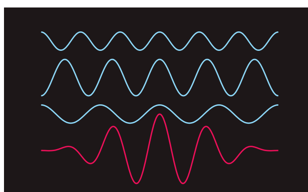
the middle of the pulse.

To make their Rutherford atom, Maeda *et al.* (1) exploit the fact that the highly excited states of the hydrogen atom, called Rydberg states (see the first figure, panel D) (3), provide a range of quantum states whose energy spacing is almost uniform, as the notes on a piano are almost uniformly spaced in frequency. When many of these states are added together, the resulting electron wave function briefly becomes localized. However, the energy spacing of the Rydberg atom is not perfectly uniform, and the wave packet quickly begins to fall apart because of dispersion (the same process that spreads white light into a rainbow).



Localizing an electron. A localized wave packet forms via a coherent superposition of states; the red wave packet is the sum of the three blue sine waves.

Highly excited Rydberg atoms are tenuous things. Even blackbody radiation from the walls of the vacuum chamber, or the electric field from a flashlight battery, can knock the electron out of its orbit. Such atoms can be tens of nanometers in size, approaching the size of features on silicon chips. Their orbital periods are slower than those of unexcited atoms by six orders of magnitude.

Rydberg atoms are thus sufficiently big and slow that the time scale of the electron motion is slowed from optical to microwave frequencies. They provide a test bed to learn about the murky boundary between quantum mechanics and the macroscopic world.

Maeda *et al.* create their Rydberg atoms from a beam of lithium atoms. They use a series of laser pulses to excite the atoms to successively higher energy levels. The authors demonstrate that a linearly polarized microwave field can counteract the dispersion and can hold the wave packet together for thousands of orbits around the nucleus, just as a sheepdog keeps a herd of sheep together. They can speed up the wave packet's orbit or slow it down by sweeping the microwave frequency up or down. They can even knock the electron wave packet out of the atom by applying a brief electric pulse at just the right moment.

Rydberg atoms are like a quantum playground. They allow single photons to be nondestructively detected (4) and can encode information as qubits for quantum computing (5). But Rydberg atoms may also have more practical applications. A gas of Rydberg atoms can spontaneously ionize and form an ultracold plasma (6). And techniques learned from experiments like those reported by *Maeda et al.* may lead to methods for cooling antimatter atoms (7).

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CELL BIOLOGY

Ras on the Roundabout

Doris Meder and Kai Simons

Proliferation and differentiation are the cell's most fundamental responses to extracellular stimuli. The two outcomes are poles apart: Proliferating cells divide into more of the same kind, whereas differentiating cells undergo profound changes in shape, subcellular organization, and metabolic activity that are often accompanied by a block in proliferation. Yet they can be initiated by the same key regulators and with identical effector molecules. The differential signaling output is fundamentally dependent on the spatial organization of the signaling molecules and their regulators within the cell. How signaling molecules are targeted to different cellular compartments is an important but poorly understood challenge for the cell. On page 1746 of this issue, Rocks *et al.* shed light on this challenge with their report that Ras signaling molecules modified by addition of palmitoyl groups (palmitoylation) continuously cycle between the plasma membrane and the Golgi complex (1).

The major signaling cascade for cell proliferation and differentiation is the mitogen-activated protein kinase (MAPK) cascade, which receives stimuli from growth factors and hormones that are transmitted to the cell through tyrosine kinase receptors. The key regulator of this pathway is the guanosine triphosphatase (GTPase) Ras. Mutations in Ras occur in human cancers, and oncogenic Ras isoforms transform cultured cells. Mammals have three different Ras genes that give rise to four highly homologous proteins differing only in the carboxyl terminus that anchors them to cellular membranes. All Ras isoforms are modified with a farnesyl group (farnesylation). In addition, N-Ras is acylated with one palmitoyl group and H-Ras with two, whereas K-Ras4B contains a polybasic stretch of amino acids in its carboxyl terminus (its splice variant K-Ras4A carries a single palmitoyl group like N-Ras). Despite their identical effector binding domains, the different signaling pathways regulated by Ras isoforms have been attributed to differences in subcellular localization. K-Ras4B is confined to the plasma membrane, whereas H-Ras and N-Ras have also been detected in the Golgi. Originally, Ras signaling was believed to occur exclusively at the plasma membrane, but recent data suggest that the Golgi serves as an additional signaling platform (2). How the different Ras signaling pathways are segregated in different cellular compartments remains unclear.

