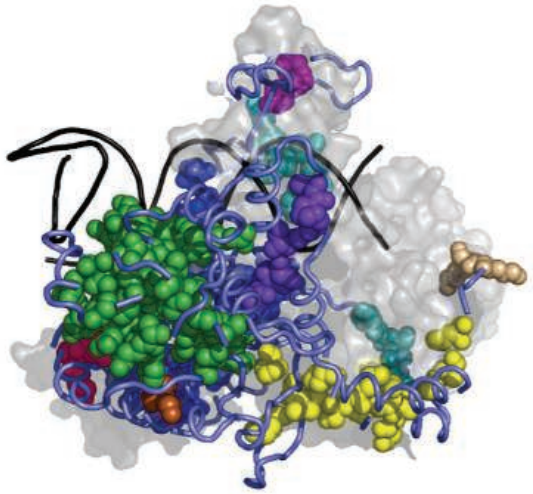
MOLECULAR BIOLOGY

Facing in Two Directions



The inward-facing domain (green) of Ku80; DNA, black strands.

The ends of DNA molecules can be extremely dangerous to a cell because of their potential to recombine with other DNA sequences, which would cause large-scale disruption of genome integrity. Double-stranded DNA ends are found naturally at the termini (called telomeres) of linear eukaryotic chromosomes and also at sites of spontaneous genomic damage. Exposed ends at both locations are recognized by the evolutionarily conserved Ku heterodimer, which is required for the nonhomologous end-joining (NHEJ) repair of broken DNA as well as for the silencing of genes at telomeres. How does Ku orchestrate such distinct functions? The Ku heterodimer consists of the structurally and evolutionarily related Ku70 and Ku80 proteins, which together form a ring that wraps around DNA ends. The N-terminal domains of the two subunits face in opposite directions when bound to DNA, with Ku70 oriented toward the DNA ends. Ribes-Zamora *et al.* have carried out a mutagenesis study of yeast Ku and show that an α helix in the Ku70 N-terminal domain is required for DNA repair, possibly as a surface to which NHEJ factors are recruited. The equivalent helix in Ku80 is required for telomeric silencing, which is consistent with its facing toward the bulk of the telomeric structure when Ku is bound at telomeres. Prokaryotes contain a single Ku gene that is involved in DNA repair, and most lack telomeres, having circular genomes. The advent of linear chromosomes and telomeres in eukaryotes probably favored the duplication of the Ku gene and the subsequent functional differentiation of the Ku70 and Ku80 subunits. — GR

Nat. Struct. Mol. Biol. 10.1038/nsmb1214 (2007).

CHEMISTRY

Lactide Loops…

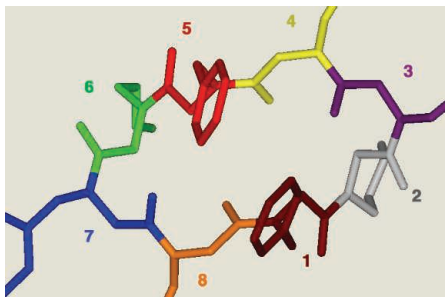
Selective routes to cyclic polymers must overcome the dual challenges of enthalpic strain and unfavorable entropy. Culkin *et al.* have found that an N-heterocyclic carbene substituted with two bulky mesityl groups can catalyze the polymerization of lactide to yield macrocycles with molecular weights on the order of 20 kD and polydispersities of ~1.2 to 1.3. The authors had previously shown the effectiveness of this catalyst for generating linear poly(lactide) in the presence of alcohol initiators; the cyclic products result when the initiators are omitted. Polymerization of optically pure lactide proceeds with retention of stereochemistry. The narrow polydispersities and observation of a product molecular weight increase with reaction time suggest that propagation outpaces the macrolactonization step that liberates the carbene catalyst. — JSY

Angew. Chem. Int. Ed. **46**, 10.1002/anie.200604740 (2007).

CHEMISTRY

…and Peptoid Polygons

The potential therapeutic usefulness of peptides is often limited by their degradation via proteolysis, and a number of peptide mimics have been developed that avoid degradation by using a different backbone linkage. Peptoids, which are composed of glycine monomers substituted at the nitrogen atom, can develop helical secondary structure if they bear bulky chiral side chains, but in solution they often exhibit some disordering and conformational heterogeneity.



Octapeptoid structure.

