bisphosphorylated phosphoinositides (containing phosphate at the 4-position of the inositol ring), such as $PI(4,5)P_2$ (phosphatidylinositol-4,5-bisphosphate), a phospholipid highly enriched within the plasma membrane. A cocrystal structure of the tubby domain with the head group of $PI(4,5)P_2$ revealed a basic pocket that is crucial for binding of tubby to this phospholipid. Furthermore, overexpression of an activated form of the heterotrimeric GTP-binding protein $G\alpha_q$—which stimulates activation of phospholipase C–β and the hydrolysis of $PI(4,5)P_2$—resulted in movement of tubby into the nucleus. In addition, expression of the serotonin receptor $5HT_{2c}$, which activates $G\alpha_q$, also resulted in relocation of tubby to the nucleus. A further twist to the story came with the finding that either activated or nonactivated forms of $G\alpha_q$ could bind to tubby in vivo, suggesting that $G\alpha_q$ helps to position tubby at plasma membrane locations where $PI(4,5)P_2$ hydrolysis occurs. This would ensure efficient release of tubby from the plasma membrane even when a relatively small fraction of total $PI(4,5)P_2$ is hydrolyzed. It is also possible that the water-soluble inositol polyphosphates, IP_3 and IP_4, that accumulate when $PI(4,5)P_2$ is broken down could contribute to the sustained dissociation of tubby from the membrane by competing with $PI(4,5)P_2$ for binding to tubby (see bottom figure).

The findings of Santagata *et al.* raise new questions about the involvement of PI turnover in cellular signaling. It has been assumed that the primary task of hormone-stimulated PI turnover is to increase cytosolic calcium, which then regulates a host of calmodulin-mediated events (such as calcineurin-dependent NFAT translocation). Calcium ions, however, do not appear to be primary players in tubby translocation because in experiments with a calcium ionophore (which allows calcium ions to flow into cells), tubby did not relocate to the nucleus. Interestingly, $PI(4,5)P_2$ in yeast can also be hydrolyzed by a phospholipase to generate IP_3. This pathway, however, does not appear to be linked to calcium ion regulation but rather is involved in the synthesis of more highly phosphorylated forms of inositol polyphosphates that are required for mRNA export and transcriptional regulation (*6*). Additionally, $PI(4,5)P_2$ is involved in the polymerization of actin filaments through its direct binding to a host of proteins that mediate this process. Thus, it is likely that $PI(4,5)P_2$ synthesis and its hydrolysis to IP_3 evolved for diverse purposes that are independent of calcium ion regulation. Moreover, IP_3-dependent increases in intracellular calcium are probably a relatively late (although still very important) adaptation of this pathway in higher eukaryotes.

There is much yet to learn about tubby. The high level of expression of both tubby and the $5HT_{2C}$ serotonin receptor in the paraventricular nucleus of the hypothalamus and the observation that $5HT_{2C}$-deficient mice (*7*) have mature-onset obesity and other characteristics similar to those of mice lacking tubby imply that tubby is controlled by this receptor in vivo. However, a host of other hormone receptors—including the bombesin, dopamine D1, melanocortin 4, and melanin concentrating hormone receptors—are coupled to $G\alpha_q$ and could regulate tubby in vivo. In addition, insulin has been shown to stimulate tyrosine phosphorylation of tubby, and this could impose an additional level of regulation (*8*). Finally, there is much yet to learn about the part that tubby plays in regulating downstream genes that control obesity. The study by Santagata *et al.* lays the foundation for future progress in this important area of research.

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PERSPECTIVES: CHEMISTRY

A New Twist on Chirality

Ben L. Feringa

One of the great mysteries in science is the homochirality (single handedness) of the essential molecules of life. Natural sugars are almost exclusively right-handed; natural amino acids are almost exclusively left-handed. Current life forms could not exist without the uniform chirality of these monomers, which form the building blocks of polysaccharides and proteins. Uniform chirality is also essential for information storage and processing, as demonstrated by the supramolecular chirality of the DNA helix. But we still do not know the origin of this biomolecular homochirality.

