ited to the Northern Hemisphere, however: Wolff and Suttie (9) have shown that the mean Pb content (2.5 pg/g) of Antarctic snow deposited in the 1920s was five times that of background (~0.5 pg/g); pollution records before this time remain to be ascertained. Lower Pb levels in Antarctic compared to Arctic regions are attributable to smaller emission intensity in the Southern Hemisphere.

Studies of other types of deposits have confirmed the global nature of Pb pollution dating back to ancient times. Analysis of lake sediments from various parts of Sweden found a peak in Pb deposition around 2000 years before present (B.P.) and steady increases that began from around 1000 years B.P., reached 10 to 30 times background levels by the beginning of the Industrial Revolution, accelerated during the 19th century, and usually peaked in the 1970s (*10*). Records in ombrogenic bog at Etang de la Gruyere, Switzerland, show rates of Pb deposition by 2000 years B.P. that were an order of magnitude above background as well as the usual highly elevated values in recent deposits (*11*). Similar records with peaks in Pb deposition during Roman times have also been reported in peat bogs in other parts of Europe, including northern Scotland, Gordano Valley near Bristol, and Featherbed Moss in Derbyshire (*7*).

Hemispheric-scale pollution in ancient times apparently was not limited to Pb. The latest paper by Hong *et al.* (*2*) provides evidence for widespread atmospheric contamination with Cu from Roman mines and smelters. Ombrogenic bogs, aquatic sediments, and snow fields are distributed widely throughout the globe. These deposits can potentially be used to trace the broad temporal and spatial differences in mineral resource exploitation. The report by Hong *et al.* should serve as a beacon to the unexplored research opportunities in the use of geochemical methods to "read" the exciting archives of mining and smelting activities in different parts of the world. It is somewhat surprising that paleopollution study has remained an unexplored tool in the field of archaeology.

The rate of metal emission to the atmosphere depends on the quantity of ore smelted and the technology used. Hong *et al.* (*2*) related the ice core records primarily to the quantity of Cu mined. Advances in mining technology are driven by the need to exploit new ore minerals or to improve the recovery efficiency. Either impetus has a major impact on metal emission rate. Retrospective geochemical monitoring hence represents a potential tool for evaluating historical developments in mining technology. For instance, the development of the *patio* process (or mercury amalgamation process) into an industrial-scale operation stimulated massive production of silver in South and Central America and left behind an unparalleled legacy of Hg pollution in the area. Between A.D. 1580 and 1900, annual loss of Hg in the silver mines averaged 612 tons/year (in a range of 292 to 1085 tons/year) and totaled about 196,000 tons (*12*). So far, little attempt has been made to "read" the geochemically archived records to determine the pattern of dispersion and deposition of such massive quantities of Hg at the local, regional, or global scale. The archives, one suspects, will likely show that the current problem of Hg pollution associated with the gold rush in Brazilian Amazon is only a faint reenactment of a major old tragedy.

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Cell Shape Determination: A Pivotal Role for Rho

Howard Bussey

Morphogenesis, the complex process that shapes cells to their myriad forms, has long fascinated biologists. Two reports in this issue (*1*, *2*) move us closer to an understanding of why one particular cell—a yeast cell—has its characteristic shape.

Cells of the yeast *Saccharomyces cerevisiae* bud to form daughters in their own image. Once a mother cell commits to undergo a new mitotic cycle, a bud site is chosen through an elaborately regulated biochemical hierarchy (*3*). With a site chosen, cellular polarity is established and the bud emerges and grows, receiving a full complement of cellular components; after cytokinesis, the bud forms a daughter cell. It is during bud construction that the distinctive yeast cell shape is established by the architecture of cell wall glucan deposition. Construction of the bud begins at the bud tip, and many components need to be marshalled at this site to ensure their ordered elaboration: The actin cytoskeleton polarizes the secretory apparatus to the bud tip to provide the necessary building materials for cell wall assembly.

