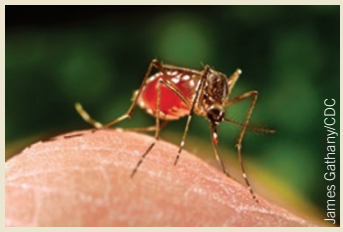
Aedes aegypti mosquito sequenced



The *Aedes aegypti* mosquito is an important disease vector in Asia and Africa as it can harbor both the yellow fever and dengue flaviruses. Each year, yellow fever affects hundreds of thousands and causes ~30,000 deaths in unvaccinated populations; dengue fever accounts for ~50 million infections. Thus, the completion of the genome sequence of *Aedes aegypti* is welcome news to those working to break the infection cycle. At 1,376 million base pairs, the *A. aegypti* genome is five times the size of that of *Aedes gambiae*, the malaria vector, whose sequence was completed four years ago. Much of the size difference relates to the large number of transposable elements in the former, which occupy nearly 50% of the genome. Because transposable elements are distributed within and around coding sequences, automated gene annotation was not an option for Nene *et al*. Rather, masking of the transposable elements and manual inspections were required to ferret out gene-coding regions. Despite this difference in gene structure (*A. aegypti* genes are four to six times larger than those of *A. gambiae*), higher order genome organization shows remarkable conservation; 77% of single-copy genes are contained in syntenic blocks. Comparative studies of immune-related genes in these species and in fruitflies by Waterhouse *et al.* have already shown that different elements of the immune repertoire evolve by different mechanisms, which suggest ways in which these pests adapt to environmental challenges. (*Science* **316**, 1718–1723;1738–1743, 2007). *LD*

Decoy RNAs sequester microRNA

Recent years have witnessed rapid progress in our understanding of the role of small RNAs in gene regulation. Now the identification of noncleavable RNAs in *Arabidopsis thaliana* that form a nonproductive interaction with a microRNA (miRNA) involved in phosphorus homeostasis suggests the existence of yet another level of regulation. Phosphorous regulation in plants is tightly regulated by miRNAs like miR-399, which carries out site-specific cleavage of *PHO2* mRNA, which in turn encodes an E2 ubiquitin conjugase–related protein involved in phosphate mobilization in the root. Paz-Ares and colleagues show that the nonprotein coding gene *IPS1* (induced by phosphate starvation 1) from *A. thaliana* contains a highly conserved motif with sequence complementarity to miR-399, but critical mismatches that prevent miR-399-guided cleavage. Overexpression of *IPS1* and a close *IPS1* paralog, *At4*, inhibits miR-399 activity, thereby resulting in increased *PHO2* expression. In addition, noncleavability of *IPS1* RNA by miR-399 appears to be critical for its function, because a mutant form of *IPS1* with perfect complementarity to miR-399 has no effect on expression of a *PHO2* reporter construct. Finally, the authors show that this mechanism of miRNA-activity inhibition, which they coin 'target mimicry', can be used as a tool to study the function of other miRNAs. Whereas overexpression of cleavable miR-156 and miR-319 targets has weak effects, overexpression of target mimics results in distinct mutant phenotypes. (*Nat. Genet.* **39**, 1033–1037, 2007) *JWT*

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The benefits of NetworKIN

Reversible phosphorylation events are fundamental in controlling the interactions of many proteins in signaling networks. Although approaches based on high-throughput mass spectrometry have identified thousands of protein-phosphorylation sites, systematically assigning the more than 500 human kinases to these targets remains a formidable challenge. Pawson and colleagues more than double the accuracy with which kinase-substrate relationships can be predicted by taking into account the biological context of the substrate. Their algorithm, NetworKIN, improves on purely motif-based methods by incorporating factors such as subcellular localization, protein–protein interactions and coexpression patterns. The predictive potential of this integrative computational approach is demonstrated by its ability to identify novel substrates for three protein kinases. NetworKIN should be equally valuable in elucidating how other post-translational modifications participate in complex and dynamic signaling networks. (*Cell* **129**, 1415–1426, 2007) *PH*

Closer look at TLR4 and lipid A

Immunostimulatory molecules that bind toll-like receptors (TLRs) can act as adjuvants and improve vaccine responses by stimulating cellular responses to antigens. One molecule that has shown promise in the clinic, monophosphoryl lipid A (MPLA), has been the object of scrutiny because of its similarity to *Escherichia coli* lipopolysaccharide (LPS), which is pro-inflammatory and causes immunotoxic syndromes such as sepsis. Two recent papers in *Science* take a detailed look at these molecules and their interaction with TLR4. Mata-Haro *et al.,* in mapping out the cellular response in mice to LPS and MPLA, find that whereas both molecules show similar patterns of T-cell expansion, subsequent events diverge. Of the four possible adaptor molecules that TLR binding can activate, MPLA initiates only the TRIF-TRAM signaling pathway, resulting in the production of type 1 interferons, whereas LPS initiates both TRIF-TRAM and MyD88 pathways, producing pro-inflammatory cytokines via NFκb. Because binding of both phospholipids to TLR4 is mediated through a costimulatory molecule, MD-2, it's not clear why different pathways are initiated. Yet another paper, by Ohto *et al.,* may provide the answer; their crystal structure of MD-2 bound with a phospholipid reveals that not all the phosphates on the phospholipid are engaged by MD-2. This suggests that the free phosphates may interact with TLR4 domains, resulting in distinct signaling outcomes. (*Science* **316**, 1628–1632; 1632–1634, 2007) *LD*

Epiblast stem cells

Two recent papers in *Nature* report the derivation of mouse epiblast stem cells, a pluripotent stem cell from the postimplantation epiblast stage of development. Embryonic stem (ES) cell lines arise from cultures of the inner cell mass of blastocyst-stage embryos, whereas the epiblast is a later tissue derived from the inner cell mass. The discovery of epiblast stem cells promises to shed light on a poorly understood difference in the signaling pathways used by mouse and human ES cells. Mouse ES cells are generally cultured in medium containing leukemia inhibitory factor to maintain them in a pluripotent state, whereas human ES cells are cultured in the presence of activin/nodal. Like human ES cells, epiblast stem cells depend on activin/nodal rather than on leukemia inhibitory factor. The two papers identified several other notable differences between mouse ES and epiblast cells—in morphology, in susceptibility to trypsin passaging and in epigenetic state. Brons *et al.* also generated epiblast stem cells from the rat, an animal for which ES cells have not been isolated. (*Nature* **448**, 191–195; 196–199, 2007) *KA*