Macroscopic chiral selection—which usually goes unnoticed in daily life, for instance, when one shakes hands or uses a corkscrew to open a bottle of wine—seems to bear no relation to chirality at the molecular level. But on page 2063 of this issue, Ribó *et al.* (*1*) report that simple stirring can lead to chiral selection. At first sight, these results seem hard to believe, but the authors provide strong support for their claim.

Pasteur tried, without success, to induce a preference for right- or left-handed molecules by performing reactions in a centrifuge and even by rotating growing plants to change the handedness of their natural products (*2*). Ever since, scientists have tried to generate excess left- or right-handed chiral molecules from achiral precursors without the intervention of any preexisting molecular chirality.

This problem, termed absolute asymmetric synthesis, has turned out to be a major challenge (*3*). Recent successful studies have used photochemistry with circularly polarized light (*4*), chiral selection based on the electroweak interaction (although disputed) (*5*), and the combination of a magnetic field and nonpolarized light (*6*). Numerous attempts have also been made to perform asymmetric synthesis by clockwise or counterclockwise rotation during the chemical conversion of an achiral compound. But the resulting indications of chiral selection are usually discarded as irreproducible or as artifacts. These failures are not unexpected if one realizes that the applied external chiral force must directly exert a polarizing effect on the reaction path, a condition not satisfied by bulk rotation (*3*).

Nevertheless, the vortex motion used by Ribó *et al.* acts as a true chiral force (*7*). How can it lead to chiral selection? In Ribó *et al.*'s system (*1*), stirring does not act on a chemical reaction but rather on an aggregation process. The assembly of identical achiral molecules into large chiral fiber-type structures under the direct influence of the external force created by stirring is biased to a particular handedness.

Ribó *et al.* use achiral disklike porphyrins that have a zwitterionic structure, that is, they contain both negatively and positively charged moieties (see the figure). These properties allow the molecules to aggregate through electrostatic interactions and hydrogen-bonding. A dilute solution of the porphyrin is slowly concentrated while being stirred, thereby stimulating the aggregation. The disk-shaped molecules stack side by side to form strands (called J-aggregates), which combine to form fibers and bundles of fibers.

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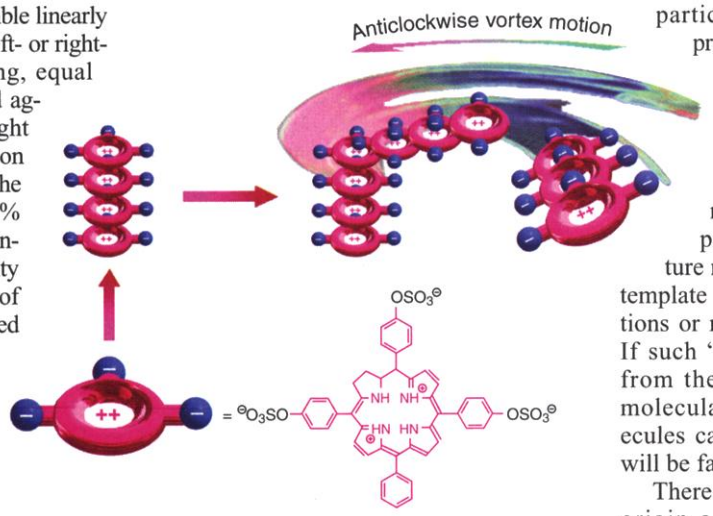
The individual disks can assemble linearly in a growing strand or can form left- or right-handed helices. Without stirring, equal amounts of left- and right-handed aggregates are formed, as one might expect. Depending on the direction of the vortex during aggregation, the porphyrin disks arrange with 85% probability in opposite helical orientations. In other words, the chirality of the supramolecular ensemble of disk-shaped molecules is controlled by the direction of stirring during the aggregation process. The left- or right-handed orientations of the stacked porphyrins can be readily detected by the strong difference in absorption between left- and right-circularly polarized light.



Chiral selection under the influence of vortex motion. In this hierarchical model, aggregation of disk-shaped porphyrins involves two stages. First, zwitterionic porphyrins spontaneously assemble into stacks as a result of electrostatic and hydrogen-bonding interactions. Next, small aggregates assemble into fiberlike structures. The helical orientation in the fiber (anticlockwise shown) in the second stage of the assembly process is controlled by the direction of the vortex motion.

