Inherited adaptation of genome-rewired cells in response to a challenging environment

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One of the fundamental dogmas of biology since Darwin is that evolution of life is the result of the ability of organisms to adapt to changes in their environment. It is widely believed that adaptation proceeds by two distinct and independent steps: genetic mutations and selection of the organisms with mutations that favor their survival under the new conditions. According to the neo-Darwinian view, mutations are random, rare and independent of the selection process; the logically attractive alternative of directed mutations is at the moment largely rejected by the community of evolutionary biologists.

Recently, a group of physicists and biologists led by Erez Braun from the Technion, have demonstrated that when a population of genome-rewired yeast cells is subjected to a severe and unforeseen environmental challenge, adaptation proceeds via a path that does not involve the selection of rare random mutations but rather through a heritable change of gene expression simultaneously in numerous individual yeast cells. Yeast cells can grow on both galactose (Gal) and glucose (Glu) media (though growth is faster in the presence of the latter nutrient), by expressing the GAL genes in the former or strongly repressing them in the latter. In both cases, growth requires the presence of various essential amino-acids one of which is histidine, that have to be either present in the growth medium or produced by the cells via the histidine biosynthesis pathway of which the HIS3 gene is an essential component. Using genetic engineering, the HIS3 gene was placed under the regulation of the GAL system so that when the rewired yeast cells were placed in a Gal-his (rich in galactose but lacking histidine) medium, they could express simultaneously both the GAL and the HIS3 genes and live happily ever after in this environment (since the optimal amounts of products of the two types of genes are quite different, there was a transient period in which the expression of HIS3 was adjusted to the other genes of the histidine pathway).

When rewired cells were placed in a medium rich in both glucose and histidine, they rapidly adjusted to consume the more favorite nutrient by expressing the GLU genes and switching off the expression of the coupled GAL and HIS3 genes and, as expected, they grew and reproduced even faster than in a galactose-rich medium. When such rewired cells were placed in a chemostat (a flow device in which the rate of cell division is controlled by the addition of nutrient and a steady state population of dividing cells population is achieved by adjusting the rate at which cells are removed from the flow chamber) which contained a glucose-rich but lacking histidine (Glu-his) medium, a complicated population dynamics resulted. Initially, in stage I that lasted for about 8 generations (about 5 hours between cell divisions, controlled by the dilution rate of the chemostat), the population in the chemostat increased exponentially, presumably because a limited amount of histidine (or of the His3p protein needed to produce it) was available from the previous period in histidine-rich galactose. Then, in stage II that lasted for 10-30 generations, the histidine shortage became acute and the population exponentially decreased to less than 1% of the steady state value. In stage III, the population increased exponentially again until a new steady state was reached in stage IV indicating that the system has adapted by adjusting the production ofHIS3 (accompanied by genome-wide changes in the expression of other genes), in spite of its initial strong repression following the repression of the GAL system. The entire process of adaptation lasted between 20-40 generations, far smaller than that observed in experiments involving the fixation of spontaneous mutations (from hundreds to thousands of generations).

In order to test the adaptation of individual cells during the above process of adaptation of the entire cell population, Braun and coworkers sampled each phase at high temporal resolution by extracting individual cells from the chemostat at given time points and placing them on Glu-his plates. For comparison, they put such cells also on rich medium plates (containing both glucose and histidine), on which they formed uniform colonies after 2-3 days. Consequently, cells that would form such colonies in 2-3 days were defined as adapted organisms. They found that colonies on these plates began to appear only after 6-20 days and therefore none of the cells extracted from the chemostat and placed on Glu-his plates were adapted in the above sense. The probability that a given cell could form a colony in the chemostat, decreased exponentially with time (measured from the beginning of phase I); cells harvested at the beginning of phase I had a

50% chance of forming a mature colony on a Glu-his plate (and therefore had a potential for adaptation), while at the end of this phase only 1% of the cells could adapt. The observed initial (in stage I) decline of the adaptive potential over time suggests that adaptation was achieved only after the transition to the challenging environment and provides strong evidence against the neo-Darwinian view that adaptation is the result of preexisting rare mutations which give rise to a small subpopulation of cells able to thrive on Glu-his plates. In the latter case, one would expect the adaptive potential to increase in time since the progeny of the advantageous mutants will win the competition against the normal rewired cells and readily grow in this environment.

Some other interesting and intriguing observations reported by Braun et al:

1. Once a mature colony has appeared on a Glu-his plate, many of its cells were fully adapted in the sense that each cell could form a new colony within 2-3 days after being removed from the original plate and placed on a new Glu-his plate.
2. While in stage I (chemostat population increases with time), the adaptation potential of rewired cells decreased with time, in stage II (population decreases with time) the adaptation potential of cells increased in time.
3. The exponential growth rate of non-adapted cells in phase I was quite similar to that of adapted cells in phase III and the maximal cell densities at the end of both phases were similar as well, suggesting that non-adapted and adapted cells in phases I and IV respectively, have similar metabolic states.
4. The state of adaptation is inheritable and stable; upon switching back and forth between Gal-his and Glu-his environments, cells do not require a repeat of the adaptation period.

The mechanism of adaptation remains unknown at present. Even though rare and random preexisting mutations as a source of adaptation can be ruled out by the above experiments, other possibilities include directed mutations (a dirty word in the evolutionary biology community) and inherited patterns of gene expression.