signalling. The Rab5 small GTPase, for example, is a regulator of endosome fusion that is also required for EGFR internalization. Recent work indicates that Rab5 activity is itself regulated by EGF signalling and that it may also engage in signalling pathways by recruiting effectors such as PI 3-kinase. Similarly, Cbl and Hrs are proposed to regulate endosomal sorting while also acting as adaptor proteins to recruit signalling proteins. Clague and Urbé suggest that these proteins are representatives of a class of scaffold protein whose function incorporates coordination of receptor signalling and trafficking.



Post-transcriptional silencing in plants (p. 3083) *Commentary*

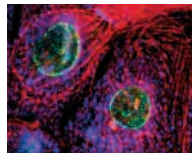
Post-transcriptional gene silencing (PTGS; also known as co-suppression) in plants is a form of RNA silencing that is similar to RNA interference in animals and 'quelling' in fungi. In each case, a population of mRNA is specifically degraded following transcription, owing to the presence of an exogenous or transgene-derived double-stranded RNA. Hervé Vaucheret and co-workers discuss our understanding of PTGS, highlighting work that indicates that PTGS forms part of a mechanism for plant resistance to viruses. Triggering/maintenance of PTGS appears to correlate with transgene methylation and chromatin rearrangements, in which the *Arabidopsis* MET1 methyl transferase and DDM1 chromatin-remodelling enzyme are implicated, respectively. Generation of the dsRNA requires an RNA-dependent RNA polymerase, which in *Arabidopsis* might be encoded by the *SGS2/SDE1* gene. Since plants that exhibit impaired PTGS are hypersusceptible to viral infection, it appears to constitute a resistance mechanism that degrades viral RNA. Some viruses, however, manage to evade PTGS - for example, by activating endogenous negative regulators of PTGS, such as the calmodulin-related protein rgs-CaM.



Compartmentalization of osteoblast transcription (p. 3093)

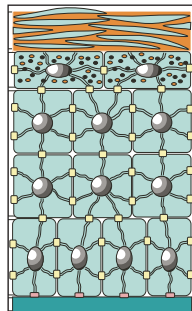
Compartmentalization of the cell nucleus plays a key role in control of nuclear metabolism: DNA

replication, transcription and splicing all occur in distinct subnuclear domains, and many transcription factors appear to localize to dynamic macromolecular complexes connected to the underlying nuclear architecture. The Stein and Lian laboratories have examined the importance of transcription factor localization in regulation of bone-specific gene expression. They show that Runx2 (also known as Cbfa1) - a transcription factor necessary for osteoblast-specific transcription of the osteocalcin gene - contains a nuclear-matrix-targeting sequence (NMTS) in its C-terminus that targets it to discrete subnuclear foci. Furthermore, they show that removal of the Runx2 NMTS not only stops it localizing to the correct nuclear compartment but also dramatically reduces its ability to stimulate transcription of the osteocalcin gene. The authors' findings illustrate the importance of transcription factor targeting as a mechanism for tissue-specific gene regulation. They are particularly significant given that a naturally occurring Runx2 mutant that causes cleidocranial dysplasia (CCD) lacks the identified NMTS.



mAKAP: connecting cyclic AMP and Ca²⁺ signalling (p. 3167)

A-kinase-anchoring proteins (AKAPs) are scaffold proteins that impart specificity on cyclic AMP signalling by binding to cyclic-AMP-dependent kinase (PKA) and targeting it to particular subcellular locations and substrates. MuscLE AKAP (mAKAP) is one example: it interacts with both PKA and PDE4D3 (a phosphodiesterase that forms part of a negative feedback loop in cyclic AMP signalling) and localises them to the nuclear envelope (NE) of cardiac myocytes. Michael Kapoloff and co-workers now reveal that mAKAP also binds to protein phosphatase 2A (PP2A) and NE-resident ryanodine receptors (RyRs) - high-conductance channels that release Ca²⁺ from perinuclear stores. They demonstrate that mAKAP, PKA and RyR form a complex at the myocyte NE and that mAKAP-bound RyR is a substrate for associated PKA. Since RyRs are implicated in nucleoplasmic Ca²⁺ signalling, the authors propose that mAKAP underpins a supramolecular signalling complex at the NE that integrates Ca²⁺ and cyclic AMP signalling to myocyte nuclei.



The cornified envelope (p. 3069) + poster) *Cell Science at a Glance*

The cornified cell envelope is a barrier that forms beneath the plasma membrane of terminally differentiating stratified squamous epithelia in mammalian skin. It comprises a thick layer of covalently linked ceramide lipids and proteins, around which ordered lamellae of extracellular lipids are deposited. In this issue's Cell Science at a Glance poster, Peter Steinert and co-workers detail the three stages of envelope assembly - initiation, formation of the

corniceocyte envelope, and its reinforcement with proteins such as loricrin - which establish a durable protective layer that is impermeable to water and protects the skin from mechanical stress.



Sticky Wicket - communication in the lab (p. 3067)

Lab meetings are a regular event in the life of most scientists - a chance for young scientists to gain experience presenting work and a forum for discussing results and future directions.

Caveman acknowledges the importance of lab meetings but feels there is no substitute for spontaneity. He believes that the most rewarding discussions are informal chats during a stroll round the lab.

In the next issue of JCS

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How do you cross an armadillo with a porcupine and other problems that arise from naming proteins. Caveman
- CELL SCIENCE AT A GLANCE
Endogenous inhibitors of angiogenesis. C. Ruhrberg
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Mechanism and role of PDZ domains in signalling complex assembly. B. Z. Harris and W. A. Lim
- Targeting of Ran: variation on a common theme?** M. Künzler and E. Hurt
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RP-A/Ku foci in *Xenopus* in vitro system. P. Grandi et al.
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Cds1 inactivation at entry into M-phase. T. Gotoh et al.
Regulation of PKA-AKAP450 anchoring. C. R. Carlson et al.
AKAP95 and PKA regulate chromosome dynamics. H. B. Landsverk et al.
Syntaxin 1A sorting in epithelial cells. J. Rowe et al.
Active Rho mobilizes Citron-K in cytokinesis. M. Eda et al.
Urokinase inhibits cancer cell apoptosis. Z. Ma et al.
Role of Sec31p in the malaria parasite. A. Adisa et al.
Invasin induces collagenase. E. Werner et al.
BFA blocks polar endocytic sorting. E. Wang et al.
Focal adhesion supermaturation. V. Dugina et al.
FGF requirement for actin-based processes. G. Davidson et al.
Regulation of cell adhesion by PKA. J. D. Whittard and S. K. Akiyama