Rocks *et al.* focused their investigation on the two Ras isoforms that are palmitoylated: H- and N-Ras. Fluorescently labeled H- and N-Ras expressed in cultured canine kidney cells were localized to the plasma membrane and to the Golgi membranes. After photobleaching of the Golgi area, fluorescence was regained by accumulation of unbleached molecules from other compartments. Similarly, when fluorescence was selectively activated in the plasma membrane, the Golgi also became labeled over time. The finding of retrograde flow from the plasma membrane to the Golgi is important, because Ras was previously believed to pass through the Golgi only on its way out to its final destination in the plasma membrane (3).

Interestingly, the recovery kinetics were faster for N-Ras carrying one palmitoyl group than for H-Ras carrying two, indicating the involvement of palmitoylation in this process. Indeed, inhibition of palmitoylation abolished Ras trafficking from the plasma membrane to the Golgi. Given that palmitoylation is a reversible form of protein modification, Rocks *et al.* tested whether depalmitoylation was also a prerequisite for exchange of Ras between the plasma membrane and Golgi. To this end, two fluorescently labeled N-Ras molecules were chemically synthesized, one in which the palmitate was attached by a cleavable thioester bond and the other in which the

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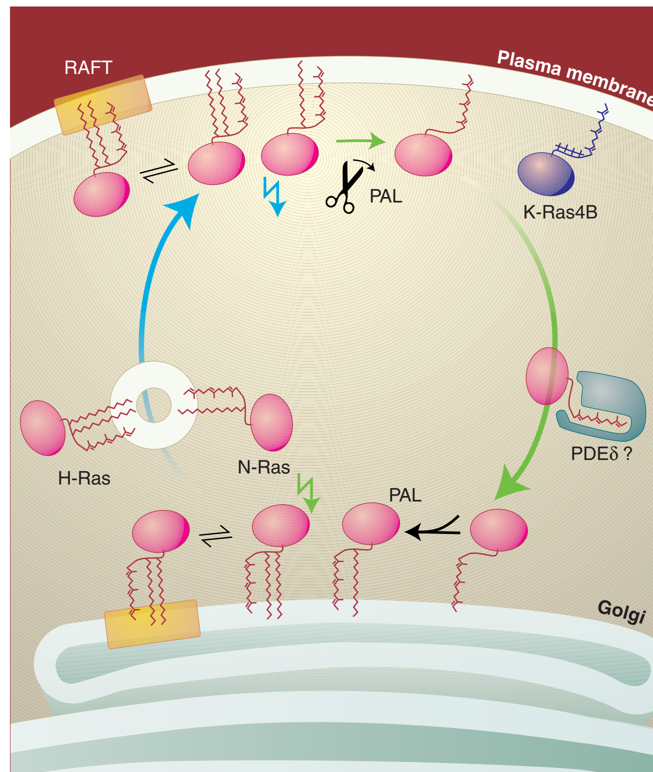
thioether bond could not be cleaved. When these two proteins were microinjected into canine kidney cells, the first one behaved like wild-type N-Ras and cycled between the plasma membrane and Golgi. In contrast, the depalmitoylation-defective variant was randomly distributed to all cellular membranes and did not display movement between the plasma membrane and Golgi. The authors therefore argue that it is the depalmitoylation-repalmitoylation cycle that defines the specific distribution of Ras between the plasma membrane and Golgi. Ras is depalmitoylated at the plasma membrane and subsequently "falls out" of the plasma membrane into the cytosol. Then it becomes randomly inserted into the membranes of cellular organelles and finds itself kinetically trapped in the Golgi, where it is repalmitoylated and thus again becomes stably anchored to the membrane. Although palmitoylated Ras joins the vesicular secretory pathway from the Golgi to the plasma membrane, retrograde transport in the opposite direction is probably not vesicular. It is unclear whether farnesylated Ras diffuses freely in the cytosol, or whether it is bound to a chaperone (as is the case for Rab and Rho GTPases). A possible chaperone candidate is PDEδ, a structural homolog of Rho-GDI (guanine nucleotide dissociation inhibitor), which binds to the carboxyl terminus of H-Ras in vitro and in vivo (*4*).

