Their strategy, pursued for several years, has been marked by clear vision with few compromises. The particular diamondlike structure that Noda *et al.* fabricate is sometimes called the stack-of-logs structure, or the layer-by-layer structure introduced by the Iowa State group (*7*). (Actually, all 3D photonic crystal structures can be built up layer by layer.) The stack-of-logs structure (see the figure) represents the cubic <100> face of a diamond crystal. Its main advantage is that each face has a rectilinear appearance, easily programmed into electron-beam–writing lithography equipment. When the layers are precisely stacked above one another, the 3D structure emerges as diamondlike, with a strong photonic band gap.

The stacking of successive layers can be accomplished by wafer fusion, where temperature and pressure allow two semiconductor crystal layers to merge. Here, Noda *et al.* have realized an excellent strategy. To make a full crystal requires many layers, each step necessitating exacting alignment, allowing errors to creep in. The authors noticed, however, that after stacking the first two layers, they could then work with both to stack four at a time, thus reducing the number of fabrication steps. Eight layers already make a respectable photonic crystal but require only three stacking and alignment steps (*2*).

This fabrication strategy has been fully vindicated by the excellent results presented in this issue. The internal waveguides demonstrated in the 3D crystal structure of Noda *et al.* may be the precursor of photonic integrated circuits. Soon we can expect to see tiny electromagnetic cavities, fully isolated from their surroundings in all three dimensions, that will exhibit unusual quantum effects.

Nevertheless, there are competing approaches. It has been noted that full 3D confinement, although meritorious, is not always essential. Excellent results have emerged recently in thin film semiconductor slabs perforated by a hexagonal array of holes, which form two-dimensional (2D) photonic crystals (*8*). These structures are much easier to make than 3D structures, while providing adequate index guiding in the third dimension. Recently, nanocavity lasers were demonstrated in such 2D photonic crystals (*9*). It appears that the race for technological supremacy will continue.

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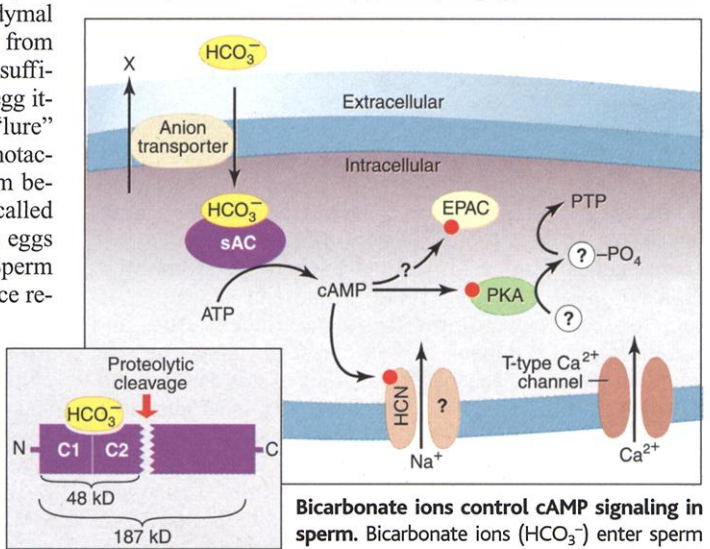
PERSPECTIVES: CELL BIOLOGY

A Universal Bicarbonate Sensor

U. Benjamin Kaupp and Ingo Weyand

Sperm cells are equipped with a limited repertoire of behaviors that exclusively subserve their purpose—to fertilize eggs (*1*). When produced in the testis, sperm are immotile; they acquire the ability to swim as they transit through the epididymal tract of mammals or after ejaculation from invertebrates. But motility alone is not sufficient to direct a sperm to an egg. The egg itself (or associated structures) must "lure" the sperm by releasing diffusible chemotactic factors (*2*). After mammalian sperm become motile, they mature (a process called capacitation) and are able to fertilize eggs within the female reproductive tract. Sperm and egg initially interact through surface receptors, then the proteolytic contents of the sperm's acrosomal vesicle are released. This proteolytic cocktail helps the sperm to penetrate the outer coat of the egg and to reach the egg's plasma membrane.

