Local Peeling of Graphene
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dem repeats enriched in guanine near active genes (*10*–*13*).

Features intrinsic to repetitive elements—such as DNA bending and the propensity to adopt so-called G-quadruplex structures—can adversely affect nucleosome occupancy, and the ATRX-DAXX complex might re-establish H3.3-containing nucleosomes at these elements in a replication-independent manner. Defective nucleosome assembly pathways likely lead to increased DNA damage and genome instability. At telomeres, the ATRX-DAXX complex is required to suppress aberrant DNA repair that can result in telomere fusion (*14*). Furthermore, defects in chromosome congression, cohesion, and centromere function caused by the loss of ATRX may promote missegregation of chromosomes and consequential aneuploidy (*15*). A recent study found that 98% of PanNETs exhibit substantial chromosomal alterations (*16*).

Originally associated with familial endocrine tumors, the *MEN1* gene is the most frequent genetic lesion in both heritable and sporadic neuroendocrine tumors, including 43% of the PanNETs in the study by Jiao *et al*. *MEN1* encodes the transcription factor Menin, which recruits the H3K4me3 histone methyltransferase mixed-lineage leukemia (MLL) complex. *MLL2* and *MLL3*, which encode methyltransferase components of MLL complexes, are frequently mutated in childhood medulloblastomas (*5*). Given the prevalence of *ATRX*, *DAXX*, and *MEN1* mutations in PanNETs, it is conceivable that inactivation of either or both complexes is required for tumorigenesis. In addition to their pleiotropic functions during development, these epigenetic regulators therefore appear to function as potent tumor suppressors in pancreatic islet cells.

Although the molecular mechanisms of their tumor suppressor activities have yet to be defined, Menin and the ATRX-DAXX complex are part of a growing list of chromatin-associated tumor suppressors. Several recent cancer exome studies have identified mutations in pathways involved in either the methylation or demethylation of H3K27, a histone modification associated with genomic silencing (*3*, *6*, *17*). Mutations in chromatin-remodeling complexes related to ATRX-DAXX were identified in a variety of cancers. Nearly half of all clear cell ovarian tumors contain mutations in the *ARID1A* gene, encoding the BAF250 subunit of the human SWI-SNFa chromatin-remodeling complex (*4*, *8*). The gene encoding another human SWI-SNF subunit, BAF180, is mutated in 41% of clear cell renal cancers (*7*). Mutations in other human SWI-SNF subunits have previously been identified in a variety of specific cancers.

Much work remains to define the role of these and other epigenetic regulators in different tumor types. A major unresolved question is how mutations in different subunits of multiprotein complexes lead to disparate types of cancers. The occurrence of these mutations in defined subsets of tumors suggests that epigenetic factors may act in a tissue-specific manner to suppress oncogenic pathways upstream of master regulators common to a broader range of tumors. Identification of this diverse set of "backseat drivers" through technological advances in genome-wide analysis will provide spectacular opportunities for advanced diagnostics and treatments for a wide variety of human cancers.

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MATERIALS SCIENCE

Local Peeling of Graphene

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A technique is demonstrated that allows single layers of graphene to be removed one layer at a time.

"Perfection is finally attained not when there is no longer anything to add, but when there is no longer anything to take away," noted Antoine de Saint-Exupéry (*1*). He could have been writing about graphene sheets, just an atomic layer or two thick, which have properties much more interesting than those of the bulk. From the time when graphite would be rubbed on an insulating surface with the hope that one of the exfoliated flakes would be a single layer, graphene manufacture has progressed rapidly and is now routinely grown on or transferred onto many substrates, even up to sizes large enough for TV displays (*2*). Despite such advances, reproducible spatial control over the number of graphene layers has not been achieved. On page 1168 of this issue, Dimiev *et al*. describe a technique that overcomes this limitation and allows peeling of graphene layer by layer at predetermined locations of the surface (*3*).

Achieving such control is important because electrons in a double layer of graphene (a bilayer) behave quite differently from those in a single layer (a monolayer). A monolayer of graphene is a semimetal with no band gap and conical-shaped conduction and valence bands close to the Fermi level. Although the conical dispersion leads to exceptional electronic transport properties, the lack of a band gap limits monolayer graphene's use in conventional electronics—without a band gap conduction through the device cannot be switched on and off. One route to a band gap is to cut graphene into nanoribbons so that the electrons are laterally confined. Although nanoribbons have been formed by several groups, the routine fabrication of ribbons with widths of 2 to 50 nanometers is challenging, as rough edges scatter electrons, thereby masking the desired electronic properties (*4*). A different route to a band gap is using bilayer graphene that has the same stacking (Bernal) as natural graphite. In this particular stacking configuration, the additional layer results in a more typical parabolic dispersion but, more importantly, produces a controllable band gap in the presence of an electric field normal to the plane (*5*). Devices that capitalize on both the conical dispersion of monolayer graphene and the controllable band gap of bilayer graphene should be especially powerful.

