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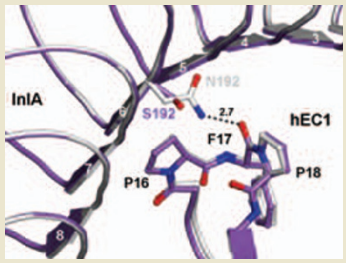
'Murinizing' a pathogen



The narrow host range of the food-borne pathogen *Listeria monocytogenes* prevents use of mouse models to study its pathogenesis. Now, Wollert and colleagues engineer an *L. monocytogenes* strain that can infect mice—a process they term 'murinization'. They accomplish this by making two amino acid substitutions within the recognition interface of listerial InlA, the invasion protein that binds human E-cadherin. Affinity of the altered protein for the human receptor is increased 6,700-fold and recognition of murine E-cadherin is such that the engineered bacterium can establish an infection comparable to that seen in humans. Whereas others have created 'humanized' mice by modifying the receptors to interact with human pathogens, such changes may have other consequences for the host. This is the first time that a novel strain with an extended host range has been created by rational modifications of a virulence factor, a process which mimics the natural route of pathogen evolution. *Cell* **129**, 891–902 (2007). *AL*

FlAsH-light on calcium nanodomains

Understanding how rapid and local changes in the concentration of intracellular Ca^{2+} selectively regulate numerous physiological responses requires identifying spatially and temporally restricted regions of high calcium. But changes in Ca^{2+} concentrations within nanometers of a protein of interest cannot be assessed using Ca^{2+}-responsive dyes and use of large fluorescent protein–based Ca^{2+} sensors is hampered by their sluggish responses to changes in Ca^{2+} levels. Now, Tsien and colleagues extend their FlAsH (fluorescein arsenical hairpin) technology, which exploits the high affinity of tetracysteine motifs for biarsenical compounds, to create Calcium Green FlAsH (CaGF). This ~1-kDa molecule, comprising a biarsenic domain and a Ca^{2+} sensor, reports highly localized fluctuations in Ca^{2+} concentrations on the millisecond timescale around a component of gap junctions and an L-type, voltage-gated, Ca^{2+} channel, each tagged with a noninvasive tetracysteine motif. The relatively low affinity of CaGF restricts its activation to the immediate vicinity of Ca^{2+} sources. (*Nat. Chem. Biol.* **3**, 423–431, 2007) *PH*

ENCODE catalogs genome complexity

The Encyclopedia of DNA Elements Consortium (ENCODE) pilot project, supported by the US National Institutes of Health, has mapped a plethora of functional sequences in a 30-megabase portion (1%) of the human genome. This effort of 35 research groups has generated 200 data sets, 400 million data points and 200 Mb of comparative sequence, now described in a *Nature* article and 25 papers in *Genome Research*. Not surprisingly, this mammoth undertaking uncovered some surprises. What the human genome lacks in sequence complexity—having at last count a mere 21,000 genes, barely more than a fruit fly—it makes up in transcriptional complexity. Detailed mapping revealed an intricate pattern of overlapping transcripts involving virtually all of the sequence analyzed, although only half of it encodes protein. In addition, regulatory sites are dispersed throughout the genome; transcription start sites—identified by sequencing the 5′-end of mRNAs or by mapping transcription factor binding sites—are often great distances from the closest promoter, suggesting that many genes have multiple start sites (5.4 per locus). Finally, interspecies sequence comparisons revealed that only 40% of conserved sequences are found in areas with known function; conversely, only 50% of sequence with known function appears to be evolutionarily constrained. Taken together, these findings lead to a modified concept of the gene as "a union of genomic sequences encoding a coherent set of overlapping functional products." (*Nature* **447**, 799–816, 2007) *LD*

Polyketides from the deep

Actinomycetes are a prolific source of structurally diverse natural products, including microbial antibiotics. Now Udwary *et al.* have unraveled the complete genome sequence, including biosynthetic gene clusters, of *Salinispora tropica*—a marine actinomycete that produces the experimental anticancer agent salinosporamide A. Homology searches and structural analysis of fermentation products led them to claim that the microbe both boasts the most diverse assembly of polyketide biosynthetic genes and devotes the greatest percentage of sequence (~10% of total) to natural product synthesis of any organism known. For certain regions of the genome containing a high prevalence of repetitive sequences that confounded assembly, the authors then turned to nuclear magnetic resonance and mass spectrometry analysis of *S. tropica*'s secondary metabolites. One compound, salinilactam A, provided structural information from which they inferred the modular gene structure of its biosynthetic enzymes. The identification of salinilactam A demonstrates the power of genome-guided fermentation studies to reveal both novel biosynthetic gene clusters of potential therapeutic significance and a context within which to elucidate the structures of the corresponding novel natural products. (*Proc. Natl. Acad. Sci. USA* **104**, 10376–10381, 2007) *TB*

p53 directly activates microRNA expression

Although the tumor suppressor p53 is a transcription factor, several reports suggest it can repress gene expression. To determine whether p53 might repress genes by triggering the transcription of microRNAs (miRNAs), Hannon and colleagues study miRNA expression in wild-type and p53-deficient mouse cells. They find that expression of three miRNAs, miR-34a, miR-34b and miR-34c, is substantially correlated with p53 status. In addition, low levels of miR-34s are observed in p53-deficient human tumors and cancer cell lines. In various mouse tissues, physiological stress, such as DNA damage, triggers p53-dependent expression of mi-R345. Several experiments indicate that p53 induces transcription of these miRNAs by directly binding to the *mir-34* promoters. They also show that ectopic expression of either *mir-34a* or *mir-34b/c* in immortalized mouse cells and a variety of human tumor cells results in substantial growth inhibition. This response is most likely mediated by the downregulation of multiple targets, including cyclin E2 and cyclin-dependent kinase 4. The study strengthens the notion that abnormal miRNA expression contributes to tumorigenesis and also indicates the therapeutic potential of miR-34s. (*Nature*, advance online publication 6 June 2007, doi:10.1038/nature05939) *JWT*

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