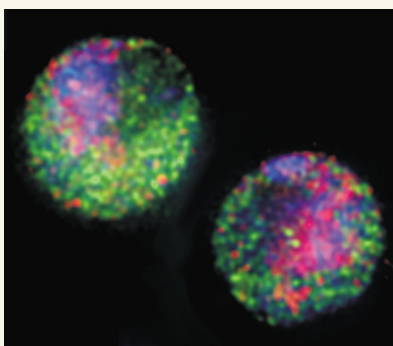


Chromatin maps by microarray

Chromatin proteins are involved in DNA transcription, replication, and repair, and a study of the binding sites of chromatin can provide insight into these roles. Methods used to determine chromatin-binding sites were cumbersome and error prone until Bas van Steensel and Steven Henikoff created a new labeling technique (*Nat. Biotechnol.* 18, 424–428, 2000). The researchers linked a bacterial enzyme called DNA adenine methyltransferase (DAM) to the chromatin proteins. When DAM-tagged chromatin binds to DNA, it methylates DNA in the local vicinity, leaving a chemical “footprint”.

In the March issue of *Nature Genetics* (27, 304–308, 2001), van Steensel and colleagues have combined DAM labeling with the power of DNA microarray technology, mapping the location of all binding sites for three chromatin proteins throughout the fruit fly genome. Van Steensel says that the next step will be to build a comprehensive database of the target loci of all chromatin proteins. “We are also adapting chromatin profiling in mammalian cells ... to study the molecular basis of transcriptional programs during cellular differentiation and in diseases such as cancer.” Chromatin maps could provide a more detailed and reproducible profiling technique than current methods using messenger RNA.

LF



Muscle-directed gene therapy

Targeting gene expression to specific tissues could overcome some of the obstacles at making gene therapy effective. Researchers at the University of Pennsylvania School of Medicine (Philadelphia) now suggest that even non-immunogenic vectors such as adeno-associated virus (AAV) could trigger an immune reaction unless the expressed protein is under the control of a tissue-specific promoter (*Hum. Gene Ther.* 12, 205–215, 2001). Lee Sweeney and colleagues used a mouse model for muscular dystrophy to test the efficacy of two different AAV vectors containing the missing sarcoglycan (gsg) protein. Two promoters were used to control protein expression—a nonspecific cytomegalovirus (CMV) promoter and a muscle-specific creatine kinase (MCK) promoter. Animals injected with the CMV-based AAV vector generated antibodies against the muscle protein, whereas the MCK-based AAV vector elicited no such immune response. Though preliminary, the results indicate that tissue-specific promoters could circumvent dangerous immune reactions in patients undergoing trials of gene therapy for muscular dystrophy.

JB

Deadly gut bug sequenced

The genome sequence of the O157:H7 strain of *Escherichia coli*—the cause of a serious gastric illness called hemorrhagic colitis—has provided some clues as to the source of this pathogen’s deadliness. Researchers led by Nicole Perna at the University of Wisconsin in Madison used the whole-genome “shotgun” approach to sequence the entire genome of the O157 strain, and compared this with sequence of a relatively harmless laboratory strain (*Nature* 409, 529–533, 2001). Surprisingly, O157 possessed 1,387 genes not present in the nonpathogenic *E. coli*. The authors suggest that these additional genes could have been transferred to O157 from other pathogenic bacteria by bacteriophages. Indeed, some of the extra genes could code for toxins or virulence factors, explaining the pathogenicity of the O157 strain. However, Perna says that the new genes could also be used as “targets for surveillance,” or to develop vaccines to clear O157 from domestic animals. Around 75,000 cases of O157 infection in humans occur each year in the United States, and there is currently no means of detection or treatment.

CM

Antibiotic resistance sized up

Directed evolution, in which natural evolution is imitated by various DNA modification techniques, can be used to model the emergence of antibiotic resistance in bacteria. Researchers at Scripps Research Institute (La Jolla, CA) and biotechnology company Maxygen (Redwood City, CA) have now shown that a combination of directed evolution and structural analysis accurately follows the evolution of β -lactam resistance in bacteria (*Nat. Struct. Biol.* 8, 239–242, 2001). In all instances, directed evolution of β -lactamase resulted in three specific mutations (E104K, M182T, and G238S), which were seen in the so-called TEM-52 clinical isolate of *Escherichia coli*. TEM-52 is more than 500-fold more resistant to the antibiotic cefotaxime than wild-type *E. coli*. Structural analysis revealed that two of the TEM-52 mutations widened access to the active site of β -lactamase, increasing its affinity for cefotaxime. However, the third mutation acted at a distance from the active site, stabilizing the previous structural alterations and further enhancing antibiotic resistance. Scripps’ Raymond Stevens, lead author on the paper, says that the team will “look at future mutations of lactamases and other enzymes that evolve based on their response to drug treatment.” In the meantime, the “stabilizer” region of the mutant β -lactamase could be used as a target for the development of new antibiotics.

LF

Resistin diabetes

The majority of individuals who have type 2 (insulin-resistant) diabetes are also obese, but to date the cellular mechanism by which fat cells become insulin resistant has been unknown. Now, researchers at the University of Pennsylvania suggest that a hormone—dubbed resistin—may be the missing link (*Nature* 409, 307–312, 2001). The researchers screened fat cells (adipocytes) for unique messenger RNAs, the expression of which was suppressed by thiazolidinediones (TZDs). (TZDs comprise a class of antidiabetic drugs that work by partially restoring insulin sensitivity of cells.) Using this novel screen, the researchers identified a unique gene product, resistin, which made adipocytes resistant to insulin. Resistin levels are elevated in obese mice, and anti-resistin antibodies and TZDs lowered their elevated glucose levels. Mitchell Lazar, senior author on the paper, says that the team is now “trying to identify the receptor [for resistin] using a candidate-gene approach, and we are also actively searching for the cellular targets of resistin.” Resistin offers an important new target for the treatment of type 2 diabetes patients.

AD

Research News In Brief written by Jackie Barlow, Alan Dove, Liz Fletcher, and Chris Morrison.