Embryo uses chemistry to tell genes apart

When male and female germ cells unite to create a new life, their genetic contributions come with tags labeling them as paternal or maternal. "Reading" these tags, the developing embryo sometimes selects the mother's gene for expression, while the father's version of the same gene stays idle. In other cases, the embryo draws on the paternal gene, leaving the maternal one unused. Activating both parental genes – or neither – can cause fetal death or a serious disorder.

Now, researchers at the Whitehead Institute for Biomedical Research in Cambridge, Mass., report that this discrimination, called genetic imprinting (SN: 5/20/89, p.312), relies on a chemical mechanism. Methylation, the addition of molecules called methyl groups to the DNA molecule, is crucial for enabling the embryo to tell the parents' genes apart. They report their findings in the Nov. 25 NATURE.

Geneticist En Li, now at Massachusetts General Hospital-East in Charlestown, says he and his co-workers showed for the first time that an embryo needs DNA methylation to selectively activate imprinted genes. Researchers had suspected that since methylation is an inherited DNA modification, it might help genes "remember" their origin. Yet no one had ever directly linked the two.

"This study goes a long way towards proving [that link]," comments M. Azim Surani, a geneticist at the Wellcome/CRC Institute of Cancer and Developmental Biology in Cambridge, England. "It provides very strong correlative evidence, although we still need more experiments to nail it down completely."

The new evidence comes from knockout mice, animals altered to disrupt the gene for the DNA methylation enzyme. "We created two mutations," explains Li. "The less severe one reduces the degree of methylation by 60 to 70 percent; the more severe one prevents methylation almost entirely. This way, we can study genetic effects and also quantify them."

Analyzing three genes, the Whitehead group found that in mutant embryos the parental imprints were erased. Moreover, mutant embryos didn't follow the normal pattern of activating only one parent's copy of a gene. It appeared as if they could not distinguish which gene came from which parent, Surani says.

Take, for example, H 19, a gene of still mysterious function. Normally, only the maternal copy gets expressed, while the parental one is repressed. In the mutant embryos, however, the lack of DNA methylation lifted that repression, causing both genes to become active.

That finding fit nicely with an assumption about DNA imprinting: that it represents a way to inhibit a gene. It turned out not to be that easy, though. The other two genes, one encoding a protein called insulin-like growth factor 2 (Igf-2) and one encoding the Igf-2 receptor, showed just the opposite behavior.

Rather than activate the normally silent gene, the mutation silenced the normally active gene, thus thwarting the production of the corresponding proteins in the embryo, Li says. This finding indicates that methylation activates some imprinted genes but keeps a lid on others, Li explains.

Adding another twist is the finding that DNA methylation seems to act on some genes directly but uses genetic go-betweens, called gene silencers, to act on others. Depending on their methylation status, these silencers could determine the fate of imprinted genes. However, this is speculation, Li admits. "Nobody has evidence yet to pin down a silencer and prove what it's doing."

Not all genes are equally sensitive to the loss of DNA methylation, he notes. The imprint of the Igf-2 receptor gene vanished only in embryos carrying the more severe mutation, perhaps because this gene enjoys preferential treatment, Li suggests. The less severely mutated embryos might rally their remaining methylation capacity to secure adequate methylation of the Igf-2 receptor gene, while somehow deeming other genes less important, he speculates. *– G. Strobel*

New nanotubes self-assemble on command

Microscopic tubes just a few nanometers wide have recently jumped to the forefront of materials research.

These so-called nanotubes now come in two main classes: concentric ring carbon nanotubes, which look like little straws, and zeolite nanotubes, porous structures that serve as molecular sieves with industrial applications.

Now, chemists report fabricating an entirely new class of nanotube built out of peptides, or protein fragments, with potential biological applications.

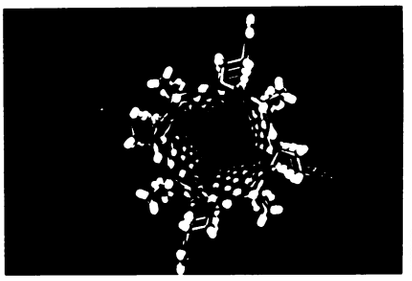
M. Reza Ghadiri, a chemist at the Scripps Research Institute in La Jolla, Calif., and his colleagues describe the design, synthesis, and characterization of this new class of organic nanotube in the Nov. 25 NATURE.

"For the first time, tubular structures on the molecular scale can be used in biological settings," Ghadiri says. "These nanotubes may be able to form molecular channels, self-assembling inside cell membranes and acting like junctions for transferring molecules into and out of, or between, cells."

"From another point of view, these nanotubes may also be useful for [delivering] cell-specific cytotoxins" – for example, to destroy cancer cells or even viruses, he adds. "Since different kinds of cells have unique membrane properties, we think it would be interesting to look at cell-specific targets."

Given that these nanotubes are made entirely of molecules commonly found in biological systems, their ability to self-assemble is both unusual and intriguing, Ghadiri says. When tripped off chemically – using a method called "proton triggering" – a loose conglomeration of disk-shaped peptide rings will suddenly stack themselves together, forming regular tubes hundreds of nanometers long and only 7 to 8 angstroms in diameter.

Moreover, the dimensions of these hollow, open-ended rods lie completely within the chemist's control – a feature that makes them particularly appealing for certain kinds of applications.



Ghadiri

A cyclic polypeptide organic nanotube.

"They're like little test tubes in which we can perform reactions or confine the growth of a material placed inside it, sort of like a cast or mold," says Ghadiri. "We can rigorously control the tubes' sizes and shapes, their internal dimensions, and fine-tune their surface properties. This control gives us many interesting options."

For biological systems, the researchers see membrane channels as a strong possibility. "So are novel transport devices and drug delivery systems," Ghadiri says. In the area of materials research, "We'd like to try to build semiconducting or copper nanowires with interesting optical and electrical properties inside these confined structures," he adds.

New types of molecular devices and catalysts could also emerge from these biologically based nanotubes, according to Juan R. Granja, a Scripps chemist and report coauthor. The key to finding such new uses will come from tinkering with the amino acid sequences and adjusting tube dimensions to get the best fit for particular molecules to be placed inside.

Chemists may even attempt to grow crystals within these new nanometer-size molds – given that the tubes' inner dimensions, which would serve as the template, can be controlled to within a few angstroms. "This has been very difficult to do so far because of a lack of uniformly shaped tube devices," says Ghadiri. *– R. Lipkin*