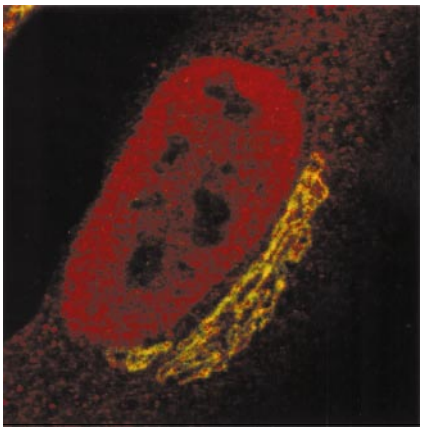
Caspase-2 in the Golgi Complex

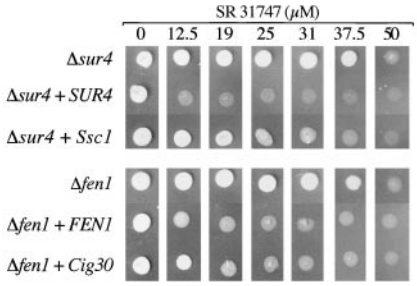
Beginning on page 603, Mancini et al. describe studies on the localization and substrate specificity of the protease caspase-2, which has a key role in apoptosis. The results show that caspase-2 localizes to the Golgi complex, where it cleaves the protein golgin-160 at a unique site, suggesting that the Golgi complex, like mitochondria, may be involved in transducing apoptotic signals.



Earlier studies demonstrated that caspase-2 is found in the cytoplasm and nucleus, but the specific localization and downstream substrates of this protease were unknown. Using indirect immunofluorescence microscopy, the authors localized endogenous caspase-2 to both the Golgi apparatus and nucleus in several cell types. The protease cleaves the Golgi-specific protein golgin-160 early in apoptosis, and inhibiting golgin-160 cleavage delays disintegration of the Golgi complex during apoptosis. The authors suggest that the Golgi apparatus, by virtue of its central location in cellular membrane trafficking pathways, may sense the condition of the cell and may be important in regulating apoptosis. In addition, the results add to a growing body of evidence showing that different caspases may act within distinct subcellular compartments, performing specialized functions during apoptosis. The authors are now exploring the function of golgin-160 and the possibility that it is the target of specific pro-apoptotic signals directed at the Golgi complex.

Mammalian Synthesis of Very Long Chain Fatty Acids

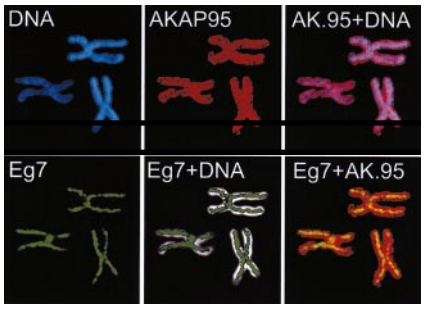
Tvrdik et al. (page 707) have identified a new family of mammalian genes that are involved in the synthesis of very long-chain fatty acids (VLCFA). Though VLCFA are known to be required for many biological processes, the highly hydrophobic enzymes involved in synthesizing these molecules in mammalian cells have been difficult to identify biochemically. In the new work, the authors used the mouse genome EST database to circumvent this problem.



In earlier work, the team identified *Cig30*, an inducible gene associated with activation of brown adipose tissue. Since the *Cig30* gene product shares homology with several genes in yeast and *C. elegans*, the authors reasoned that the mouse genome would also contain multiple genes in this family. A search of ESTs uncovered two novel genes, designated *Ssc1* and *Ssc2*. *Ssc1* can rescue normal sphingolipid synthesis in yeast *sur4/elo3* mutants that are defective in VLCFA synthesis, and *Cig30* rescues the phenotype of the *fen1/elo2* yeast mutant that has reduced levels of VLCFAs. Myelin-deficient mutant mice with a diminished ability to elongate fatty acid chains also show decreased levels of *Ssc1* mRNA in brain tissue, and *Cig30* expression in brown adipose tissue correlates with an increase in fatty acid chain elongation. These findings support a key role for the new gene family in the synthesis of VLCFAs. The expression levels of the newly discovered genes also suggest that mammalian cells express different VLCFA-synthesizing enzymes in tissue-specific patterns.

Role of AKAP95 in Chromosome Condensation

By studying the distribution and effects of the nuclear A-kinase anchoring protein AKAP95 in HeLa cell mitotic extracts, Steen et al. (page 531) found that AKAP95 targets a component of the human condensin complex to chromosomes, leading to chromosome condensation. The results support a model in which AKAP95 is relocalized during mitosis from the nuclear matrix to chromatin, where it recruits hCAP-D2/Eg7, a subunit of the condensin complex.