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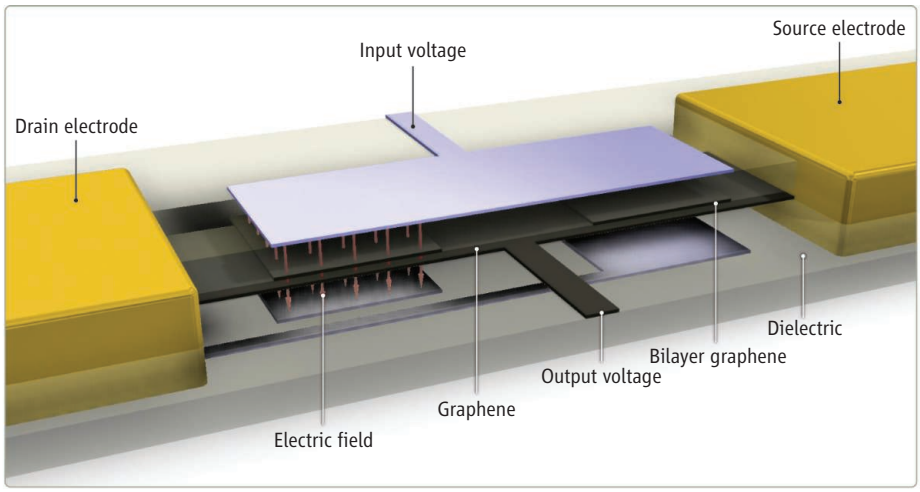

A peeling potential. An idealized graphene device that would take advantage of local layer-by-layer peeling (*3*). The central black layer contains regions of monolayer and bilayer graphene and is insulated with a dielectric from the top and bottom gate electrodes. Application of an input voltage to the top gate that matches that of the drain (or source) electrode would generate an electric field in the left (or right) bilayer graphene region. The electric field suppresses conduction, leading to an output voltage matching that of the source (or drain) electrode, effectively inverting the input voltage.

The technique of Dimiev *et al*. provides reproducible control over the number of graphene layers spatially on a surface. They first sputter thin films of zinc metal onto selected areas of few layer graphene. Exposing the zinc-coated sample to a mild aqueous solution of HCl removes only the areas in contact with the zinc, leaving both the uncoated and the underlying layers intact. Additional experiments suggest that the process works when the metal (i) damages the graphene during deposition, (ii) has a large oxidizing potential, and (iii) reacts with the etching solution to form hydrogen gas. The process is surprisingly robust, capable of peeling layers from several different varieties of graphene, including graphene oxide. Notably, they demonstrate that the process may be repeated to generate multiple patterned layers. Thicker films of graphene may be selectively thinned and patterned to generate the final device.

There is great potential for combining different thicknesses of graphene in a device structure such as a complementary metal-oxide semiconductor inverter, a cornerstone of digital electronics (see the figure). Such a device could be fabricated by depositing a Bernal-stacked bilayer of graphene onto existing electrodes and then peeling some areas away to form monolayers. The bilayer graphene regions in the center are transistors that ideally conduct only in the absence of a vertical electric field. Vertical electric fields in the bilayer regions are controlled by gate electrodes in the top and bottom layers of the device that are electrically insulated from the central layer. Monolayer graphene, which remains an excellent conductor in the presence of these fields, is an ideal lead material to the source and drain electrodes. Note that this device could be truly "all carbon" by making both the top and bottom gates from graphene. Moreover, insulating forms of graphene generated through fluorination (*6*) could serve as thin and effective gate dielectrics. Clearly, several practical challenges (for example, small band gap and cleanliness) remain; however, this device does illustrate one of many new structures more readily achieved with this new fabrication technique.

The exact mechanism for graphene peeling remains unclear, so other metals or materials might also be effective. The details of graphene's reaction with energetic metal ions would be particularly interesting because in the current process only a few of the deposited metal atoms have sufficient energy to modify the graphene. Moreover, the lateral resolution of the technique is ripe for exploration, given the desire for ever smaller electronic devices. Ultimately, the ability to peel just a single layer of graphene from a desired area with such a simple and robust technique is exceedingly useful. Local graphene peeling should become a routine tool for researchers to explore new devices.

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MICROBIOLOGY

Establishing the Secretion Hierarchy

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A large complex of type III protein secretion system components helps bacteria to invade their hosts.

Type III protein secretion systems (T3SSs) are specialized complexes of molecules in Gram-negative bacteria that mediate the introduction of virulence proteins directly into eukaryotic host cells. These supramolecular structures span the bacterial membranes, cross the extracellular space, and penetrate host cell membranes. The proper function of these systems depends on sequential secretion of the needle components, the proteins that enable translocation across the host cell membrane (translocases), and the effector proteins that carry out virulence functions (*1*). How this hierarchical process is regulated, however, has been unclear. On page 1188 of this issue, Lara-Tejero *et al*. (*2*) demonstrate that a large complex of T3SS proteins in *Salmonella enterica* serovar Typhimurium serves to sort components of the system for secretion in the appropriate sequence. Also, on page 1192, Schraidt and Marlovits (*3*) define the precise symmetry and stoichiometry of proteins that constitute the base of the needle complex.

T3SSs are present in many bacterial pathogens, including *Salmonella* spp., *Shi-*

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