The depalmitoylation-repalmitoylation cycle is not a unique feature of H- and N-Ras; it also operates for other palmitoylated proteins such as GTPase activating protein GAP-43, heterotrimeric GTP-binding protein subunit $G\alpha_{i1}$, and endothelial nitric oxide synthase. Current research is investigating whether this cycle is linked to Ras activation and signaling. Earlier studies showed that upon stimulation with epidermal growth factor (EGF), Ras is initially activated at the plasma membrane, but that this activation is transient and is usually followed by a more sustained activation of Ras in the Golgi (*2*). Ras activation is typically detected with the fluorescently tagged molecule RafRBD (the Ras binding domain of the downstream target Raf), which binds only to the GTP-loaded active form of Ras but does not discriminate between the different Ras isoforms. To assess H-Ras and N-Ras activation separately, Rocks *et al.* used fluorescence lifetime imaging as a measure of fluorescence resonance energy transfer between H- or N-Ras tagged with cyan fluorescent protein and RafRBD tagged with yellow fluorescent protein. Activated H-Ras was first detected at the plasma membrane and appeared at the Golgi only after a 15-min delay, whereas activated N-Ras was observed at the Golgi immediately after activation at the cell surface. The kinetics of Ras activation thus mimic the kinetics of the plasma membrane–Golgi cycle and suggest that, in this case, Ras is loaded with GTP at the plasma membrane and then is transported to the Golgi in its activated form. However, the cycle seems to operate independently of the activation state of Ras, so that GTP loading could also occur in the Golgi.



A cellular compartment of one's own. The largely homologous Ras proteins H-, N-, and K-Ras regulate distinct signaling pathways. These proteins are able to regulate separate signaling pathways because they inhabit different compartments within the cell. Whereas K-Ras4B is exclusively available for signaling at the plasma membrane, N-Ras and H-Ras cycle between the plasma membrane and Golgi depending on whether they carry a palmitoyl group or not. An increased rate of depalmitoylation leads to accumulation of N- and H-Ras in the Golgi, whereas increased palmitoylation leads to their accumulation at the plasma membrane. Palmitoylated Ras isoforms are incorporated into secretory vesicles for anterograde transport from the Golgi to the plasma membrane. Because depalmitoylation correlates with detachment from the plasma membrane, retrograde transport from the plasma membrane to the Golgi is nonvesicular and possibly involves a farnesyl-binding chaperone such as PDEδ. A second level of spatial organization comes from the subcompartmentalization of the Golgi membranes and plasma membrane into different domains separated by lipid rafts (orange). Doubly palmitoylated H-Ras has an affinity for lipid rafts that is modulated according to its activation state.

The subcellular site of Ras activation is determined by the localization of specific guanine nucleotide exchange factors (GEFs) and GAPs. In T lymphocytes, low-grade stimulation of the T cell receptor activates an alternative signaling pathway that acts simultaneously on a Golgi-resident Ras-GEF and a plasma membrane–resident Ras-GAP and thus leads to activation of N-Ras exclusively in the Golgi (*5*). To keep activated Ras in the Golgi for sustained signaling, scaffolds that bind to the activated protein and keep it in place are most likely needed. Such effector-mediated stabilization in the membrane has been described for Rab GTPases (*6*). Recently, the first Golgi-resident Ras effector (*7*) and a Golgi-associated MAPK scaffold (*8*) were identified. Nonetheless, the function of the palmitoylation cycle might go beyond targeting Ras to different cellular compartments and may provide a way to tune Ras signaling. Depalmitoylation ensures removal of Ras-GTP from the plasma membrane, leading to transient plasma membrane signaling, as others have reported (*2*). Furthermore, changing the rates of palmitoylation or depalmitoylation would shift Ras either to the Golgi or to the plasma membrane and thus prime the signaling cascade with a high number of Ras molecules in the location where activation is needed.

The palmitoylation cycle provides a way to allocate Ras signaling pathways to different subcellular compartments. A second level of subcompartmentalization comes from the possible partitioning of Ras isoforms into different membrane domains. Such dynamic assemblies could vary in their concentration of activated tyrosine kinase receptors or downstream effectors and targets, and consequently could mediate distinct signaling outputs. Two principal Ras activators have affinities for membrane lipid rafts, ordered assemblies composed of sphingolipids with saturated, long-chain fatty acids and cholesterol that are dynamically segregated from the bulk of the membrane due to the immiscibility of their lipids with those of the rest of the membrane (see

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the figure). T cell receptors activate their signaling pathways from lipid rafts (*9*), and signaling by EGF receptors is differentially regulated by raft lipids. The ganglioside G_{M3} inhibits EGF receptor autophosphorylation by binding to its extracellular domain, but administration of another ganglioside (G_{D1a}) enhances EGF-mediated signaling by increasing dimerization of EGF receptors, thus priming them for binding to EGF (*10*).