The three principal events in sperm mobilization—motility (and chemotaxis), capacitation, and the acrosome reaction—each depend on the intracellular cyclic nucleotides: adenosine 3′,5′-monophosphate (cAMP), or guanosine 3′,5′-monophosphate (cGMP), or both (*1*). It has been established that bicarbonate ions activate sperm capacitation and that this activation can be blocked by membrane-permeant cAMP analogs. This suggests that sperm capacitation is activated by a rise in intracellular cAMP induced by bicarbonate ions (*3*). Now, on page 625 of this issue, Chen *et al.* (*4*) provide compelling support for this possibility. They show that bicarbonate ions directly stimulate the soluble form of adenylyl cyclase (AC), the enzyme that synthesizes cAMP from adenosine triphosphate. Activation of this enzyme results in an increase in cAMP and induction of the signaling pathway that brings about the capacitation response.



Bicarbonate ions control cAMP signaling in sperm. Bicarbonate ions (HCO_3^-) enter sperm through an anion transporter in the plasma membrane and activate the soluble adenylyl cyclase (sAC), resulting in increased synthesis of the signaling molecule, cAMP. The precursor of sAC has a molecular weight of 187 kD. As sperm transit through the epididymal tract, sAC is proteolytically cleaved into several fragments including a 48-kD form that contains the two catalytic domains, C1 and C2 (inset). Potential targets of cAMP in sperm are protein kinase A (PKA), the hyperpolarization-activated, cyclic nucleotide-gated (HCN) channel and guanine-nucleotide-exchange factors (EPAC). HCN channel-mediated depolarization of sperm might lead to Ca^{2+} influx through T-type Ca^{2+} channels. cAMP also stimulates protein tyrosine phosphorylation (PTP).

The soluble form of AC (sAC) in sperm is thought to be different from the transmembrane form (tmAC) found in other cells. The activity of tmAC is controlled by heterotrimeric GTP-binding protein (G protein)–coupled receptors through stimulatory or inhibitory G proteins; in contrast, sAC does not require G proteins for activation. Moreover, forskolin, a powerful stimulator of tmAC, has no effect on sAC, whereas bicarbonate ions increase the production of cAMP in sperm (*5*–*7*). Recently, Chen and colleagues (*8*) showed that sperm sAC is structurally distinct from G protein–regulated tmACs and that, together with AC from cyanobacteria, it falls into a separate family. Notably, its two catalytic domains (C1 and C2) more closely resemble those of cyanobacterial AC than those of mammalian tmACs.

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Purified sperm sAC has a molecular weight of 48 kD (*6, 8*), whereas its cDNA predicts a protein of 187 kD (*8*). A truncated form of sAC similar to the 48-kD protein exhibits a 20-fold higher specific activity than does the 187-kD form (*8*). This finding argues that proteolytic processing of a larger version of the enzyme is required for full activity. In the testis, the 187-kD protein is the predominant form, whereas sperm contain the 48-kD protein (and other proteolytic fragments). This suggests that sAC is converted from an inactive to an active form as sperm transit through the epididymis. Interestingly, the extracellular bicarbonate ion concentration decreases from 25 to 5 mM along the length of the epididymis (*9*) and rises again when sperm are mixed with seminal fluid during ejaculation. Thus, the proteolytic activation of sAC is likely to be regulated by bicarbonate ions in the extracellular environment.

In the new work, Chen *et al.* demonstrate that the activity of purified sAC, both from rat testis and from a mammalian cell line expressing the sAC gene, is stimulated by physiological concentrations of bicarbonate ions. They further show that AC from cyanobacteria is also sensitive to bicarbonate ions. Thus, sAC appears to be a universal bicarbonate sensor conserved across phyla millions of evolutionary years apart. This finding is likely to have implications beyond the world of sperm and bacteria because sAC has been detected in mammalian kidney and choroid plexus.