In these experiments, the sensitivity to the asymmetric force at the bifurcation point of the aggregation process seems to be crucial. The random choice at this point to form left- or right-helical aggregates is biased by the vortex motion. Another important feature is the formation of rigid and stable assemblies. In a dynamic assembly, removal of the vortex would lead to equilibrium and loss of chiral selection.

The authors propose a hierarchical organization model (see the figure) to explain their results. In this model, the porphyrins assemble into small aggregates, which are progressively incorporated into growing fibers. Chiral selection takes place at the second stage of this process, where the vortex motion controls the trajectory of the aggregates to be incorporated into the growing helical fiber in a clockwise or counterclockwise manner. The small chiral bias is amplified in the aggregation process.

It is important to realize that the chiral selection thus occurs at the supramolecular level. Exactly how a particular handedness is imposed by the stirring direction remains unclear; nor do we know how general this phenomenon is or what its implications are for chiral selection at the molecular level. Nonetheless, this appears to be the first unequivocal demonstration of chiral selection induced by stirring. The present findings will likely stimulate further studies of the effect of vortex motion on other assembly processes, particularly of helices, which play a prominent role in many supramolecular structures, including peptides, oligomeric metal complexes, hydrogen-bonded assemblies, liquid crystals, and gels (*8*).

It will not be easy to control molecular chirality by this approach. The supramolecular structure may, however, act as a homochiral template for subsequent asymmetric reactions or may function as a chiral catalyst. If such "transfer of chiral information" from the vortex motion via the supramolecular aggregate to individual molecules can be realized, the consequences will be far-reaching.

There are many theories regarding the origin of biomolecular homochirality, from photochemistry to the electroweak force (*4*–*6*). It has been suggested that vortex motion during key aggregation processes at some stage of chemical evolution may have led to biomolecular homochirality. Ribó *et al.* provide some support for this theory. More experimental work is needed to establish whether we must consider simple stirring as a serious candidate for chiral selection in prebiotic stages of evolution. This promises to be an exciting endeavor.

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PERSPECTIVES: PLANT BIOLOGY

One for All?

Brian E. Ellis and Godfrey P. Miles

The genomics revolution provides almost daily confirmation of the relatedness of eukaryotes, especially when it comes to core activities such as cell division and signal transduction. Against this background of common heritage, it is the differences among eukaryotes that become particularly interesting. In this issue of *Science*, reports by Ullah (page 2066) and Wang (page 2070) highlight one of the striking differences between signaling pathways in plant and animal cells—the degree to which each kingdom relies on heterotrimeric GTP-binding proteins (G proteins) to transduce signals from plasma membrane receptors to the cell interior (*1*, *2*).

In animals, the heterotrimeric G-protein complex—made up of Gα, Gβ, and Gγ subunits—links an extensive array of heptahelical transmembrane receptors to downstream effector molecules. These effectors control a wide range of cellular activities, including cell division, pathogen defense, tolerance to stress, apoptosis, and the generation of action potentials in nerve cells (*3*). The heterotrimeric G-protein complex is inactive when guanosine 5′-diphosphate (GDP) is bound to the Gα subunit. After activation of a G protein–coupled receptor (GPCR) by its ligand, the G-protein trimer interacts with the activated receptor, GDP is exchanged for guanosine 5′-triphosphate (GTP) and the G-protein complex dissociates into GTP-Gα and Gβγ subunits. Both GTP-Gα and Gβγ serve as mobile second messengers that modulate the activities of target enzymes (such as protein kinases, phosphatases, and phospholipases) either within the plasma membrane or in the cytoplasm. The GTP bound to Gα is eventually removed through hydrolysis by the intrinsic GTPase activity of the Gα subunit, and the resulting GDP-Gα reassembles into an inactive GDP-Gα·Gβγ complex.

Mammalian genomes reflect the advantages of this signaling complex, encoding more than 20 Gα, 5 Gβ, and 12 Gγ isoforms and more than 1000 different GPCR recep-

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