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Review Article

The Evolution of Drug-Resistance, a Retrograde Evolutionary Process

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Abstract

The evolution of drug-resistance is a common occurrence in the practice of general medicine. This process is an example of retrograde evolution, also called devolution. In some cases, the devolution of drug resistance can be reversed as demonstrated by the Lenski Long-Term Evolution Experiment. The occurrence of drug-resistant bacteria variants does not require the existence of the drug selection pressures but the way physicians use these drugs can and does increase the frequency of the drug-resistant variants in the population of bacteria colonizing patients. This paper is intended to help the clinician in the use of these selection pressures and minimize the selection of these drug- resistant variants. 57

Keywords: drug-resistance; retrograde evolutionary; drug-resistance

Introduction

Devolution, or retrograde evolution is discussed by Vitas and DuBose in reference [1]. In that paper, they "discuss the role of Darwinian selection in evolution and pose the hypothesis that Darwinian selection acts predominantly as a retrograde driving force of evolution. In this context we understand the term retrograde evolution as a degeneration of living systems from higher complexity towards living systems with lower complexity." If one looks at the Wikipedia article on "Devolution", we get the following explanation of the process: "Devolution, de-evolution, or backward evolution (not to be confused with dysgenics) is the notion that species can revert to supposedly more primitive forms over time. The concept relates to the idea that evolution has a purpose (teleology) and is progressive (orthogenesis), for example that feet might be better than hooves or lungs than gills. However, evolutionary biology makes no such assumptions, and natural selection shapes adaptations with no foreknowledge of any kind. It is possible for small changes (such as in the frequency of a single gene) to be reversed by chance or selection, but this is no different from the normal course of evolution and as such de-evolution is not compatible with a proper understanding of evolution due to natural selection." [2] 72

An Example of Devolution: The Lenski Long-Term Evolution Experiment (LTEE) [3] is an example of devolution or retrograde evolution. This is because the energy-limited environment that the Lenski team subjects his populations to causes his populations to evolve to a state where they use the minimum amount of energy to survive and replicate. The populations are losing the ability to produce a cell wall because the production of the cell wall puts an energy burden on those members of the population and the cell wall in this environment is not needed for survival and replication. This process is driven by the first and second laws of thermodynamics. The first law, conservation of energy, applies because population growth is limited by the energy (glucose) supplied. The second law applies to the descent with modification where replications give the possibility of random (adaptive) mutations occurring. This is an entropy-producing process. The mathematics of this entropy-producing process is described in reference [4]. 84

The biological competition that these E. Coli bacteria are doing is causing a loss of cell wall production

in the more fit members of the populations in this experimental environment. It is known that the bacterial cells in the LTEE are increasing in size. [5] At the same time, the bacteria are becoming more osmotically fragile. [6] The genes that form cell walls in the bacteria are losing their function to be more re-productively fit in this environment. 90

The Founder Bacteria in the LTEE have Drug-resistant Variants in their Populations: The founder bacteria in the LTEE had drug-resistant variants in that population even though this population had never been subjected to antibiotic selection pressure. [7] These drug-resistant variants appear in the founder's population by neutral evolution. The founder populations were not stressed by starvation. This allows variants with reduced fitness to survive with the drug-sensitive variants (that have greater relative fitness with respect to the drug-resistant variant) and not be selected out by biological competition. It is only when these founders are placed in the starvation selection condition environment that these drug-resistant variants are selected out and replaced by drug-sensitive variants. This is a case where the retrograde evolutionary process can be reversed and the drug-resistant variants can progressively evolve into drug-sensitive variants. At the same time as drug resistance is being selected out in these populations, the members of the population are losing their cell walls to minimize the energy burden imposed by the starvation selection condition. 103

Retrograde Evolution vs Progressive Evolution: The LTEE is demonstrating retrograde evolution with the loss of the bacterial cell wall, while at the same time, demonstrating progressive evolution with the evolution of drug-sensitive variants. Can these bacteria that have performed

a retrograde evolutionary process be "progressively" evolved to their previous state where they have a cell wall? It is known that the Lenski team keeps a history of this evolutionary process by freezing mixed population samples every 500 generations (75 days). [8] What would be the selection pressure to do this progressive evolutionary process? The obvious answer would be osmotic stress. Do any of his stored populations that have mutated portions of the genome that codes for cell wall production have those mutated portions mutate back to fully functional cell wall producing genes? If that is possible, is it possible for all the stored populations or does the evolutionary process become impossible after a ertain number of generations of devolution? What happens to these genes in these bacteria later in the experiment? Have so many mutations accumulated in these genes that they serve no biologically functional process? Can these genes be mutated back to functional status by Darwinian evolution?

