surveyed to milli-Jansky sensitivity (1 milli-Jansky = 10^{-29} W m^{-2} Hz^{-1}) are detected (*13*) by these telescopes. The detected quasars have far-infrared luminosities of ~10^{12} to 10^{13} solar luminosities ($L_\odot$), and implied dust masses of ~10^8 $M_\odot$. Some of them exhibit molecular gas emission from CO, indicating molecular masses of ~10^{11} $M_\odot$ (*14*). The detection of large reservoirs of molecular gas provides strong circumstantial evidence of possible active star formation in the quasar host galaxy.

If the dust were heated by massive young stars that formed in the quasar vicinity, the observed dust and CO emission would indicate a star-formation rate in the host galaxy of ~10^{13} $M_\odot$ per year. However, dust may also be produced by outflow from the area close to the black hole, and heated by the strong radiation field of the central quasar (*15*).

To elucidate the dust-heating mechanism and reveal star formation in the quasar host galaxy, it would help to be able to measure the spatial distribution of the dust and molecular gas around the central quasar. Spatially resolving the quasar host galaxy is very difficult for these distant and faint objects. But one system, quasar PSS 2322+1944 (redshift 4.12), provides an ideal opportunity to study the gas distribution on small scales. This is the object studied by Carilli *et al*. (*1*).

PSS 2322+1944 is the brightest known CO source at high redshift, and is gravitationally lensed (see the figure). The lensing effect not only magnifies the quasar emission by a factor of ~2.5, but also stretches and distorts the image of the host galaxy. In the figure, the molecular gas emission is shown as having a disk structure. When observed behind the lensing galaxy, the image is stretched to two almost connected arcs. This magnification and distortion help to resolve the spatial structure of the quasar at a resolution higher than is possible with direct imaging using current telescopes.

Carilli *et al*. used the Very Large Array to map the CO emission from this quasar at radio wavelengths. They found the CO image of the quasar to be an almost complete ring, the so-called "Einstein ring" (see the figure), caused by gravitational lensing when the quasar is located directly behind the lensing galaxy. This highly magnified and distorted image of the quasar host galaxy allows them to model the spatial structure of the molecular gas. The best model is a gaseous disk with a scale length of ~2 kpc (1 kpc = 3 × 10^{16} km) and a substantial velocity gradient (~100 km s^{-1} kpc^{-1}) across the disk. This is the first time the structure of the molecular gas in a distant quasar has been spatially resolved.

If one assumes that the gas and dust have the same spatial distribution (which is highly likely), then the quasar simply cannot provide enough energy to heat the dust over the entire disk revealed by gravitational-lensing observations. The dust emission has to come from star-forming regions. After correcting for lensing, Carilli *et al.* estimate the star-formation rate in the quasar host galaxy to be 900 $M_\odot$ per year.

With the help of gravitational lensing, the system studied by Carilli *et al.* provides the best case-study to date of the simultaneous formation of a supermassive black hole in a luminous quasar and a young star-forming galaxy at high redshift. Future high-resolution observations of high-redshift quasars, combined with more detailed understanding of black hole population from local systems, will help us to eventually understand the relation of black hole and quasar formation to star formation, and the role of black holes in the formation of galaxies.

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MOLECULAR BIOLOGY

A Place to Die, a Place to Sleep

Marvin Wickens and Aaron Goldstrohm

Messenger RNAs (mRNAs) move through the cellular landscape as their lives unfold. They are born and mature in the nucleus, then pass through the nuclear pores. Many of them then zip to specific destinations in the cytoplasm to be translated into protein. Ultimately, even the most productive mRNAs deteriorate. On page 805 of this issue, Sheth and Parker (*1*) show that in their final act, mRNAs move to a special location in the cell to die. Their findings emphasize the importance of location in determining the fate of mRNAs, and bring spatial control of molecules within the cell to center stage.

