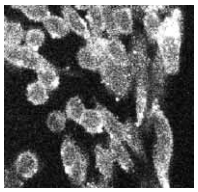
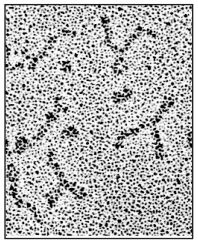
When Cdc2 became CDK1

Cdc2 lies at the heart of the eukaryotic cell cycle. We now know that it is active only when associated with a cyclin partner – indeed it is the defining member of a family of cyclin-dependent kinases (CDKs). Fifteen years ago things were not so clear. The importance of *Cdc2* as a conserved, cell cycle control gene was evident; however, the connection between Cdc2, the periodically degraded cyclins and the elusive maturation-promoting factor (MPF) first described in 1971 remained to be established. In a Commentary on p. 2461, Marcel Dorée and Tim Hunt look back at the series of experiments that made this connection. Purification of MPF by several groups revealed that it contains Cdc2, and Cdc2 was subsequently shown to co-precipitate with cyclins. There was then no precedent for a kinase that required an accessory subunit; the cyclin was instead thought to dissociate an inhibitory subunit from the kinase. Studies in which the M-phase-specific kinase was purified to homogeneity, however, revealed that the active enzyme is a Cdc2–cyclin-B heterodimer that has MPF activity, re-defining Cdc2 as CDK1.



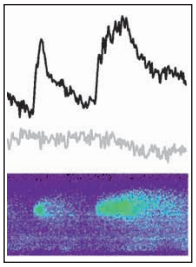
Lipid rafts in innate immunity

Lipid rafts – ordered membrane microdomains rich in glycosphingolipids and cholesterol – are implicated in both membrane sorting and signal transduction. In the acquired immune response, they appear to play an important role in T-cell activation, serving as platforms for assembly of the signalling machinery. Kathy Triantafilou and co-workers now show that rafts also function in innate immune recognition (see p. 2603). They demonstrate that several proteins involved in the cellular response to bacterial lipopolysaccharide (LPS) exist in lipid rafts: the GPI-linked LPS receptor CD14 and the heat shock proteins Hsp70 and Hsp90 are permanently present in rafts, and chemokine receptor 4 (CXCR4), growth differentiation factor 5 (GDF5) and Toll-like receptor 4 (TLR4) enter rafts after stimulation of cells by LPS. The authors also demonstrate that agents that disrupt raft integrity (e.g. nystatin) block LPS-induced secretion of tumour necrosis factor α (TNF-α). They therefore conclude that that concentration of signalling molecules involved in transducing LPS-recognition signals in lipid rafts is required for an effective innate immune response to pathogenic bacteria bearing this molecule.



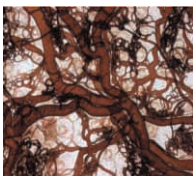
Integrins: three is the magic number

The ability of cell surface integrins to link the extracellular matrix (ECM) to the actin cytoskeleton is central to cell motility: if an ECM-anchored integrin is attached to the cytoskeleton, the cytoskeleton can pull on it and so drive the cell forward. Cytoskeletal attachment appears to require integrin clustering, but how big must each cluster be? Harold Erickson and co-workers have approached this question by examining the number of integrin molecules needed to translocate fibronectin-coated beads across the surface of a cell at constant velocity – an assay for cytoskeletal attachment (see p. 2581). They find that beads coated with fibronectin constructs containing three or five cell-adhesion domains, which should produce clusters of three and five integrins, respectively, bind strongly to and translocate across the cell surface. Fibronectin constructs containing one or two adhesion domains (which would form only integrin monomers/dimers) by contrast exhibit only brief binding and random movement. A cluster of at least three integrins thus seems to be required for productive cytoskeletal interactions – which is an interesting contrast to the paradigm of receptor dimerization in signalling.



The spontaneous side of ryanodine receptors

Ryanodine receptors (RyRs), like IP_3 receptors, are ER Ca^{2+} channels that release Ca^{2+} into the cytosol in response to specific signalling pathways. In muscle and neurons, these channels localize to particular regions of specialized ER in order to generate specific Ca^{2+} signals; in other cells, such compartmentalization is less evident. To compare the intrinsic properties of RyR subtypes, Vincenzo Sorrentino and co-workers have expressed RyR1 and RyR3 in HEK 293 cells, which lack a specialized form of ER and do not normally express RyRs (see p. 2497). The authors find that, as expected, both RyR1 and RyR3 generate global ER Ca^{2+} signals in response to the agonist caffeine. Significantly, they also show that RyR3-expressing HEK 293 cells (but not those expressing RyR1) exhibit spontaneous, local Ca^{2+} transients, which are restricted to a few regions of the ER. This indicates not only that different RyR isoforms can generate distinct Ca^{2+} signals but that a channel itself, rather than a specific cellular environment, can confer spontaneous local Ca^{2+} release.



Angiogenic effects of placenta growth factor

Vascular endothelial growth factor (VEGF) is a crucial regulator of angiogenesis that stimulates proliferation of endothelial cells and increases vascular permeability. Placenta growth factor (PlGF) is a member of the VEGF family that binds to VEGF receptor 1 (VEGFR-1) and can heterodimerize with VEGF. Its role in angiogenesis, however, is the subject of some debate. Teresa Odorisio and co-workers have examined the function of PlGF by generating transgenic mice that overexpress PlGF in the skin (see p. 2559). They find that the mice exhibit increases in the number, size and branching of blood vessels, as well as enhanced vascular permeability, which indicates that PlGF has a potent angiogenic effect. (The levels of homodimeric VEGF are reduced in keratinocytes from the transgenic mice probably owing to formation of VEGF-PlGF heterodimers.) Moreover, in contrast to mice overexpressing VEGF, mice overexpressing PlGF have strongly increased vessel sizes and hypervascularization persisting in adult life. The authors therefore conclude that the biological effects of PlGF are different from those of VEGF and do not simply reflect its postulated role as a decoy for its relative.

Sticky Wicket – publishing papers

What are the dos and don'ts of submitting a paper to a journal? And what exactly do they mean when editors say, "We *should* be happy to consider your manuscript further if..."? Having shed blood, sweat and tears on more than one manuscript, Cavewoman Anaya, a new contributor to the Sticky Wicket column, is well qualified to offer advice. On p. 2453, she provides some pointers for those about to submit papers and some interpretations of 'editorspeak'.

In the next issue of JCS