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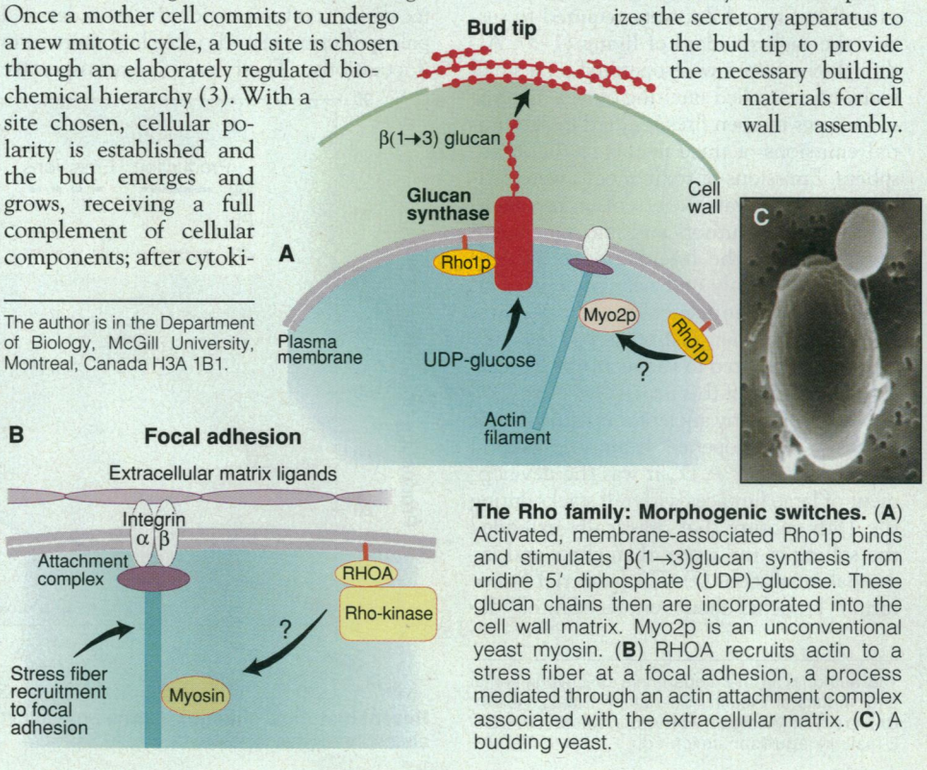

The Rho family: Morphogenic switches. (**A**) Activated, membrane-associated Rho1p binds and stimulates β(1→3)glucan synthesis from uridine 5′ diphosphate (UDP)–glucose. These glucan chains then are incorporated into the cell wall matrix. Myo2p is an unconventional yeast myosin. (**B**) RHOA recruits actin to a stress fiber at a focal adhesion, a process mediated through an actin attachment complex associated with the extracellular matrix. (**C**) A budding yeast.

The synthesis of wall polymers, such as glucan, must also be ordered to couple bud growth with the cell cycle.

A small Ras-like guanosine nucleotide binding protein yeast Rho1p serves as a morphogenic coordinator. Such small guanosine triphosphatases (GTPases) act as molecular switches in many contexts, although most participate in signal transduction cascades that contain heterotrimeric GTP-binding proteins (G proteins) and protein kinases. Rho1p itself acts downstream of the G protein cascades for bud site selection (*3*) and it also activates a protein kinase, but now a long-anticipated downstream target involved in bud construction—glucan synthase—has been identified.

Prenylated Rho1p colocalizes with cortical actin to the inner surface of the plasma membrane at the growing bud tip and at the mother-daughter neck at cytokinesis (*4*). *RHO1* is an essential gene, and if it is absent, the cells stop growing when they have only tiny buds, which are bounded by cell walls that burst at their tips. One reason for this phenotype is that Rho1p is required to activate yeast protein kinase C, Pkc1p, which activates a mitogen-activated protein kinase signal transduction pathway required for cell wall integrity (*5*, *6*). But Rho1p has an additional function in cell wall biogenesis. The two new papers (*1*, *2*) show that activated GTP-bound Rho1p is a positive regulatory subunit of β(1→3)glucan synthase, the enzyme responsible for much of cell wall glucan synthesis. Although still incompletely characterized, β(1→3)glucan synthase contains two related, integral membrane protein subunits, Fks1p and Fks2p (*7*). Biochemical studies indicate that glucan synthase activity is stimulated by GTP, likely through a G protein (*8*). Rho1p is now identified as this activator, and Fks1p is shown to colocalize with Rho1p at the tip of growing buds and at the mother-daughter neck at cytokinesis. Thus, Rho1p regulates glucan synthesis so that it occurs at sites of wall growth and remodeling (see the figure).