What are the molecular targets of cAMP in sperm (see the figure)? Protein kinase A (PKA), the classic cAMP target, catalyzes the phosphorylation of several flagellar proteins, thereby regulating sperm motility (*10*). In mammalian sperm, the cAMP-PKA signaling pathway also induces phosphorylation of several proteins required for the capacitation response (*3*). A second possible target of sperm cAMP is a family of ion pacemaker channels known to control the rhythmic electrical activity of brain neurons and cardiac cells. Unlike other voltage-dependent channels, pacemaker channels open by hyperpolarization rather than by depolarization and their activity is enhanced by cyclic nucleotides in the absence of phosphorylation—hence, they are also called HCN (hyperpolarization-activated, cyclic nucleotide–gated) channels (*11*).

One HCN channel that is exquisitely sensitive to cAMP has been identified in the flagellum of sea urchin sperm (*11*); mRNA transcripts of the mammalian isoform, HCN4, have been found in human testis (*12, 13*). These pacemaker channels may generate the rhythmic activity that controls the beating motion of the sperm flagellum. In fact, sperm cells and rhythmically active neurons contain an astoundingly similar collection of channels including low-threshold T-type Ca^{2+} channels and HCN channels (see the figure) (*14*). Analogous to HCN channels in neurons, sperm HCN channels may open more often in response to increased cAMP, thereby resulting in depolarization of the sperm plasma membrane. This depolarization in turn may result in opening of sperm T-type Ca^{2+} channels and an increase in intracellular Ca^{2+}, which initiates signaling pathways that regulate motility. A third target of cAMP could be a family of guanine nucleotide exchange factors (*15, 16*) that activate Rap1, a member of the small GTP-binding protein superfamily. It will be interesting to discover whether sperm contain cAMP-activated guanine nucleotide exchange factors.

Now that the major players in sperm mobilization—sAC, PKA, and HCN—are unmasked, the next sequence of events regulated by cAMP signaling should soon be revealed.

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PERSPECTIVES: NANOTECHNOLOGY

Beyond Gedanken Experiments

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Interest in creating functional devices at nanometer scales is fueled by the desire to shrink the size of electronic integrated circuits and to create mechanical systems at nanoscale. In the minds of most futuristic thinkers, submicrometer-scale machines will move atoms and molecules and create new artificial structures, performing work in a nanoworld. At this scale, however, physical manipulation poses unique challenges. Machining, positioning, and assembling parts by hand are easy at macroscopic scales, but these abilities are far from routine at the molecular scale.

On page 602, Cumings and Zettl (*1*) report an important step toward "machining" building blocks for molecular devices in a controlled manner, by constructing bearings and mechanical switches out of multiwalled carbon nanotubes (MWNTs) with diameters of a few tens of nanometers. Using a manipulator inside a high-resolution electron microscope, they are able to peel off a few outer layers of an MWNT fixed at one end (*2*). By spot-welding a tip to the inner shell(s) and moving it back and forth, they study the mechanical properties of this nanobearing. They find that the system is an ideal low-friction and low-wear bearing. Because of the restoring force of the van der Waals interaction acting on the extruded nanotube, such an assembly can also be used as a switch with a very short reaction time.

The raw materials for making the bearings, MWNTs, have been known since 1991 (*3*). Studies aimed at applications started 4 to 5 years ago, when mass production became possible (*4*) and samples with sufficient purity could be made (*5*). In high-resolution transmission electron microscopy, the carbon nanotubes appear as long fibers consisting of several graphene sheets rolled up and embedded in each other (*3*). The tubes are closed at the end, and each tubule appears to close on itself. The entire structure thus resembles a Russian doll. Their diameters range from a few to many tens of nanometers. Made of hexagonal lattices of carbon atoms, nanotubes are extremely strong, light structures (*6*).

An MWNT bearing is exactly the structure foreseen by Drexler as the most efficient bearing for nanomechanical needs (*7*). His suggestion was to take two flat sheets of graphite, bend them into two cylinders of slightly differing diameter, and insert the smaller one into the larger one. But this idea remained just a gedanken experiment until Cumings and Zettl carved out the bearing from an MWNT with a shaping electrode. The outer layer or layers form the sleeve and the inner ones the shaft. Because the surfaces are atomically perfect and the spacing between the shaft and the sleeve is just the van der Waals distance in graphite, there is no room for grit to enter between them, and consequently the problem of wear can be avoided. The bearing may still get stuck at certain preferred positions where the atomic potentials of the sleeve and the shaft are commensurate, resulting in mini-

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