matic wound to the epidermis. However, there is likely a healthy amount of dermal fat and an unhealthy amount. Zhang et al. address this in part by studying a high-fat diet. Interestingly, induction of adipogenesis in mice through a high-fat diet also increased the production of cathelicidin by the proliferating adipocytes. However, mice harboring disabling mutations in the receptor for leptin—a hormone produced by fat cells that suppresses food intake—gain weight and develop type 2 diabetes, but are more susceptible to *S. aureus* infection (10). Likewise, in humans, obesity has been associated with an increased risk of skin and soft tissue infection (11). One possible explanation for this discrepancy is that insulin resistance or other aspects of metabolic syndrome perturb the infection-adipogenesis-cathelicidin pathway identified by Zhang et al. Thus, signaling by adipose-derived hormones that control energy expenditure (adipokines) could influence the expression of cathelicidin. This antimicrobial peptide also is posttranslationally cleaved to its active form, a process that may also be influenced by obesity and metabolic syndrome.

The mechanism underlying the recognition of *S. aureus* by adipocytes remains unclear, although it likely involves toll-like receptor 2 (TLR2). Adipocytes express many members of the toll-like receptor family, including TLR2 (9, 12), which recognizes lipopeptides produced by bacteria. This may be an operative pathway that controls cathelicidin production. Moreover, a TLR2-ZFP423-PPAR-γ-cathelicidin pathway might be augmented pharmacologically by PPAR-γ agonists, thereby increasing host resistance to infection in susceptible individuals such as those with diabetes and metabolic syndrome.

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**EVOLUTIONARY GENOMICS**

**Conundrum of jumbled mosquito genomes**

Multiple *Anopheles* mosquito genome sequences reveal extreme levels of mixing

*By Andrew G. Clark* and Philipp W. Messer*

Malaria is caused by injection of *Plasmodium* parasites into the human bloodstream via the bites of infected mosquitoes. This simple description overlooks a fantastic biological complexity: Some 60 anophelean mosquito species can serve as vectors for five distinct species of *Plasmodium* that produce varying levels of illness in many animal species. Comparative genomic studies may shed light on the mechanisms whereby *Anopheles gambiae* specifically target humans, why the mosquitoes can tolerate *P. falciparum* infection, and how the parasite has adapted to this lifestyle. In this issue, Neafsey et al. ([1], page 43) and Fontaine et al. ([2], page 42) analyze the genome sequences of 16 species of anophelean mosquitoes and reveal a complex pattern of evolution that defies the classic concept of a phylogenetic tree.

Sequencing of multiple related species has revealed many attributes of the evolutionary pressures faced by those species (3–6). For example, multiple genome alignments can show which genes are most conserved and which evolve the fastest. In general, *Anopheles* genomes appear to evolve faster than do *Drosophila* genomes, perhaps because the former depend on hosts that may provide opportunities for coevolutionary arms races. This is especially evident in the families of closely related genes that formed from the duplication of a single original gene. Fontaine et al. show that the 16 *Anopheles* species gain and lose such gene family members at five times the rate of the 12 sequenced *Drosophila* species.

*Anopheles* genomics also sheds light on the genes involved in the specialization of *An. gambiae* on human hosts. Olfactory and gustatory receptors help the mosquitoes to identify and be attracted to hosts. Although these gene families are generally highly conserved across *Anopheles* genomes, *An. gambiae* shows a remarkable gain of 12 olfactory receptors, suggesting a possible role for these genes in guiding human host preference [as seen in *Aedes* mosquitoes (7)]. Many of the olfactory and gustatory receptors also display accelerated protein evolution, consistent with response to positive natural selection. Future studies should test the adaptive benefit of specific odorant chemicals and the specific associations between odorant chemicals and odorant receptors.