Humans have a Rho1p homolog called RHOA; this GTPase is 72% identical to its yeast counterpart, and it is able to partially substitute for Rho1p in yeast (*9*). One role for RHOA in mammals is to regulate the formation of actin stress fibers, structures that emanate from small patches of the plasma membrane called focal adhesions, which allow the cytoskeleton to pull against the extracellular matrix and alter cell morphology. At these adhesions, integrin receptors bind to extracellular matrix proteins. These focal adhesions are formed in a RHOA-dependent manner in response to growth factors and phospholipids (*10*). How do stress fibers form? As shown in the figure, activated GTP-bound RHOA can bind to and activate protein kinases, including one called Rho-kinase, and may trigger a transduction cascade that ultimately results in stress fiber formation.

These provocative findings prompt an attempt to integrate the roles of Rho1p and RHOA in modulating polarized cell surface assemblages in yeast and mammals. Whether RHOA activates extracellular matrix polysaccharide biosynthesis in mammals is unknown. However, focal adhesion formation is triggered by extracellular signals, and human RHOA has partially retained the ability to replace Rho1p in yeast (*9*). Thus, RHOA may also promote ordering of the mammalian cell surface with the actin cytoskeleton at these focal contacts, possibly through the integrin or ERM-CD44 complexes (*11*). Pursuing this comparative theme, a bud could be viewed as a singular, specialized focal adhesion that consolidates its location by spinning an external glucan net.

There is still much to be learned; we do not fully know how Rho1p is localized or regulated, or how it acts as a multifunctional switch. The Rho subfamily of G proteins has five known members in yeast, some of which are required for bud growth (*12*). These may also activate other downstream targets effecting morphogenesis, such as localized cell wall chitin deposition. A process that can be recruited to form structures as apparently disparate as a yeast bud and a mammalian focal adhesion is likely to participate in creating an even wider range of cellular form. Rho1p and RHOA and their kind seem worth examining in other eukaryotes as regulators linking cellular polarity to morphogenesis.

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Arousal: Revisiting the Reticular Activating System

Mircea Steriade

Physiologists and clinical neurologists of the 18th and 19th centuries were aware that a structure located deep within the brain controls mental alertness. In the last few decades, neuroscience has defined this arousal system more clearly: It originates in the upper brainstem reticular core and projects through synaptic relays in the thalamus to the cerebral cortex, where it increases excitability (see figure) (*1*).

This arousal system was postulated to contain neurons with extensive dendritic and axonal domains that are driven by virtually all sensory modalities and have widespread projections to many cerebral structures (*2*). However, this concept fell into desuetude for more than three decades, because the connectivity and chemical codes of the hypothesized neural paths were unknown. In the past 10 to 15 years, the brainstem to cortex circuit, relayed through intralaminar and other thalamic nuclei (see figure), has been identified, and the main neurotransmitters (acetylcholine and glutamate) and their actions have been defined (*3*). Further, humans participating in a task requiring alertness and attention display increased regional blood flow (a measure of neuronal activity) in the midbrain reticular formation (MRF) and thalamic intralaminar nuclei (*4*); conversely, individuals with bilateral lesions of thalamic intralaminar nuclei are lethargic or somnolent (*5*). Now, two reports in this issue (*6*, *7*) describe how this arousal system changes the excitability of the cortex.

Ironically, this far-reaching concept of an ascending reticular system governing arousal was formulated on the basis of electroencephalographic (EEG) recordings in experiments on anesthetized animals in which the behavioral state did not change (*2*). In these initial experiments, MRF stimulation caused low-voltage or flattened EEG waves (*2*), similar to those of awake animals, suggesting an unexpected decrease in brain electrical activity (see figure, top). The epigones often used the term "desynchronization" to describe the EEG correlate of wakefulness [as well as that of rapid eye

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