In eukaryotes, the decay of mRNAs is commonly preceded by deadenylation, that is, removal of the poly(A) tail, a string of adenosines at the 3′ end of virtually all mRNAs (*2*). In the yeast *Saccharomyces cerevisiae*, loss of the poly(A) tail triggers cleavage of the 5′ structure that caps the mRNA, a process called "decapping." The rest of the mRNA is degraded from 5′ to 3′ by an exonuclease. Messenger RNAs also can be degraded in the opposite direction by the exosome, a protein complex composed of 3′ to 5′ nucleases. The balance between these two pathways varies among mRNAs and organisms (*2*).

Sheth and Parker (*1*) show that proteins in the decapping decay pathway are localized to specific sites in the cytoplasm of *S. cerevisiae* (see the first figure), as has been found in mammalian cells (*3*–*5*). These foci, which they term processing bodies or P bodies, contain decapping enzymes (Dcp1p and Dcp2p), the 5′ to 3′ mRNA exonuclease (Xrn1p), proteins that bind to the mRNA after deadenylation (the Lsm proteins), and two other proteins that enhance decapping (Dhh1p and Patlp). Several of these proteins are known to interact, and may be present as complexes in P bodies (*2*). The number of P bodies is remarkably low—just two or three per cell (see the first figure). The localization of decay factors in P bodies immediately suggests that mRNA turnover might occur in special places within the cell.

The investigators tested this idea by localizing mRNA decay intermediates in which digestion by Xrn1p had been blocked by insertion of specific RNA sequences. The decay intermediates accumulated in P bodies, providing the smoking gun—decay can and does occur inside the P bodies. Decay also may take place outside of the P bodies, using external decapping enzymes and Xrn1p, as well as the exosome, to destroy mRNAs.

What triggers movement of decay intermediates to foci in the yeast cytoplasm? Ccr4p, an enzyme that removes the mRNA poly(A) tail, is spread diffusely throughout the cytoplasm, whereas decapping enzymes are located in P bodies (*1*). The

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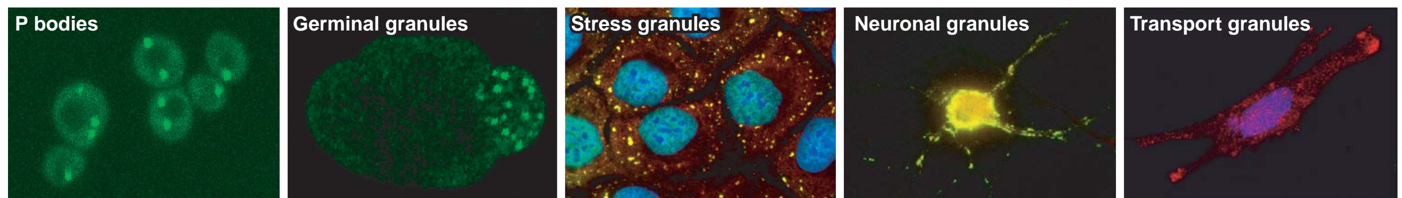


Particulate purgatory for mRNAs. In the yeast *S. cerevisiae*, the decapping protein Dhh1p (green) is localized together with mRNAs in P bodies. In the worm embryo, germinal granules (P granules) in the cytoplasm contain GLD-2, a poly(A) polymerase (green). Stress granules in the cytoplasm of cultured human cells contain the enzyme TIAR [T cell internal antigen-1 related protein (green)] and the translation initiation factor eIF3p116 (red), visualized as yellow spots due to colocalization of the proteins. Neuronal particles in cultured rat hippocampal neurons contain both Staufen1 protein and BC1 mRNA, which appear as small yellow spots in the thin neuronal processes. In chick fibroblasts, cytoskeletal actin mRNA (red) is contained in transport granules, and mRNA particles accumulate in the termini of lamellepodia (DNA is blue).

