Searching Evolutionary Pathways

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CONSTRAINTS ON BACTERIAL RESISTANCE

Mutations are the stuff of evolutionary change, but whether a mutation is beneficial or not depends on its context. New evidence shows that some mutations may only confer fitness in certain genetic backgrounds, such that many of the roads in the theoretical fitness landscape are not taken.

Evolutionary biologist Daniel Weinreich and colleagues at Harvard University have examined the genetics of bacterial resistance to the antibiotic cefotaxime. Working backward from a known resistant strain to look at the various ways resistance may have been achieved, they found that many potential pathways are not available. The study was published in the 7 April issue of *Science*.

Resistance is conferred by a ß-lactamase gene with five point mutations. The scientists constructed 32 possible combinations of these mutations, transformed competent *Escherichia coli* with them, and tested each for cefotaxime resistance. Most of the mutants—those with four of the five mutations—failed to increase drug resistance in certain combinations.

Alleles of a gene can influence the expression of other alleles through epistatic interactions. The authors use the term "sign epistasis" to refer to mutations that increase fitness in some allelic backgrounds and decrease it in others. It points to intramolecular activity (characteristic of missense mutations in general) that is conditional and limits evolutionary pathways.

The authors calculate that of the 120 possible trajectories along the five-step path to the highly resistant form, just 18 are available, and of those just about half are likely. The other 102 trajectories involve intermediates that are not selectively advantageous. And yet the mutations are all beneficial when present together.

POSSIBLE NEW VULNERABILITY IN BACTERIA

Beta-lactam antibiotics, such as the aforementioned cefotaxime, are based on penicillin and its mode of action: killing bacteria by inhibiting transpeptidases from crosslinking the peptidoglycan layer of the cell wall. Other classes of antibiotics, to which bacteria also have been evolving resistance, interfere with protein synthesis in a variety of ways. Yet until now a step in prokaryotic translation, recently elucidated by Sean Studer and Simpson Joseph, of the University of California–San Diego, has been overlooked. The new findings, published in the 7 April issue of *Molecular Cell*, present targets against which a new class of antibiotics may be produced.

In bacteria, the first step of protein synthesis, translation initiation, is the interaction of a messenger RNA (mRNA) with the small 30S ribosomal subunit, three initiation factors, and an initiator transfer RNA. mRNAs are single stranded and fold into secondary structures that influence their ability to bind to the 30S subunit. Studer and Joseph synthesized and fluorescently labeled mRNAs with translation initiation regions (TIRs) of varying lengths to study how the necessary unfolding occurs.

The researchers verified the "standby model" of mRNA initiation, a two-step process that involves rapid binding of the 30S subunit to a region of the mRNA other than the TIR, followed by slow unfolding of the mRNA and binding of the TIR to the 30S subunit complex. Though the mechanism is analogous to some aspects of initiation in eukaryotes, it is unique to bacteria and may provide a basis for the development of novel antibiotics.

ANTIFREEZE GENES FROM ANTARCTIC HAIRGRASS

Australian scientists at the recently launched Victorian AgriBiosciences Centre (VABC) in Victoria, Australia, have initiated a new type of genomics research they call "xenogenomics," literally "strange genomics." Scientists at VABC are bioprospecting for novel genes in uniquely adapted plants. Their goal is to find and characterize genes that confer tolerance to such stresses as salt, drought, toxic aluminum levels, and freezing temperatures, ultimately for their potential application in agriculture.

In a poster presented at the 14th Annual International Convention of the Biotechnology Industry Organization this April in Chicago, plant geneticists German Spangenberg and Ulrik John of VABC announced they have isolated a gene for freeze tolerance from a cold-adapted plant species, *Deschampsia antarctica*. Also known as Antarctic hairgrass, it is one of two flowering plants capable of thriving at subzero temperatures in Antarctica.

Freeze tolerance in *D. antarctica* is due to a protein called ice recrystallization inhibition protein (IRIP), which binds to small ice crystals and prevents consolidation into crystals large enough to shrivel, or plasmolyze, cells. IRIP is localized in the extracellular spaces where freezing occurs, and its expression is induced by acclimation to cold (5 degrees Celsius).

When plants of the botanical model organism *Arabidopsis* were genetically modified to carry the *IRIP* gene from *D. antarctica* with an enhanced promoter, they exhibited strong recrystallization inhibition activity.

This finding makes possible the enhancement of economically important crop and pasture plants, say the scientists, and illustrates the utility of the xenogenomics approach.

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