to reset the mammalian clock. There have been several suspects along the way. The most obvious pigments in the eye, the opsins in the rods and cones of the retina (which form visual images), are surprisingly unimportant for mediating light effects on circadian rhythms: Light easily resets the clocks of mice with no rods or cones and of people who are completely blind. Another pair of suspects has been the cryptochromes, flavin-based pigments that absorb blue light and are present in retinal ganglion and inner nuclear cells, but recent evidence has knocked cryptochromes almost entirely out of the line-up. The phenotype of mice missing both cryptochrome 1 and 2 suggests that cryptochromes are not required for entrainment of the circadian rhythm, and their interaction with other clock components does not require light, as would be expected if they were light receptors.

The new prime suspect is melanopsin, an opsin found only in the cells of the mammalian inner retina. Melanopsin is much more like invertebrate opsins than mammalian ones, including the substitution of an aromatic residue for a Schiff's base counterion, which in the usual mammalian opsins allows local regeneration of the chromophore. The melanopsin in retinal ganglion and amacrine cells far away from the chromophore-regenerating retinal pigment epithelium would require such local regeneration for function. To add to the argument, these melanopsin-containing cells have the same frequency and distribution as the retinal cells that project directly to the suprachiasmatic nucleus, the site of the clock. Finally, the peak of the circadian light response is at a wavelength expected from an opsin-based photopigment (like melanopsin), rather than a flavin-based photopigment. At this point, the evidence remains circumstantial and several other pigments in the retina must remain in town for questioning. Nonetheless, melanopsin is emerging as a likely culprit as a receptor for the light that keeps mammalian bodies in tune and in time. — KK

J. Neurosci. **20**, 600 (2000).

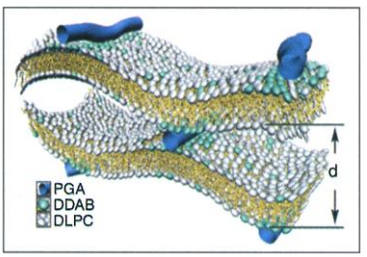
CREDIT: SUBRAMANIAN *ET AL., J. AM. CHEM. SOC.* **122**, 26 (2000).

CHEMISTRY

In a Pinch

Complexes of cationic lipids and DNA have been used for gene delivery. For certain concentration ranges, complexes of neutral and cationic lipids with DNA form lamellar structures in which intercalated DNA forms well-ordered two-dimensional arrays.

Analogous complexes have recently attracted interest for protein or drug delivery. Subramanian *et al.* have now examined the structure of complexes of mixtures of neutral and cationic lipids with a high-molecular-weight peptide (polyglutamic acid) using small-angle x-ray and neutron scattering. Near the isoelectric point of these complexes, dilution with neutral lipids increased the membrane spacing from 4 to 6 nanometers. In their model for these complexes, the interaction of the polypeptide and the lipid layers pinches off pockets of water locally. The authors suggest that these pinched regions could be used, for example, in drug delivery. — PDS



Pinching off a pocket.

J. Am. Chem. Soc. **122**, 26 (2000).

Science's stke

Restoring Retinoid Signals in Cancer Cells

Retinoids have multiple biological effects, including inhibition of proliferation of certain cancer cells. The retinoids often act through heterodimers of two nuclear receptors, the retinoic acid receptors (RARs) and the retinoid X receptors (RXRs). In normal cells, the expression of RARb is enhanced through transcriptional activation in response to retinoids, but many cancer cell lines lose their ability to response even though the RAR and RXR proteins are still expressed. Lin *et al.* now show that such retinoid-insensitive cells may be missing another nuclear receptor, the orphan receptor COUP-TF. In cancer cell lines lacking COUP-TF, expression of COUP-TF restored retinoid-induced expression of RARb as well as the apoptotic and growth inhibitory effects of retinoic acid in these cells. COUP-TF appears to enhance the interaction of RAR with the transcriptional coactivator CBP through DNA binding. This mechanism of action of COUP-TF is distinct from its effects on other genes, where it has its own transactivation activity through recruitment of a different coactivator. — LBR

Mol. Cell. Biol. **20**, 957 (2000).