CREDIT: (FIRST FIGURE) FROM LEFT, U. SHETH, R. PARKER/UNIV. OF ARIZONA–TUCSON; L. WANG, M. WICKENS, J. KIMBLE/UNIV. OF WISCONSIN; N. KEDERSHA/HARVARD MEDICAL SCHOOL; M. MALLARDO, B. GOETZE, P. MACCHI/MAX-PLANCK-INSTITUTE, TÜBINGEN; Y. OLEYNIKOV, R. SINGER/ALBERT EINSTEIN COLLEGE OF MEDICINE, NEW YORK

simplest view is that removal of the poly(A) tail precedes movement of mRNAs to the P bodies (see the second figure). Mutations that eliminate decapping or the *Xrn1p* exonuclease increase the size and number of foci, that is, clogging the pipeline seems to obstruct passage through the system. The *xrn1* yeast mutants are particularly striking: Without the nuclease, tens of foci dot the cytoplasm. Formally, the mutants might affect P-body architecture or assembly, but engineering yeast with active-site mutations should resolve this issue unambiguously.

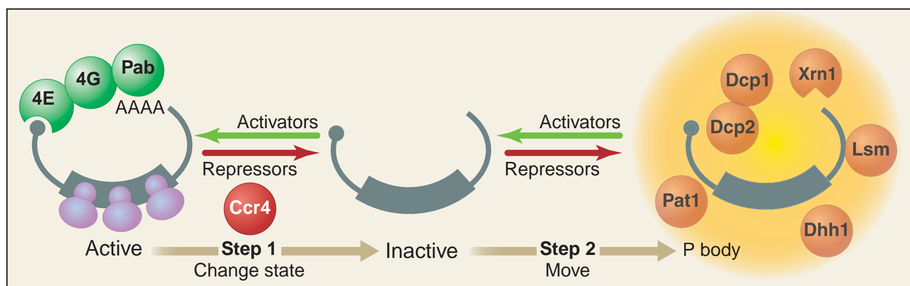
Entry into and exit from P bodies could provide a new means for mRNA control. Between deadenylation and decay, many different factors, such as the Lsm complex and decapping proteins, bind to mRNAs. It is unclear in which order these factors bind and whether they do so before mRNA movement to P bodies begins. Many repressors that bind to mRNAs cause deadenylation (*6*). One repressor, Puf3p, is spread diffusely throughout the cytoplasm. However, it (and other regulators) could bring mRNAs to P bodies and deposit them "at the gates" of these particles. Indeed, in other particles associated with mRNA repression, protein constituents move in and out in just seconds (*7*). The proteins in the presumed intermediate are not yet identified (see the second figure), but are likely to encode the signal that targets mRNAs to P bodies. Repressed mRNAs gather in specific particles during many different biological processes (see the second figure). During oogenesis, inactive mRNAs congregate in large granules together with many proteins that act on mRNAs—RNA-binding proteins, helicases, poly(A) polymerases, and repressors that bind to 3′-untranslated regions (UTRs). These granules—variously called polar granules, P granules, or germinal granules, depending on the species—become segregated in germline cells, and their constituents direct germline development (*8*). In mammalian cells under stress, many mRNAs are repressed and gather in specific cytoplasmic foci. These "stress granules" contain inactive mRNAs associated with 40*S* ribosomal subunits, and certain 3′-UTR regulators (*7*). Finally, many mRNAs are transported through the cytoplasm to specific locations where they ultimately will be translated. En route, the mRNAs often are repressed and packaged into large particles (*9*). For example, in the axons and dendrites of neurons, repressed mRNAs are transported in large neuronal granules (*10*, *11*); in fibroblasts, actin mRNA is packaged into particles and presumed to be inactive as it travels to the cell's moving edges (*12*).

The new data bear directly on mRNA turnover, but can be extrapolated to include translational control. Dhh1p, an RNA helicase, is required for mRNA decay (*13*) and is found in P bodies (*1*). But in early animal embryos, Dhh1p homologs are required for translational repression, and are associated with inactive mRNAs (*14*). More generally, events that cause mRNA decay in yeast may cause repression in other cells and species (*6*, *13*).