The genome sequences generated by Neafsey et al. provide the opportunity to investigate whether the observed evolutionary patterns in sequence divergences between the 16 mosquito species are consistent with a single phylogenetic tree. That the *Anopheles* phylogeny might be complex has been suspected since the first *An. gambiae* genome was sequenced (8) from a lab strain that included two distinct subtypes [today recognized as two separate species, *An. gambiae* and *An. coluzzii* (9)]. The observations that these two species readily hybridize and also have largely overlapping ranges suggest that there might be gene flow between them. Despite this, the *Anopheles* phylogeny has generally been described by a species tree, constructed from the informa-

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progression on the X chromosome, especially introgression is surprising without more information. This much interspecific hybridization is surprising, but the level of introgression varies across different species. For example, in the An. gambiae complex, introgression into the X chromosome is quite high. This much interspecific introgression is plausible, but the level of introgression may not necessarily be consistent with the true species tree.

Jumbled mosquito genomes. (A) The "true species tree" and major introgression events (red arrows) inferred from the X chromosomal sequences by Fontaine et al.: An. coluzzii (col), An. gambiae (gam), An. arabiensis (ara), An. quadriannulatus (qua), An. melas (mel), and An. merus (mer). (B) Locally inferred trees. The bars show the proportions of 50-kb windows on each chromosome that yield phylogenies consistent with one of the three topologies shown above. Large portions of the genome indicate that ara and col gam are sister groups (dark blue); other regions of the genome also group together qua and mer (light blue), compatible with the two major introgression events. Only windows on the X chromosome predominantly recover the species topology, grouping together ara and qua (red). Altogether there are 85 tree topologies, and the gray areas correspond to other topologies distinct from the three depicted ones.

In light of Neafsey's result that the X-to-autosome rate of transfer is unusually high in anopheline mosquitoes, further, the timing of the gambiae-arabiensis introgression remains unclear. In particular, it is not clear whether introgression is still happening (in which case arabiensis must still be undergoing hybridization with both gambiae and coluzzii) or whether hybridization ceased some time ago. Fontaine et al. have done a marvelous job in highlighting the truly odd character of these genomes, and their explanation is consistent with the data, but it raises many additional questions that warrant deeper study.

The breakdown of tidy bifurcating trees with distinct species at the tips has been seen in many systems (10). When there is extensive exchange across species, the phylogeny is no longer treelike but rather has a web of crossing lineages in the form of a network (see the second figure). This so-called reticulate evolution is especially evident in bacteria, where genetic exchange can be so pervasive that the concept of species becomes quite slippery (10). Reticulate evolution has been seen in many other species groups, but the pattern in the gambiae complex of mosquitoes is so extreme that it, too, challenges any clear definition of species in this group. Fontaine et al. adhere to a classical view that there is a "true species tree," presumably the phylogeny that is shown by the genes that mediate male and female fertility. But given that the bulk of the genome has a network of relationships that is different from this true species tree, perhaps we should dispense with the tree and acknowledge that these genomes are best described by a network, and that they undergo rampant reticulate evolution.

Beyond these two papers, additional tests of whether Anopheles mosquitoes have an accelerated rate of evolution with extensive introgression between species may come from contrasts of observed and expected patterns of polymorphism within species, requiring the sampling and sequencing of multiple individuals from within each species (11, 12). Such a population genetic approach may be the simplest way to resolve the lingering puzzles about this system. In particular, the sizes and sequence diversity of introgressed segments could be used to model the past timing and extent of hybridization events. The ability to detect positive selection for genomic features that might confer human host adaptation would also be greatly improved with polymorphism data. Additional sequencing to characterize polymorphism in An. gambiae would answer some questions, but would undoubtedly also raise new ones. For now, the two papers succeed in dramatically advancing Anopheles genomics and providing baseline resources to answer many questions beyond those pursued here.

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More web than tree. The pattern of evolution seen in the An. gambiae species complex resembles a network more than a tree. This type of evolutionary network is referred to as reticulate evolution (10).

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