Of the four Ras isoforms, only H-Ras with its two palmitoyl chains has a definite affinity for lipid rafts, depending on its activation state. The current interpretation is that H-Ras is in dynamic equilibrium between at least two types of small (10 to 15 nm) membrane domains. One domain is formed by lipid-lipid interactions and is cholesterol dependent, whereas the other is stabilized mostly by protein-protein interactions and is cholesterol independent. H-Ras is thought to be shifted from the former to the latter when loaded with GTP (*11*). The assemblies formed by GTP-loaded H-Ras are dependent on galectin-1, a cytosolic protein that binds to galactose moieties as well as to H-Ras and plays a crucial part in Ras signaling (*12*). Another admittedly speculative view is that galectin-1 organizes GTP-loaded H-Ras into cholesterol-independent raft nanoclusters from which signals are relayed. But the question is how. It is possible that galactosylceramide when flipped to the cytosolic lipid leaflet could serve as a raft anchor for galectin-1.

The importance of membrane domains in Ras signaling is obviously an open issue. The question raised here is whether transiently specialized raft assemblies could form through protein-lipid and protein-protein interactions that do not result in the accumulation of other raft markers. Their formation would not be restricted to the plasma membrane but could take place equally in Golgi membranes, which contain all of the components needed for raft assembly. The rapid time scale of the interaction between Ras and Raf (*11*), followed by depalmitoylation and dissociation from the membrane, will further complicate the analysis of these nanoscale Ras signaling platforms.

Ras proteins have been identified and characterized and their posttranslational modifications established for more than 25 years. With more than 25,000 PubMed entries, Ras proteins are probably the most extensively studied signaling molecules ever. Nonetheless, the individual roles of the different isoforms in cell proliferation, differentiation, and oncogenic transformation are still not understood, nor are the signaling outputs of their specific effector pathways. Unfortunately, good tools for selectively assessing the function of a single Ras isoform without resorting to overexpression experiments are still missing. Thus, the spatiotemporal analysis of endogenous Ras signaling remains a big challenge for the future. Why is Ras signaling localized to the Golgi? One advantage of the Golgi is its close proximity to the nucleus, the ultimate destination for activated MAPK. Computer modeling of the MAPK signaling cascade predicts a strong attenuation of the phosphorylation signal from the plasma membrane toward the nucleus (*13*). Signaling from the Golgi would bring the process closer to the target site and therefore would be especially suited for transcriptional regulation.

The paper by Rocks *et al*. is an important piece in the Ras puzzle but it is also of much more general value, because it describes a targeting mechanism that has not received much attention by researchers in the protein sorting field. It could well be that there are many more proteins that are sorted by reversible posttranslational modifications and that cycle between different cellular sites. On the roundabouts as well as at the exits, there are probably more surprises to come.

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APPLIED PHYSICS

Toward Quantum-Information Processing with Photons

Ian A. Walmsley and Michael G. Raymer

The emerging field of quantum technology uses individual atoms, molecules, and photons to construct new kinds of devices. Quantum objects are not limited to the binary rules of conventional computing, but can be in two or more logical states at once. When a group of objects collectively occupy two or more states at once, they are said to be entangled. Photons interact very weakly with their environment, and therefore entangled states of photons hold considerable promise for applications ranging from imaging and precision measurement to communications and computation.

In every quantum-information processing scheme, bits of information must be stored in the states of a set of physical objects, and there must be a physical means to effect an interaction between these quantum bits (qubits). But when one tries to use individual photons to store and process information, a problem arises: Photons interact extremely weakly or not at all, and it might thus seem unlikely that they can be used directly for quantum-information processing.

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Remarkably, a scheme for effective quantum interactions between photons has been invented that does not require the photons to interact physically. When a group of photons are in an entangled state, the measurement of one or more of these photons' states causes the state of the remaining photons to "collapse." Such a state collapse can be viewed as an effective interaction between the remaining photons (*1*). The nature of the interaction depends on the outcomes of the measurement on each observed (ancilla) photon. The occurrence of certain predetermined outcomes of the ancilla measurements signals (heralds) the effective interaction of the remaining photons.

This approach can be used to implement "heralded" quantum logic gates in a scheme called linear-optical quantum computing (see the first figure). Substantial progress toward linear-optical quantum computing has been made, such as the design (*2*) and demonstration (*3*) of a teleportation gate and of a controlled-not (C-NOT) logic gate (*4*), and the preparation of entangled states of two photons (*5*). But serious challenges remain.

When using photons as qubits to encode information, each photon must be created in one of two distinct quantum states or in a superposition of these two states. If the photons occupy more states in an uncontrolled

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