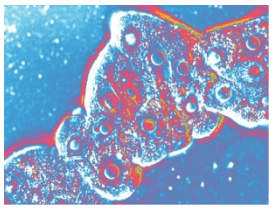
COVER STORY

The stimulation of myocyte β-adrenergic receptors (βARs) increases cardiac output in moments of stress. To produce high-fidelity signaling, cell-surface βARs are arranged into distinct signaling islands or signalosomes, in which their quantity and composition are known to define the basis of adrenergic stimulation. Despite their importance, however, these structures have never been visualized in myocytes. Using a technique called near-field scanning optical microscopy (NSOM), Pezacki and coworkers were able to image individual cell-surface βAR clusters of cardiac myocytes from rats, neonatal mice and embryonic mice. The authors found that between 15% and 20% of the receptors were co-localized into calveolae. Tagging of β_2ARs with fluorescently labeled antibodies enabled the authors to estimate the density of receptors in the signalosomes. Upon stimulation, no change in receptor density was observed, which suggests that the receptors are prearranged in these signaling complexes. The visualization of the βAR signalosomes demonstrates the power of NSOM as an imaging tool. [**Letters, p. 196; News & Views, p. 184**] *GW*

Halting transcription



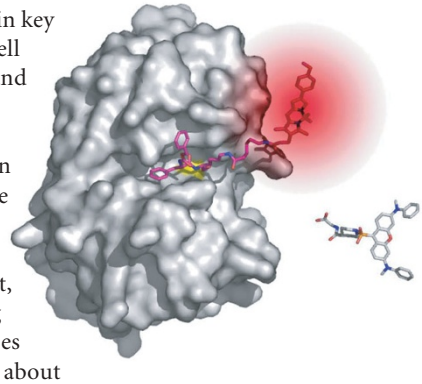
Gene silencing is a powerful tool for studying and controlling cellular processes. Although the disruption of gene expression by RNA interference or antisense techniques has been widely explored, the direct targeting of genes by the antigene approach has received less attention. Two papers by Corey and coworkers now report gene inhibition achieved by targeting DNA transcriptional start sites with complementary sequences of antigene protein nucleic acids (agPNAs) and antigene RNAs (agRNAs). Because all genes contain an initiation site for transcription, Corey and coworkers hypothesized that the binding of short oligonucleotides to transcriptional open complexes might offer a general method for gene silencing. The authors found that agPNA and agRNA sequences designed to bind the transcriptional start site of the human progesterone receptor (hPR) were both potent inhibitors of hPR mRNA production. To show the generality of their approach, the authors demonstrated that agRNA sequences designed to target the transcriptional start sites of three different genes led to potent gene silencing in cells. These studies show that the transcriptional start site of genes is a viable target for the inhibition of gene expression in cells and that inhibition of this site offers a complementary method to RNA interference. [**Articles, p. 210 and p. 216; News & Views, p. 185**] *GW*

In This Issue written by Greg Watt, Joanne Kotz and Terry L. Sheppard.

Oxidizing mitochondrial lipids

A major pathway for programmed cell death involves the release of apoptotic factors from the mitochondria, including the heme-containing protein cytochrome *c*. After release, cytochrome *c* and other proapoptotic factors function in the cytoplasm to activate caspases. Although many steps in this apoptotic pathway have been well characterized, relatively little is known about the events that directly lead to the release of factors from the mitochondria. Kagan and colleagues now provide evidence that cytochrome *c*, when in a complex with the mitochondrial lipid cardiolipin, can catalyze cardiolipin oxidation. Oxidized cardiolipin interacts more weakly with the inner mitochondrial membrane and is involved in mitochondrial membrane permeabilization. These results suggest that cytochrome *c* has a catalytic role within the mitochondria in initiating apoptosis. [**Articles, p. 223; News & Views, p. 188**] *JK*

Cathepsin lit up



Proteases are important in key cellular processes from cell death to inflammation, and have been implicated in many diseases including cancer. A protease is often generated as a propeptide that is proteolytically processed to yield the active enzyme. As a result, a genetically encoded tag or antibody detection does not provide information about whether a protease is in an active or inactive form. Activity-based probes (ABPs) are small molecules that react covalently with a residue in an enzyme active site and have been used to study protease activity. However, the use of fluorescent ABPs for *in vivo* imaging has been limited by background fluorescence. Bogyo and colleagues now report quenched ABPs for *in vivo* imaging. By synthesizing an ABP containing a donor and an acceptor fluorophore, the authors ensured that the unreacted probe has very low background fluorescence. Upon reaction of the probe with an active protease, the acceptor fluorophore is released and the probe becomes fluorescent. Using quenched ABPs specific for the cysteine protease cathepsin, the authors monitored protease activity in real time inside cells. [**Letters, p. 203; News & Views, p. 187**] *JK*

Biologists teach chemists

General chemistry is a rite of passage for first-year undergraduate students. These introductory courses provide a chemical foundation for science majors, and many nonscientists enroll in them as well. Despite major advances in chemistry as a field, the material and teaching methods in general chemistry have remained largely unchanged in the past several decades. A commentary by Godwin and Davis discusses how educational initiatives in biology have inspired curricular innovation for general chemistry courses. [**Commentary, p. 176**] *TLS*