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The double-edged sword of Lamarck Comment on "Diversity, evolution, and therapeutic applications of small RNAs in prokaryotic and eukaryotic immune systems" by Edwin L. Cooper and Nicola Overstreet

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In a famous and somewhat mysterious poem, the great Russian poet of the 20th century Osip Mandelstam wrote "*So who is that knight fighting for the honor of Nature? Why – of course, it's the fiery Lamarck!*" Indeed, many biologists over two centuries have been under allure of the Lamarckian scheme of evolution thanks to its directness and simplicity. However, the numerous attempts to discover Lamarckian phenomena in experiments on animals and plants have failed, derailing careers and even contributing to the abhorrent excesses of Lysenkoism [1]. Thus, for decades, any advocacy of Lamarckian evolution has been inadmissible in the mainstream scientific community. As it so often happens in the history of science, it all changed abruptly in 2006–2007, not through focused efforts to demonstrate the reality of Lamarckian evolution, but as a result of the unexpected discovery of adaptive immunity in bacteria and archaea. This form of immunity in prokaryotes is mediated by the CRISPR–Cas (clustered regularly interspaced short palindromic repeats and CRISPR-associated genes) system [2–4] that is discussed in detail and compared to other immunity systems in the timely review article by Cooper and Overstreet [5].

The CRISPR–Cas-mediated immunity seems to represent a bona fide Lamarckian phenomenon [6]. Indeed, the CRISPR–Cas system responds to an environmental cue, namely invasion of a foreign (phage or plasmid) DNA, by specifically modifying the host genome, i.e. inserting fragments of the invading DNA into specific loci (CRISPR cassettes). The inserted spacers are then utilized by Cas protein complexes to recognize and destroy the genomes of the cognate phage or plasmid. The function of CRISPR–Cas thus embodies all the salient features of a Lamarckian mechanism: highly specific mutations are directly caused by an environmental factor and provide equally specific adaptation to that factor. The discovery of Lamarckian-type evolution mediated by CRISPR–Cas prompted reevaluation of other evolutionary mechanisms and led to the realization that several widespread phenomena, such as horizontal gene transfer (HGT) and stress-induced mutagenesis, encompassed a substantial Lamarckian component [6,7].

What about direct analogies between CRISPR–Cas and eukaryotic immune systems? This is the main subject of the review by Cooper and Overstreet [5]. The classic adaptive immunity in vertebrates carries clear Lamarckian features but these are displayed only at the level of somatic cells so that immunity is not heritable. By contrast, a striking analogy to the CRISPR–Cas mechanism is apparent in one of the branches of RNA interference, the animal

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piRNA system [8]. Indeed, piRNA clusters in the genomes of animal germline cells incorporate transposon sequences which are then transcribed to generate piRNAs that silence the cognate transposons. Despite this direct functional analogy between the Lamarckian immune systems of prokaryotes and eukaryotes, the proteins involved are not homologous. Cooper and Overstreet acknowledge this apparent lack of homology but suggest the possibility that deep evolutionary connections remain to be identified [5]. I submit that this is not a realistic possibility given that the evolution of the Cas protein by now has been traced in great detail and no relationship with the Argonaute family proteins, the central players in RNAi, has been identified [9,10]. The CRISPR–Cas system and the piRNA system (as well as the entire eukaryotic RNAi machinery) are analogs but not homologs.

This begs the question: why was the CRISPR–Cas not inherited by eukaryotes from their prokaryotic ancestors? A plausible answer is suggested by the consideration of other prokaryotic defense mechanisms that are conspicuously absent in eukaryotes, namely toxin–antitoxin (TA) and restriction–modification (RM) systems. Both of these defense systems function through tightly controlled coexpression of a nuclease (toxin or restriction enzyme) and its antagonist (antitoxin or modification enzyme) which are encoded within the same operon [11]. When the antagonist is missing or produced in insufficient amounts, the nuclease kills the cell. Eukaryotes have lost operons at an early stage of evolution, conceivably via a recombination ratchet triggered by the precipitous drop of the HGT rate [7]. Thus, the defense systems that implement the toxin–antitoxin strategy become lethally dangerous and have been eliminated by evolution. The *cas* operons encompass genes for several nucleases that are likely to possess toxin properties, most notably, Cas2 protein which belongs to the family of mRNA interferases, the largest group of prokaryotic toxins. The presence of Cas2 and other putative toxins among the Cas proteins implies tight coupling between the immune function of CRISPR–Cas and cell suicide or dormancy induction caused by toxins [12]. Most likely, the toxins are normally kept in check via interactions with other Cas proteins that function as antitoxins but are activated when the adaptive immunity fails. In eukaryotes disruption of *cas* operons by the recombination ratchet would unleash the toxins and therefore CRISPR–Cas was wiped out by purifying selection during eukaryogenesis along with the TA and RM systems.

Although CRISPR–Cas systems are not sustainable in eukaryotes, the principle of Lamarckian adaptive immunity seems to be “too good” to be abandoned. Thus, this form of immunity was reincarnated in the piRNA system and perhaps in other defense systems still to be discovered, by employing non-toxic prokaryotic ancestors, such as the Argonaute proteins. The staggering complexity of defense systems notwithstanding, there seems to be underlying logic in their evolution that is both universal and simple.

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