

Molecular Insights into Classic Examples of Evolution

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Molecular Insights into Classic Examples of Evolution

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Molecular biology dominates the seventh annual evolution symposium.

There was standing room only at the seventh evolution symposium cosponsored by the American Institute of Biological Sciences (AIBS) and the National Evolutionary Synthesis Center (NESCent). The symposia are held annually at the National Association of Biology Teachers professional development conference, and the 2010 event in Minneapolis, Minnesota, drew a larger crowd than usual. The four invited speakers—using familiar, but gripping, examples—illustrated how advances in molecular biology are challenging our understanding of evolution.

The speakers also suggested some teaching strategies to help students understand living systems at the scale of DNA, RNA, and proteins. The rapidly expanding field of molecular biology plays an ever-increasing role in many areas of the biosciences, including genomics, biotechnology, microbiology, basic and applied research, diagnostics, and therapeutics. Students considering a career in the biological or medical sciences must be familiar with the discipline, whether they plan to work in academia or industry.

Evolutionary arms races

Edmund “Butch” Brodie III, professor of biology and director of Mountain Lake Biological Station at the



An adult garter snake (Thamnophis sirtalis) makes a meal of a toxic newt (Taricha granulosa). Photograph: E. D. Brodie III.

University of Virginia, in Charlottesville, inherited a fondness for predator-prey interactions from his father, who became interested in the subject while writing his master's thesis. The arms race that captivates Brodie is between common garter snakes (*Thamnophis sirtalis*) and their prey, newts of the genus *Taricha*, which produce a potent neurotoxin. The neurotoxin, known as

tetrodotoxin (TTX), is found in large amounts in *Taricha* skin and other tissues and is toxic to many predators.

Taricha toxicity varies across species and populations, but a single newt from certain populations has enough toxin to kill about 25,000 mice or 15 humans, even though there is no evolutionary rationale for killing multiple predators. Yet the common garter

snake has repeatedly evolved resistance to TTX; the snake's resistance—an example of a pivotal phenotype—has locked the species into a coevolutionary arms race with *Taricha*. Tetrodotoxin binds to sodium channels in a victim's nerves and muscles, and with a few key mutations, the snake has gained an advantage in relatively short evolutionary time. Resistance to TTX is completely absent outside the range of the newts.

Brodie's team sampled 40 populations of *T. sirtalis* throughout western North America to measure resistance on a quantitative scale. His group developed an assay in which snakes are raced along a track to measure their baseline speed. They are then given a known dose of TTX and raced again. The team discovered the snakes' resistance to TTX, as exhibited by their performance on the racetrack, varied geographically. Moreover, the fastest snakes were not very resistant, whereas the slow ones were more resistant. This finding holds true among related individuals, so these apparent trade-offs in performance have a genetic basis.

Further research revealed two coevolutionary hot spots: one in Oregon and one in California. In the hot spot areas, TTX resistance is two or three orders of magnitude higher than the snake's ancestral state. Beyond the hot spots, reciprocal selection is less intense. The snakes also exhibit behavioral assessment of toxicity: If faced with a very toxic newt, the snake stops ingestion and “yawns,” allowing the newt to walk away.

Another set of tests used mismatches of snake resistance and newt toxicity to reveal the dynamics of coevolution. The snakes were ahead of the newts in every mismatch—the predators sometimes “win” this particular race, but prey never do. Many more questions remain about the mechanism of TTX resistance and its evolution. At least two other species of garter snake are resistant to TTX, and other types of snakes feed on TTX-bearing prey, such as *Amphispma pryeri* in Japan, which eat local newts. Did their resistance to TTX evolve in the same way?