Shin *et al*. show that the use of the peptide coupling agent PyBOP led to remarkably efficient head-to-tail cyclization of peptoids with methoxyethyl, phenylmethyl, and azidopropyl side chains. Products ranging from cyclic pentamers up to cyclic 20-mers could be prepared with yields of ~90% or greater. These compounds have sufficient conformational ordering that several could be crystallized for structural analysis by x-ray diffraction. — PDS

J. Am. Chem. Soc. **129**, 10.1021/ja066960o (2007).

CELL BIOLOGY

Capturing Immature Components

The γ-secretase complex catalyzes proteolytic cleavage of a variety of membrane proteins, including the amyloid precursor protein that is implicated in Alzheimer's disease. The complex contains several components, including presenilin, anterior pharynx defective-1 (APH-1), and nicastrin. Spasic *et al.* have examined the intracellular assembly path of this complex and have found that a protein involved in recycling within the early secretory pathway, Rer1p, interacts with immature nicastrin either in the Golgi or in the endoplasmic reticulum (ER): the entry portal to the secretory pathway. It seems that Rer1p effectively binds to a site within the transmembrane domain of nicastrin that can also interact with APH-1 in the mature γ-secretase complex. Rer1p-binding competes with the assembly of APH-1 and nicastrin and also returns to the ER any immature nicastrin that has escaped into the Golgi. — SMH

J. Cell Biol. **176**, 629 (2007).

CLIMATE SCIENCE

Eye of the Beholder

One of the most contentious issues in the debate about the impact of global warming on hurricanes is the accuracy of hurricane records;

Continued on page 1469

Continued from page 1467

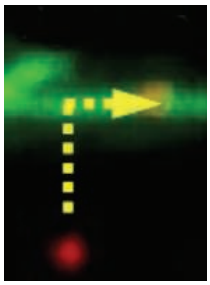
it is important for hurricane intensity measurements to be evaluated in a consistent manner, so that methodological differences do not introduce spurious trends. Kossin *et al.* take a step in that direction by constructing a homogeneous global record of hurricane intensity between 1983 and 2005, using the available satellite data archive of nearly 170,000 observations of more than 2000 tropical storms. After standardizing the spatial and temporal resolution of the images, they treat all the data (from the Atlantic, Pacific, and Indian Oceans) with a single algorithm for estimating hurricane intensity, based on the infrared brightness temperatures of the storms measured by satellites. Their analysis reveals a rise in storm intensity and the power dissipated by storms in the North Atlantic over the period of investigation, but no significant trends in the global averages. These findings would seem to contradict the assertion that hurricanes are becoming more intense as climate warms, because sea surface temperatures, the factor generally believed to have the greatest impact on hurricane strength, have risen in all ocean basins over the same period. — HJS

Geophys. Res. Lett. **34**, L04815 (2007).

CELL BIOLOGY

Turning Right or Left

During transport from the cell center to the periphery, organelles are carried long distances along microtubules by kinesin and then locally along actin tracks by myosin Va (myoVa). What do these motors do when confronted with enmeshed cytoskeletal elements, and how do they pass their cargoes onward?



MyoVa (red dot) turning right onto an actin filament (green).

Ali *et al.* have addressed these questions by watching the movement of single molecules of myoVa (labeled with quantum dots) as they encountered intersecting filaments: either actin or microtubules. At actin-actin intersections, myoVa either stepped over the crossing filament, stopped moving altogether, or turned left or right, with the direction determined by the polarity of the second filament. The ratio of stepping versus turning events correlated with the ratio of binding sites within reach of a flexible myoVa head that samples actin monomers within a target zone defined by its 50- to 95-nm stepping range. Despite a tendency to switch tracks, myoVa has a high probability of reaching the cell periphery because of the strong bias for actin filaments to be oriented with their barbed ends aimed at the plasma membrane. At actin-microtubule intersections, myoVa could not step over the obstructing element (microtubules are significantly larger than actin filaments); however, in a few cases, myoVa turned onto the microtubule and diffused randomly along it, mimicking the search it would undertake for a cargo that was being delivered to the periphery by kinesin. — VV

Proc. Natl. Acad. Sci. U.S.A. **104**, 10.1073/pnas.0611471104 (2007).

Eye of the Beholder

Science **315** (5818), 1467-1469.
DOI: 10.1126/science.315.5818.1467e