In one simple model, mRNAs exist in either of two states, active or inactive (see the second figure). Repressors and activators cause transitions in the mRNA state. A consequence of the transition might be to move the mRNA to granules in which translation is silenced or the mRNA is destroyed. This view implies additional functions for P bodies. Any condition that brings mRNAs to the inactive state could move them to P bodies for storage or destruction. Germinal granules hug the nuclear envelope, and clasp mRNAs as they emerge through pores, likely repressing them before they can be translated (*15*). P bodies might do the same. Aberrant mRNAs, such as those with premature nonsense codons or introns, are degraded through a process termed "mRNA surveillance." This too may take place in P bodies: Surveillance requires decapping of mRNAs (*16*) and proteins that bind to decapping enzymes. Traffic to P bodies may not be a one-way street; as with other mRNA granules, mRNAs could emerge from P bodies to be reactivated under specific conditions, provided they first had a way to evade decay.

P bodies appear to differ in composition from germinal granules, stress granules, and transport particles. But it is early days, and the complete compositions of each particle are not yet known. One or two decay proteins might be enough to distinguish particles that promote mRNA turnover from those that promote repression.

The different sorts of particles do share one overarching property: They conceal mRNAs from the rest of the cytoplasm. In that respect, they affect mRNAs as chromatin condensation affects genomic DNA.



P bodies control mRNAs. Active mRNAs are bound to ribosomes (purple) and to the translation initiation factors eIF4E, eIF4G, and poly(A) binding protein (Pab) (all in green). (**Step 1**) The mRNA makes a transition to an inactive state induced by deadenylation, which is catalyzed by Ccr4p and other enzymes. An inactive intermediate is generated; the proteins associated with this intermediate are not yet known. (**Step 2**) The intermediate moves to the P body (yellow). There it can be degraded by the Xrn1p exonucleases (orange). Repressors and activators of mRNAs not only regulate the change in state transition (Step 1), but may also move mRNAs into and out of P bodies (Step 2).

By hiding mRNAs away, their access to cytoplasmic factors is greatly restricted. Packaging ensures that mRNAs destined for inactivity stay repressed; at the same time, by relieving competition, translation of active mRNAs may be enhanced. These features, rather than the roles of any specific molecular constituents, may be the strategy shared by diverse particles.

To die, to sleep, to reawaken—mRNAs, like Hamlet, have pivotal decisions thrust upon them by others. The choices may require, and even hinge on, moving mRNAs from one part of the cell to another. Get the mRNA to the right place, and the rest is silence.

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STRUCTURAL BIOLOGY

Changing Partners

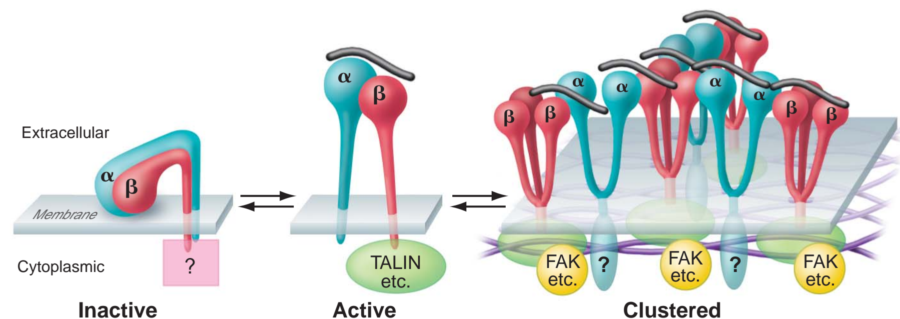
Richard O. Hynes

Biologists have developed two different models to describe how plasma membrane proteins called integrins control cell adhesion. In the first model, conformational activation of individual integrins is postulated to increase their affinity for ligands, such as fibronectin or fibrinogen. In the second model, clustering of integrins in the plane of the plasma membrane is proposed to increase the avidity of cell adhesion without affecting ligand affinity. Evidence for both models exists. Given that conformational activation and lateral clustering typically occur together, it is possible that one event leads to the other, although opinions differ as to which occurs first. On page 795 of this week's issue, Li *et al*. (*1*) present structural data revealing that conformational activation and lateral clustering of integrins are closely and inextricably coupled.

