26 broth-derived compensatory mutations. In general, most of the compensatory mutations in bacteria grown in mice provided only partial recovery of fitness, explaining the preponderance of drug-sensitive revertants. These results are somewhat surprising because it would be expected that the effects of compensatory mutations (which correct the defects in protein synthesis that accompany fusidic acid resistance) would be independent of the bacteria's environment.

The investigators also looked at streptomycin resistance conferred by a mutation in the *rpsL* gene, which encodes ribosomal protein S12. Although broth and mice were not treated with streptomycin, the adaptation to the costs of streptomycin resistance was solely through compensatory mutations and not through reversion to a drug-sensitive phenotype. Intriguingly, in broth bacteria all 14 compensatory changes were located in the *rpsD* and *rpsE* genes (extragenic), and not in the *rpsL* gene. In contrast, in all 10 mice studied, the compensatory mutations were located in *rpsL* (intragenic), within the same codon. The original *rpsL* drug-resistance mutation was a substitution (AAA to AAC) at the 42nd codon; two base changes converting AAC to AGA (which maintained drug resistance) compensated for the effects of this substitution. Unlike the case for fusidic acid resistance compensatory mutations, all of the streptomycin resistance compensatory mutations were accompanied by relatively high bacterial fitness regardless of whether bacteria were grown in broth or in mice. This led the authors to conclude that the differences between mice and broth *Salmonella* in the evolution of streptomycin resistance compensatory mutations lay in the mutation process itself, rather than in selection of mutants. An immediate implication of this finding is that making predictions about the evolution of drug-resistant pathogens in vivo requires that at least some experiments be performed in vivo. Despite the benefits of in vitro experiments, we cannot yet abandon animal models.

Regarding the problems of drug resistance, the results of the Björkman study cannot be interpreted in an optimistic light. In the case of streptomycin, at least, all of the adaptations to the cost of resistance were through amelioration of the drug-resistant mutations rather than by reversion to drug sensitivity. These findings also have implications beyond drug resistance. They suggest that in vivo the mutants generated are quite different and the mutation rate is higher than in vitro. Do compensatory mutations contribute to both acquired resistance in drug-treated hosts and the virulence of infecting microbes (*10*)? Evolution of a bacterial population in an infected host may be completely different from that taking place in a habitat outside of the host. For example, the same gene may be favored in one habitat and selected against in the other. The important findings of Björkman and co-workers raise a number of questions about why mutation and selection, the fundamental elements of bacterial evolution, are different in vivo and in vitro. Answering those questions should keep microbiologists deliciously occupied for some time to come.

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PERSPECTIVES: ASTROPHYSICS

Galaxy-Scale Mergers and Globular Clusters

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The formation of globular clusters and the origin of galaxy shapes, longstanding mysteries in astrophysics that were long viewed as disjoint, have recently turned out to be delightfully intertwined. The conceptual breakthrough came from Hubble Space Telescope observations of colliding and merging galaxies.

Globular clusters are densely packed aggregates of 10^5 to 10^7 stars (see the figure). How so many stars may have formed nearly simultaneously in a sphere only ~100 light-years in diameter has long been a mystery. Our Milky Way Galaxy features about 150 of these magnificent clusters, all nearly as old as the universe itself (10 to 14 billion years). In the 1960s, astronomers postulated that globular clusters in other galaxies were similarly old and may have formed even before their host galaxies (*1*). But problems with this view soon arose. The chemical abundances of globulars seemed to correlate with those of their hosts rather than having universally low metallicity, as one would expect of primordial objects (*2*). And some nearby galaxies were found to possess both old and young globular clusters. The image of globulars as primordial objects thus became tarnished.

Enter NASA's Hubble Space Telescope, among whose early successes were the discoveries of dozens of young globular clusters in a peculiar elliptical galaxy and in two pairs of merging spirals (*3*). Since then, systems of 100 to 1000 freshly minted clusters have been found in a variety of galaxies, often involved in collisions and mergers (see the figure). These observations have shed new light on the cluster-formation process.