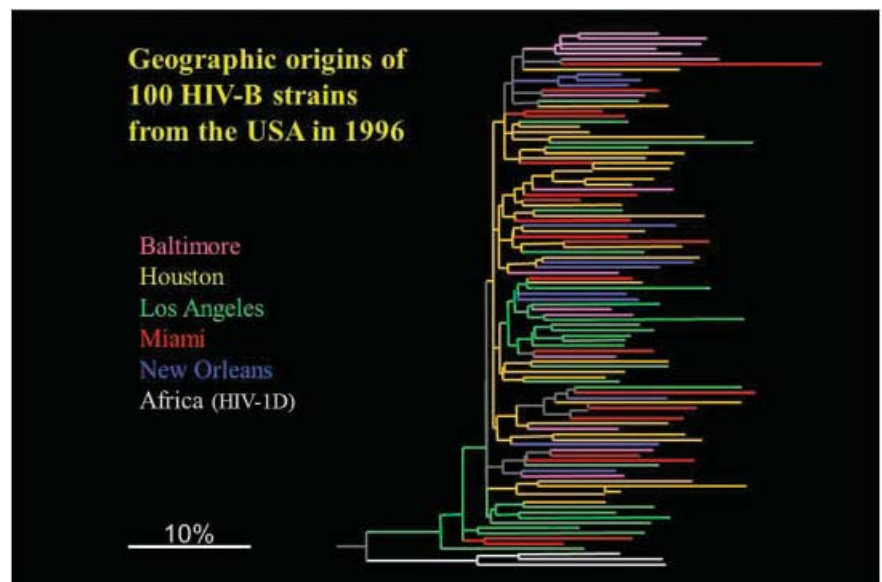
Molecular evolution in real time

Allen G. Rodrigo, professor of biology at Duke University and director of NESCent in Durham, North Carolina, illustrated how viruses challenge some of our perceptions of evolution, particularly its perceived slow pace and our supposed inability to study it. With viruses, we can actually measure evolution in real time and make inferences that enable decisions about health and disease.

The typical rapidly evolving virus is an RNA virus with an error-prone replication mechanism. Common examples are human immunodeficiency virus (HIV), influenza viruses, SARS (severe acute respiratory syndrome) coronavirus, and dengue virus. Many new pathogens transmitted from animals to humans are also examples of RNA viruses. HIV, which has now infected 40 million people globally, is typical of this group: It reverse transcribes viral RNA to make viral DNA, and because of this, there are many variants of HIV within and among hosts. The HIV envelope gene accumulates substitutions at a rate of approximately one percent a year, Rodrigo explained. By comparison, the

average eukaryotic or prokaryotic gene accumulates that much substitution in about 4 million years, and ribosomal RNA takes approximately 50 million years.

AIDS (acquired immune deficiency syndrome) was first reported in the United States mid-1981, when the Centers for Disease Control and Prevention recorded a cluster of *Pneumocystis* pneumonia in Los Angeles. Molecular epidemiologists now use phylogenetic reconstruction to infer the historical patterns of HIV and other disease transmissions. This is a particularly important method for evaluating emerging infections, to trace or rule out the potential sources of new pathogens. Rodrigo illustrated the effectiveness of phylogenetic trees using classic case studies: one case, first reported in 1987, involved a Florida dentist; the other study was conducted in 1996 to find the geographic origin of HIV strains in certain cities. In the Florida case, the constructed trees linked people infected with HIV during a certain time period to their dentist, who was HIV positive. In the latter, phylogenetic trees indicated that of the five US cities sampled,



The reconstructed phylogeny of the HIV (human immunodeficiency virus) strains from five cities in 1996 shows Los Angeles to be the closest to the base of the tree and, therefore, near the epidemic's origin. The out group is Africa. Graphic courtesy of Allen Rodrigo.

Los Angeles was closest to the epicenter of the HIV epidemic. This result is consistent with what is now known about HIV transmission in the 1980s: The two major epidemiological centers in the United States were New York and southern California.

This new field of “phylogenetics,” which weds epidemiology with phylogenetics, examines not only the origins but also the dynamics of infectious diseases. New vaccine development also depends on the use of phylogenetic methods, for example, to reconstruct the ancestral HIV sequence as a potential vaccine candidate. How is this done? Using statistical phylogenetic methods—a straightforward job when one has the right computational tools. Synthesizing a sequence, once it is known, has been simplified by the large number of companies offering this service at affordable prices.

Adaptive coloration

Hopi E. Hoekstra, an associate professor at Harvard University and curator of mammals for its Museum of Comparative Zoology, takes her inspiration for the study of mammalian pigmentation from the naturalist Francis Bertody Sumner. Sumner documented color variation among hundreds of wild mouse populations in the early 1900s. Hoekstra continues this line of research through work on the oldfield mouse (*Peromyscus polionotus*), studying how coloration affects an animal's fitness in natural environments and the role of genes in the development of color variation.

Many organisms use color for advertisement—for example, in mate choice, in mimicry, and as a warning. Oldfield mice exhibit extreme color variation among populations in the southeastern United States for a different reason: camouflage. Mice inhabiting inland, agricultural areas have dark brown coats to match the dark soil, but when some of them migrated to coastal dunes, their coloration evolved to a lighter color, allowing them to blend into the white sandy beaches. To determine the benefit of coloration for survival, Hoekstra's team placed



Dark, mainland oldfield mice such as the mouse on the left (*Peromyscus polionotus subgriseus*) are found in populations across the southeastern United States. Light beach mice (*Peromyscus polionotus phasma*, right) blend into their native habitat on the Atlantic coast of Florida. Photographs: Shawn Carey, Migration Productions (left) and J. B. Miller (right).

hundreds of decoy mice made of dark and light clay in matched and mismatched environments. Camouflage (crypsis) does work, they discovered. If the mouse had the same color as its background, its chances of avoiding detection increased 50 percent. The predators fooled by these clay models turned out to be about 50 percent terrestrial and 50 percent aerial.