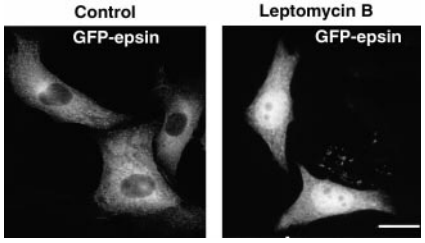
Chromosome condensation requires the localization of specialized protein complexes, called condensins, to the chromatin. Though antibody-blocking and rescue experiments have demonstrated that AKAP95 also has a role in chromosome condensation, the relationship between AKAP95 and condensins remained poorly understood. The authors found that in HeLa cell mitotic extracts, AKAP95 redistributes from the nuclear matrix to chromatin, and that AKAP95 association with chromatin is required for chromosome condensation. Recombinant AKAP95, containing only the carboxy-terminal 306 amino acids of the AKAP95 se-

quence, recruits the condensin component hCAP-D2/Eg7 to chromosomes and induces chromosome condensation in a dose-dependent manner.

Based on their results, the authors present a model in which AKAP95 resides in the nuclear matrix during interphase, while hCAP-D2/Eg7 is restricted to the cytoplasm. At the start of mitosis, AKAP95 is released from the matrix to associate with chromatin, and hCAP-D2/Eg7 is then recruited to the chromosomes by AKAP95 after nuclear envelope breakdown.

Structure and Function of ENTH Domains

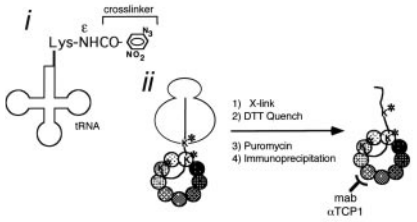
In an impressive combination of structural and functional studies, Hyman et al. (page 537) demonstrate that the amino-terminal domain of rat epsin 1, a cytosolic protein involved in clathrin-mediated endocytosis, also interacts with the transcription factor PLZF. The results underscore the importance of structural information in determining protein function, and suggest that epsin 1 may link the endocytic machinery to transcriptional regulation.



The amino-terminal 140 amino acids of epsin, known as the ENTH domain, constitute a phylogenetically conserved feature whose function has remained unknown. In an effort to illuminate the function of the ENTH domain, the authors first solved its three-dimensional structure by x-ray crystallography. The structure reveals a strong structural similarity to the *armadillo* repeat of β-catenin and the HEAT repeat of karyopherin-β, similarities that were not predicted from the ENTH sequence. Reasoning that the domains might also share functional similarities, the team identified PLZF as a binding partner for the ENTH domain in a yeast two-hybrid screen. Though the major pool of epsin localizes to the cytosol, the authors found that epsin shuttles between the cytoplasm and nucleus. The findings raise the possibility that external stimuli that activate endocytosis could control the nuclear localization of epsin and, through PLZF, the transcription of specific genes. Since ENTH domains are also found in proteins outside the epsin family, it is possible that similar regulatory pathways could affect a variety of cellular processes.

Interactions of a Chaperonin with Nascent Polypeptides

By photo-cross-linking nascent polypeptide chains of defined lengths to the eukaryotic chaperonin complex TRiC, McCallum et al. (page 591) determined that TRiC associates with nascent polypeptide chains shortly after their emergence from the ribosome. The data suggest that the chaperonin is closely associated with the translational apparatus, and the photo-cross-linking technique is likely to facilitate future efforts to identify additional components of the protein folding pathway.



Protein folding ordinarily occurs cotranslationally in the cell, but it has been difficult to study the interactions of chaperonins in the context of translation. In the new work, the authors created a series of truncated mRNAs to generate defined ribosome-bound polypeptide chains containing photoactivatable probes. Polypeptides exposing at least 50–90 amino acids outside the ribosomal exit channel were cross-linked to TRiC, indicating that the chaperonin associates with relatively short nascent chains. As the nascent chain increased in length, the pattern of cross-links became more complex, suggesting that more TRiC subunits become involved in the interaction as the chain is elongated. The data are consistent with a model in which specific substrate motifs interact with individual chaperonin subunits. Using the photo-cross-linking approach, it should now be possible to identify the subunits associated with specific motifs in nascent chains, and to identify upstream and downstream cofactors of TRiC.

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