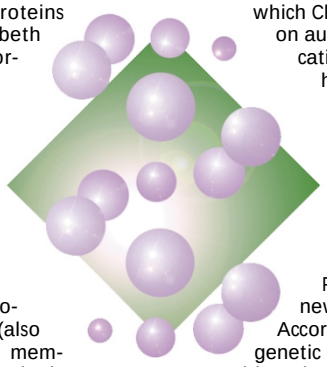
TOUCHING**base**

Patched clamp

Since its introduction in 1989, the yeast two-hybrid system has identified countless protein–protein interactions, thereby assigning potential functions to newly identified proteins whose sequences protect their secrets. Elizabeth Barnes and colleagues (of the University of California, San Diego) have identified an intriguing interaction between two well-studied proteins that has to rank as one of the more interesting associations uncovered by the two-hybrid approach (*EMBO J.* **20**, 2214–2223; 2001). In search of proteins that might regulate the nuclear-cytoplasmic traffic of cyclin B1—the regulatory subunit of M-phase promoting factor—Barnes and colleagues used a mutated version designed to mimic phosphorylated cyclin B1 as bait in a two-hybrid assay. Their experiment identified *PTCH* (also known as Patched 1 or Ptc1), a 12-pass integral membrane protein that serves as a receptor for sonic hedgehog (Shh). *PTCH* is also frequently mutated in nevoid basal cell carcinoma syndrome, which predisposes to basal cell carcinoma, the most common human cancer. Following confirmation of the interaction in a variety of assays, the authors showed that Ptch retains cyclin B1 at the plasma membrane and that Shh disrupts this interaction, allowing M-phase promoting factor to enter the nucleus and to promote cell cycle progression. By linking a developmentally important signaling pathway (Shh/Ptch) directly to the cell-cycle machinery, this work provides a possible molecular explanation for the previously identified tumor suppressor activity of Ptch, and yet another example of the fruitful interplay between developmental genetics and biochemistry in studies of the cell cycle and cancer.



"I think there must be a 'space war' gene—if natural selection puts you at Harvard you need to compulsively try to acquire other investigators' space. There is some gender specificity to this trait as well!"

—Denise Faustman

Fine sugar sorting

Cell surface glycosylation is abnormal in many congenital disorders and altered during malignant transformation, metastasis and inflammation. Investigating the underlying genetic or metabolic changes has been difficult because of the complexity of oligosaccharide biosynthesis, and current methods of measuring the carbohydrate content of glycoproteins and glycolipids, including lectin- and antibody-based detection methods, lack sensitivity. Focusing on sialic acid metabolism, Carolyn Bertozzi and colleagues (of University of California, Berkeley) have now developed a technique to measure the levels of specific glycoconjugates in cultured human cells that could be applied to high-throughput screening of mutagenized or drug-treated cells (*Nature Biotechnol.* **19**, 553–558; 2001). By treating Jurkat human T cells with an unnatural analog of *N*-acetylmannosamine, *N*-levulinoylmannosamine, coupled to biotin, they tagged sialic acid moieties displayed on surface glycoconjugates. Using fluorescein isothiocyanate-avidin and flow cytometry, they selected cells based on their levels of cell surface sialo-conjugates. And, by mutagenizing the Jurkat cells with hygromycin, they obtained mutants with phenotypes reminiscent of cells in those with congenital sialuria or of metastatic tumor cells. In the mutant cells, they found genetic aberrations consistent with sialuria and cancer: the epimerase gene is mutated and the neural cell adhesion molecule, deregulated (respectively). Whether the method will will lead to the identification of new genes in the sialic acid pathway has yet to be seen. Its cell-based and high-throughput nature, however, may help to identify drugs to treat diseases involving aberrant glycosylation.

The NPR gene

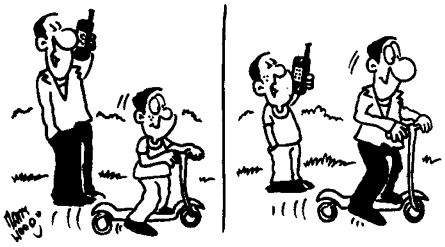
Is there a genetic effect on one's relationship with their automobile? Judging by *Car Talk*, National Public Radio's program—on which Click and Clack, the Tappet Brothers, dole out advice on automobiles—it would seem that there is. Their invocation of genetic determinism in choice of autos is hardly an isolated comment. Visitors to their web site frequently insinuate that their relationship with their cars, ranging from choice of model to brand loyalty, is governed, in part, by heredity. A Toyota Pickup driver with an enhancer polymorphism in the *INDY500* promoter: "[It] doesn't accelerate well and I really wish it did—I've got those race car genes, I guess." As to the pedigree analysis of the family Passat, when it came time for one driver to choose a new car, "my father's genes take over: hence, the '94 Accord." And drivers are going so far as to attribute genetic factors to the cars itself. One Buick Century owner, although satisfied with the car overall, quibbled that "the brakes squeak and have a click no matter who works on them—it must be in the genes".

Also hosted by National Public Radio is *Wait Wait... Don't Tell Me!*, a weekly news quiz program on National Public Radio, listeners are tested for their knowledge of current events by completing the "The Limerick Challenge". Recent news stories inspire the show's writers to write catchy poems, of which the contestant must supply the missing, ultimate word. To wit:

> Finland: Think of trees and soft breezes,
> Not seizures or wheezes and sneezes.
> Genetic disorders
> Exist past our borders.
> We're finished with Finnish _____.

The answer? Diseases. Researchers who first describe diseases often name them after the region in which they are initially recognized. For example, Salla disease, Pogosta disease and Kumlinge disease are named after regions in Finland. Doctors meeting at the World Medical Association conference in Paris last month, however, received an earful from some Finns who weary of having their country associated with disease.

How Things Change



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