What genetic changes were responsible for the color variation and patterning? Hoekstra's group allowed phenotypically distinct mice from different populations to mate in the lab. The second-generation hybrids yielded clues to the genes responsible for coloration: three regions of the mouse's genome were linked to cryptic pigment variation, and each of these regions contained a different pigmentation gene. The *Mclr* gene (short for melanocortin type 1 receptor) was of particular interest because its structure and function are already known. When researchers sequenced the gene in both dark and light mice, they found only one nucleotide mutation, which had caused an amino change in the *Mclr* protein's chemistry. When they assayed the receptor's functionality, the results showed that the mutation decreased receptor activity, leading to the production of more light pigment than dark.

In Florida, beach mice inhabit both the Gulf and Atlantic coasts, and have similarly light coats. But is the genetic

basis for light color the same on both coasts? Hoekstra's DNA studies showed that light pigmentation evolved independently two times, but although *Mclr* was a main player in the color of Gulf coast mice, there are no *Mclr* mutations in the Atlantic populations. There are many ways to arrive at similar adaptations to a common ecological problem, particularly with something as complex as coloration.

Genetic switches and wing spots

A well-known figure in evolutionary developmental biology, or evo-devo, research, Sean Carroll, professor of molecular biology at the University of Wisconsin–Madison and vice president for science education at Howard Hughes Medical Institute, pointed out that the art of evo-devo research is to find the simplest phenomenon you want to understand. This is why Carroll chose to study insect color patterns rather than a more complicated system.

Major evo-devo discoveries have often shattered expectations. For example, it was hypothesized that different sets of genes build different body forms, following the premise that the instructions for making, say, a mammal must differ from those for making fruit flies. Now we know that similar sets of *Hox* genes sculpt the body plans of all bilaterally symmetric animals. Researchers also hypothesized that vastly different structures with similar functions,



Drosophila guttifera differs from other fruit flies in that it has black spots and gray patches on each wing.
Micrograph: Nicolas Gompel and Sean Carroll.

such as limbs, evolved independently through different genetic mechanisms. Now we know that the *Distal-less* gene is involved in the formation of all sorts of appendages across the animal kingdom.

Developmental geneticists have found that a gene can have 15 to 25 different functions during the course of an organism's development. It seems cooption is a general phenomenon. For example, the *Wingless* gene product is a morphogen that induces the spot pattern in *Drosophila guttifera*, a fruit fly whose wing pattern differs from that of other fruit flies. Carroll's group traced the spots to *yellow*, a pigment-producing gene. A genetic switch for the expression of the *yellow* gene makes the spots appear in late wing development. Sometime in the evolutionary history of *D. guttifera*, *Wingless* acquired the role of switching on the *yellow* pigmentation.

Carroll also illustrated the versatility of the developmental genetic toolkit with a butterfly species from East Africa that has false eyespots on its wings. It developed these spots not to mate, as do many other butterflies, but to draw predators to its



Hopi Hoekstra, Allen Rodrigo, Butch Brodie, and Sean Carroll gave presentations at the evolution symposium in Minneapolis, Minnesota, last fall.
Photograph: Oksana Hlodan.

wings rather than to the juicier parts where its vital organs are located—another classic example of adaptive coloration. Carroll's group traced the pattern of a particular gene's expression in the wings of the East African butterfly and compared it with that of a monarch, using a stain that allows them to visualize where the gene is active. They discovered that the East African butterfly, unlike the monarch, has seven spots, each consisting of 200 cells, in which a novel gene is used for patterning.

Carroll's exploration of genetic switches leads to the conjecture that they are the short path to novelty: Genes are able to swap roles through genetic switches. The function of switches can be determined by isolating them and then comparing how they operate in different species. To change one's spots at the molecular level requires that mutations take place in the control switches.

Educational resources

The workshop that followed the speakers' presentations showed participants how to integrate molecular evolution into their teaching by helping students understand the "genotype to phenotype" relationship. Jim Smith, associate professor of biology at Michigan State University, led an activity that explored the molecular mechanisms that produce round or wrinkled peas.

More resources from the 2010 evolution symposium, including the above workshop activity, are available online. Educators can search the collection of teaching resources, including videos of speaker presentations, related articles, information about the speakers' research, and many other teaching tools, on the NESCent Web site (www.nescent.org/media/NABT2010).

Oksana Hlodan is the founding editor of *Actionbioscience.org* and has been its editor in chief at AIBS.