Globular clusters apparently form from massive gas clouds in galaxies that get seriously perturbed. Within their rotating disks of ~10^{11} stars, spiral galaxies like the Milky Way or neighboring Andromeda contain a layer of dilute atomic hydrogen interspersed with denser clouds of molecular hydrogen. The most massive of these H_2 clouds, called giant molecular clouds (GMCs), contain 10^5 to 10^7 times as much gaseous mass as our sun and are only marginally stable against gravitational collapse. The 1000 to 2000 GMCs orbiting in a spiral galaxy tend to slowly condense and form stars, but things turn catastrophic when two spirals collide and merge, causing the pressure of the dilute atomic hydrogen to increase rapidly. This results in widespread star birth and shocks the GMCs into prolific star formation on a globular-cluster scale (*4*). Evidence for this process is that the newborn clusters have a mass distribution closely resembling that of the GMCs themselves (*5*).

What does this process have to do with the origin of elliptical galaxies? Ever since Edwin Hubble arranged galaxies into a morphological sequence, astronomers have wondered why galaxies at one end of the sequence are disk-shaped and those at the other end are ellipsoidal. Elliptical galaxies were long thought to have formed shortly after the big bang through

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the collapse of low–angular momentum gas. In 1972, Alar and Juri Toomre hypothesized that ellipticals may instead have formed through major, destructive mergers of disk galaxies with nearly equal mass. Today, astronomers increasingly think of galaxy formation as a sequence of hierarchical mergers, but the debate continues between those who believe that ellipticals assembled from gaseous fragments in the early universe and those who believe that a merger of two gas-rich galaxies of comparable mass is essential in forming an elliptical galaxy. This is where galaxy and globular-cluster formation become intertwined.

Globular clusters yield some secrets. The globular star clusters of our Milky Way, such as 47 Tucanae (**top left**), are all ancient. In NGC 4038/4039, a pair of merging disk galaxies (**top right**), hundreds of new globulars have been born during the past 500 million years from molecular-gas clouds (*16*). Similar mergers long ago may have formed Messier 87 (M87), a giant elliptical in Virgo (**right**). This galaxy hosts about 14,000 globular clusters, of which a slight majority are metal-poor and the rest are metal-rich (*2, 9, 13*). The evidence suggests that the metal-rich globulars formed during the same mergers that gave birth to M87 itself.

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It has been known for nearly two decades that giant ellipticals (*6*) contain about two to four times as many globular clusters per unit luminosity as average spiral galaxies do (*7*). First perceived as evidence against the formation of ellipticals through disk mergers, the excess number of globulars turned into an argument in favor of such formation after astronomers realized that globulars might form from gas crunched in mergers (*8*), and observations of colliding and merging galaxies confirmed this process (*3*). It remained possible, however, that the early smash-up of gaseous fragments might produce as many globulars as the later merger of two major galaxies.

Recent observations show that most giant ellipticals feature globular clusters of two distinct chemical compositions: bluish clusters as metal-poor as those in the Milky Way and reddish clusters 10 to 50 times as metal-rich (*9*). This bimodality implies two major episodes of cluster formation. The only viable candidate for the second episode is a delayed merger of two (or a few) disk galaxies that had time to enrich their gas with metals synthesized in stars. This mechanism explains why remnants from recent mergers possess young globular clusters of nearly solar metallicity (*10*), why giant ellipticals often feature two fossil motion systems (*11*), and why metal-rich globulars tend to be concentrated nearer the galaxy center than metal-poor ones (*12*). It also predicts that metal-rich globulars should be substantially younger than their metal-poor cousins. Age differences of several billion years have recently been claimed from interpretations of cluster colors (*13*), but need to be confirmed by the new generation of 6- to 10-m-diameter telescopes.

In the debate about the origin of elliptical galaxies, the metal-rich globulars clearly weigh in on the side of major disk mergers, a few of which still occur in the nearby universe. However, it remains unclear how the metal-poor globulars fit into the picture. They are ubiquitous, existing in all but the most dwarfish galaxies, and hence seem unlikely to have formed during major mergers. In some rare supergiant ellipticals at the centers of rich galaxy clusters, metal-poor globulars exist in exceptionally large numbers. Do they indicate an early galaxy assembly from many gas fragments, as envisaged for the Milky Way halo (*14*), or were they accreted much later from the many surrounding dwarf galaxies (*15*)? Finally, what universal pressure squeezed those early GMCs that must have been their progenitors? With new large telescopes proliferating, answers to these questions should be in hand shortly.

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