During the past 2 years, integrin research has been fueled by several exciting discoveries. These discoveries include the structure of the extracellular domain of αVβ3 integrin (*2*), the details of interactions of integrin cytoplasmic domains (*3*–*5*), and conformational changes that lead to integrin activation (*6*–*8*). These results have led to two widely accepted notions (*9*, *10*). The α and β subunits of the integrin heterodimer are in equilibrium between an inactive state in which the stalks of the heterodimer are bent in the middle, and an active state in which the stalks straighten and separate (see the figure). Activation of integrins takes place from the outside of the cell through binding of ligand to the extracellular domain, and also from the inside of the cell through binding of the cytoskeletal protein talin to the cytoplasmic domain. Thus, activation of the ligand-binding extracellular domain is coupled with activation of the cytoplasmic domain, which is linked to the cytoskeleton and associated signaling complexes.

But what about the two integrin transmembrane segments that traverse the lipid bilayer, connecting the extracellular and cytoplasmic domains? Nuclear magnetic resonance (NMR) imaging studies suggest that the αIIb and β3 transmembrane segments of αIIbβ3 integrin are predominantly in the α-helical conformation (*11*). If, in the inactive state, the external portion of the stalks and the internal cytoplasmic domains are adjacent to each other, then the two transmembrane segments should also be associated (see the figure). However, when reconstituted in phospholipid micelles the two isolated α and β transmembrane segments do not readily interact with one another, preferring instead to form homo-oligomers (*11*). The αIIb transmembrane-cytoplasmic segment forms homodimers, whereas the β3 transmembrane-cytoplasmic segment forms homotrimers. In both cases, these homo-oligomers are in equilibrium with their constituent monomers.

In the new work, Li *et al*. (*1*) now extend analysis of transmembrane segments to the intact integrin. They have made a series of mutations in the β3 transmembrane segment of αIIbβ3 integrin, which are predicted to enhance its ability to form homotrimers. One of these mutations (G708N) did indeed enhance trimerization of the β3 transmembrane segment and, most importantly, activation of αIIbβ3 integrin in cultured cells. Activation was measured according to several criteria including binding to αIIbβ3 of (i) its natural ligand fibrinogen and (ii) an antibody, PAC-1, that mimics the natural ligand; and activation of focal adhesion kinase (FAK) in detached cultured cells. Thus, both the external and internal domains of mutant αIIbβ3 are in an "active" state, whereas wild-type αIIbβ3 remains inactive. A second mutation, M701N, which lies on the same face of the transmembrane α helix, also elicited integrin activation, whereas several other mutations in adjacent residues did not.



Altered states. (**Left**) When inactive, the integrin αβ heterodimer is bent over and does not bind to its extracellular ligands. The two cytoplasmic domains are closely apposed, possibly held together by unknown cytoplasmic proteins (pink). (**Middle**) Upon activation, the integrin αβ heterodimer is stabilized either by the extracellular ligand (black) or by intracellular cytoskeletal proteins, such as talin (green). (**Right**) Lateral clustering of integrins is stabilized by homo-oligomerization of the α and β transmembrane domains. This brings together the integrins and their associated ligands (black), intracellular proteins linked to the cytoskeleton (purple), and signaling molecules (represented by FAK, yellow). Additional, as yet unidentified cytoplasmic proteins, perhaps recruited by the α dimers, may also be part of the cluster. [Adapted from (*1*)]

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