Would osmotic stress be an adequate selection pressure to accomplish this progressive evolutionary process? Can bacteria that are known to be able to produce a cell wall but have evolved away from that capability, re-evolve the capability of producing a cell wall? This may be an interesting biological question but how does it apply to the practice of general medicine? 121

Discussion

In the practice of general medicine, clinicians use selection pressures to treat diseases in living populations. Not only is the patient living, but so is the infectious disease or cancer. The disease-causing agent replicates, some of its members get mutations (they don't replicate perfectly) and are subject to their environment with its associated selection conditions. The LTEE shows that under the right conditions, the retrograde evolution of drug-resistance caused by neutral evolution can be reversed by the starvation selection condition and drug-sensitive variants can be progressively evolved by that selection condition. The difficulty for the clinician is that the process takes thousands of generations to happen under starvation conditions. The principle demonstrated in the LTEE would require the cessation of the use of a given antibiotic for a long period to allow biological competition to reduce the frequency of the drug-resistant variant. This may be useful in the long term but not during the treatment cycle of a patient. This may become a useful area of research. How long does a particular

drug need to be withdrawn from usage before it becomes useful again? 134 The progressive evolution of drug-sensitive variants is not of any clinical use at this time. The clinician Edward Tatum in his 1958 Nobel Laureate Lecture [9]. "In microbiology the roles of mutation and selection in evolution are coming to be better understood through the use of bacterial cultures of mutant strains. In more immediately practical ways, mutation has proven of primary importance in the improvement of yields of important antibiotics – such as in the classic example of penicillin, the yield of which has gone up from around 40 units per ml of culture shortly after its discovery by Fleming to approximately 4,000, as the result of a long series of successive experimentally produced mutational steps. On the other side of the coin, the mutational origin of antibiotic-resistant micro-organisms is of definite medical significance. The therapeutic use of massive doses of antibiotics to reduce the numbers of bacteria which by mutation could develop resistance, is a direct consequence of the application of genetic concepts. Similarly, so is the increasing use of combined antibiotic therapy, resistance to both of which would require the simultaneous mutation of two independent characters." What Tatum is suggesting here is the use of the multiplication rule of probabilities in an evolutionary process to inhibit the selection of drug-resistant variants. Uses of dosages above the minimum inhibitory concentration of a drug and the use of two or more drugs that target different genetic loci mean that multiple mutations are required for adaptation to the selection pressures. The mathematics that describes this situation have been computed using two different probability methods and are shown in references [10, 11].

This mathematics shows that it takes exponentially larger populations for each evolutionary mutational step in the evolutionary trajectory. This principle is well demonstrated by the successful use of three-drug combination therapy for the treatment of HIV. 156 Unfortunately, combating drug resistance is not that simple, just by the use of combination therapy. Other factors come into play. Using more drugs at a higher concentration potentially gives higher toxicity to the patient, so that must be considered when choosing combination therapy. The patient's immune status must be considered when formulating a treatment plan. A patient with an impaired =immune system or other medications such as steroids or other immune suppressive drugs may need a greater combination of drugs. The age of the patient can be a factor in choosing medications because patient age can affect the person's ability to metabolize a drug. The resistance pattern of bacteria to a particular drug or drugs in a region will affect the choice of combinations. 165

Conclusion

The physician who practices general medicine which includes the treatment of infectious diseases requires a basic understanding of how drug resistance evolves. The clinician need not have the understanding to do thermodynamic and probability calculations but the clinician needs to have a basic understanding of how this mathematical process works. Here is a simple analogy of how the process of biological evolution works, with or without the aid of natural selection: 171 Consider if for your family to survive your family needs to win two lotteries. The probability of winning one lottery is 1 in a million, and the probability of winning the other lottery is 1 in a million. For you to win both lotteries, that probability is 1 in a million times 1 in a million equals 1 in a trillion, a very low probability indeed. But let's say, you win one of those lotteries. And because of this, you are a very wealthy man and you can raise a very large family. And all your descendants start buying tickets to the second lottery. As soon as you have enough descendants, there will be a high probability that one of your descendants will win that second lottery for your family. 179 The probability of an adaptive mutation occurring on some variant in a population depends on the number of replications that variant does and the mutation rate, nothing else. There are lots of factors that affect that variant from doing the necessary number of replications for the next adaptive mutation.

Competition is one of those factors. It is also possible that a single adaptive mutation does not exist for the given selection conditions. But it all comes down to the fact that the number of replications and the mutation rate determine that probability. Adaptive evolutionary events don't add, they are linked by the multiplication rule as are your chances of winning two lotteries. 187 Biological evolution, whether it is progressive evolution or retrograde evolution needs to be understood by the clinician when treating an infectious disease (or any other disease involving a replicating population). Understanding the physics and mathematical behavior of a problem gives a way of finding a solution to that problem.

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