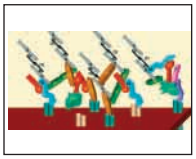
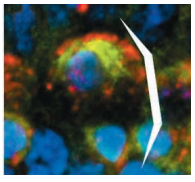


Focal adhesion organization (p. 3577 and p. 3583) Commentary

Focal adhesions (FAs) are specialized, transmembrane complexes that mediate integrin-dependent adhesion between cells and the extracellular matrix (ECM). The submembrane plaque at these sites contains more than 50 known proteins that link the actin cytoskeleton to the membrane. In Cell Science at a Glance on p. 3577, Eli Zamir and Benny Geiger provide a FA 'wiring diagram', showing the known components and their reported interactions. Then, in a Commentary on p. 3583, Zamir and Geiger discuss the complexity, diversity and dynamics of FAs in more detail. The complexity of FAs is further extended by post-translational modifications, proteolytic processing and alternative splicing of many of their components. Furthermore, the latter can potentially assemble in numerous ways to generate distinct supramolecular assemblies, such as fibrillar adhesions and focal complexes. These structures are by no means static: activation of Rho causes focal complexes to mature into 'classical' FAs, and studies using GFP-tagged FA components indicate that both FAs themselves and their molecular components are highly dynamic.

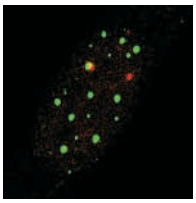
Breast cancer genes and the DNA damage response (p. 3591) Commentary

Mutations in the breast-cancer-susceptibility genes *BRCA1* and *BRCA2* predispose individuals to a variety of cancers. But what are the functions of the BRCA1 and BRCA2 proteins in normal cells, and can a single biological role account for their apparent tumour suppressor activity? Ashok Venkitaraman discusses recent work that has implicated these two, unrelated, proteins in the biological response to DNA damage. Studies of *Brca1*- and *Brca2*-deficient cells indicate that they exhibit defective repair of DNA double-strand breaks (DSBs). Indeed, BRCA2 appears to control the intracellular transport and activity of RAD51 - a protein necessary for repair of DSBs by homologous recombination. The mode of action of BRCA1 is less clear but might involve direct regulation of the MRE11 exonuclease required for creation of resected ssDNA at sites of DSB repair. Significantly, both BRCA1 and BRCA2 are implicated in activation of DNA damage checkpoints: BRCA1, for example, is phosphorylated by the checkpoint kinase Chk2, and this appears to be critical for the cellular response to DNA damage.



Cornetto: linking Inscuteable to the mitotic spindle (p. 3655)

Asymmetric division of *Drosophila* neuroblasts is a critical developmental process: it ensures that one daughter cell inherits cell fate determinants such as the transcription factor Prospero and consequently acquires a fate different from that of its sibling. During this process, the protein Inscuteable is required for localization of cell fate determinants to the basal cortex and orientation of the mitotic spindle along the apical-basal axis. Jürgen Knoblich and co-workers have identified and cloned a novel Inscuteable-binding partner, Cornetto, which they demonstrate can bind to microtubules. The authors show that Cornetto is apically localised in neuroblasts in late mitosis and that this localization depends on Inscuteable function. Significantly, disruption of the actin cytoskeleton abolishes apical localization, causing Cornetto instead to associate with spindle microtubules. Knoblich and co-workers propose that Cornetto is a molecular link between the spindle and Inscuteable and anchors the spindle during mitosis. Furthermore, they conclude that, given the apical localization of Cornetto, Inscuteable must be involved not only in basal protein localization but also in apical targeting.



Association of PML bodies and MHC genes (p. 3705)

Promyelocytic leukaemia (PML) bodies are distinct nuclear domains that contain a variety of important nuclear proteins. They have been proposed to function as storage sites, but studies showing that highly acetylated chromatin and nascent RNA are associated with PML bodies indicate that these domains might play a role in transcription. Paul Freemont, Denise Sheer and co-workers have analysed the spatial relationship between PML bodies and several gene-rich/gene-poor regions of the genome. They show that there is a strong association between the major histocompatibility complex (MHC) on chromosome 6 and PML bodies. The association between the MHC and PML bodies is specific, since it occurs in cells in which a subregion of the MHC has integrated into chromosome 18. Furthermore, it appears to be stable, being cell cycle independent and unaffected by agents that regulate MHC transcription. The authors' findings mirror the observed association of another nuclear domain - the Cajal body - with U2 genomic loci and suggest that PML bodies represent a functional compartment involved in regulation of MHC transcription.

PARP-1 gain of function during apoptosis (p. 3771)

Poly(ADP-ribose) polymerase 1 (PARP-1) is a DNA-binding enzyme that helps to maintain genomic integrity after DNA damage: it catalyses the transfer of ADP-ribose from NAD^+ to nuclear substrates that regulate processes such as DNA base excision repair (BER). Control of PARP-1 activity appears to be important during cell death, since caspase-mediated cleavage of PARP-1 is a hallmark of apoptosis, and overactivation of PARP-1 results in necrosis. But why does PARP-1 cleavage occur, and what is its significance for apoptosis/necrosis? Guy Poirier and co-workers demonstrate that cleavage of PARP-1 by caspases, which generates two PARP-1 fragments (p24 and p89), abolishes its catalytic activity. Significantly, however, the p24 fragment retains the ability to bind to DNA. Moreover, the authors show that it becomes a potent dominant-negative inhibitor of uncleaved PARP-1 and completely blocks BER. Poirier and co-workers conclude that the combined action of these mechanisms for PARP-1 inhibition has three pro-apoptotic effects: it prevents DNA-repair-induced cell survival, NAD^+-depletion-induced necrosis, and depletion of ATP required for the execution phase of apoptosis.

Sticky Wicket - portentous words (p. 3575)

Hippocrates stated of science and opinion that "the former begets knowledge, the latter ignorance". Caveman believes that this is as true today as it ever was and provides a few other examples of pithy statements that, although not necessarily aimed at scientists, are nonetheless highly applicable to modern science.

In the next issue of JCS

STICKY WICKET

Of caves, caverns, big brother and big science. Caveman

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Inner nuclear membrane proteins and the nuclear lamina. R. Foisner

COMMENTARIES

Microtubules and Rho GTPases in motile cells. T. Wittmann and C. M. Waterman-Storer

The Dis1/TOG family of MAPs. H. Ohkura et al.

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COP is not the photoreceptor for behavioural responses. M. Fuhrmann et al.

Chagasin, an endogenous cysteine protease inhibitor of *T. cruzi*. A. C. dos Santos Monteiro et al.

Physiological FIGQY phosphorylation of L1 CAMs. S. M. Jenkins et al.

The Dis1/TOG family of MAPs. H. Ohkura et al.

TGF-β1 regulation of PAI-1 expression. S. M. Kutz et al.