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Striving for clarity about the "Lamarckian" nature of CRISPR-Cas systems

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Abstract

Koonin argues that CRISPR-Cas systems present the best-known case in point for Lamarckian evolution because they satisfy his proposed criteria for the specific inheritance of acquired adaptive characteristics (IAC). We see two interrelated issues with Koonin's characterization of CRISPR-Cas systems as Lamarckian. First, at times he appears to confuse an account of the CRISPR-Cas *system* with an account of the *mechanism* it employs. We argue there is no evidence for the CRISPR-Cas system being "Lamarckian" in any sense. Second, it is unclear whether the mechanism is more "Lamarckian" than many other forms of genetic change already well-characterized in Darwinian terms. We present three conceptually distinct senses in which the mechanism of IAC may be considered Lamarckian and argue that only the strongest sense of *goal-directed* IAC would be difficult to accommodate in a Darwinian account. As the CRISPR-Cas mechanism does not qualify as "Lamarckian" in this strong sense, we argue there is no conceptual value in calling it "Lamarckian". Finally, we suggest that CRISPR-Cas systems do hold the potential for genuinely non-Darwinian, directed evolution in a way that Koonin did not discuss, involving their potential (mis)use as a human gene-editing tool.

Keywords CRISPR · Lamarckism · Characteristics · Immunity · Gene-editing

Introduction

Koonin argues that "CRISPR-Cas systems present the best-known case in point for Lamarckian evolution" (Koonin 2018), describing them as having a "(quasi) Lamarckian character" (Koonin 2018) and operating "via a genuine Lamarckian mechanism, i.e. Inheritance of Acquired adaptive Characteristics (IAC)."

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Specifically, he claims that CRISPR-Cas systems fulfil his characterisation of the two aspects of IAC: "(1) specific, heritable changes in the genome caused by an external factor, (2) specific phenotypic effect of those changes that constitutes adaptation to the causative factor" (Koonin 2018).

We see two interrelated issues with Koonin's discussion of these points. First, at times he appears to confuse an account of the CRISPR-Cas *system* with an account of the *mechanism* it employs; second, it is unclear whether the mechanism is more "Lamarckian" than many other forms of genetic change already well-characterized in Darwinian terms. Here we argue that there is no evidence for the CRISPR-Cas system being "Lamarckian" in any way, and there is no particular conceptual value in calling the CRISPR-Cas mechanism "Lamarckian". Finally, we suggest that CRISPR-Cas systems do hold the potential for a genuinely non-Darwinian, directed evolution in a way that Koonin did not discuss.

Evolution of the CRISPR-Cas system is not "Lamarckian"

As Koonin describes, CRISPR-Cas systems initially "acquire" their immunological function only once they have encountered a pathogen, by incorporating a chunk of that pathogen's DNA into their own array. They are then able to transcribe CRISPR-RNA to target pathogens with similar DNA, and the CRISPR-Cas systems of offspring retain this ability to specifically target the pathogen's DNA. Therefore, the CRISPR-Cas system can be considered to employ two general *mechanisms* (acquisition of pathogen DNA and transcription/targeting), the former being germane to the discussion here. However, Koonin appears, at times, to claim the *system* is Lamarckian (for example, in statements such as "As in the case of CRISPR-Cas, [piRNA] is a defense system with genomic memory, i.e. a (quasi)Lamarckian system" (Koonin 2018) and "these findings push the CRISPR-Cas systems into the domain of 'quasi-Lamarckian' phenomena" (Koonin 2018). We think it is important to be clear that the debate is over whether the acquisition *mechanism* is "Lamarckian" or not. The inappropriateness of terming special cases of recombination phenomena like the CRISPR-Cas system "Lamarckian" based on the specific mechanism they employ has been highlighted previously (see Poole 2009; Weiss 2015). There is no evidence that the CRISPR-Cas system *itself* requires explanation in anything other than Darwinian terms: it is reasonable to suppose that, at the population level, the system conferred a selective advantage, on average, to those individuals who possessed it. The question, therefore, turns to whether the acquisition mechanism is "Lamarckian" in nature or not.

Three kinds of "Lamarckian" evolution

Before addressing Koonin's contention that the acquisition mechanism is Lamarckian, we first want to define what could be meant by 'Lamarckian'. This is partly because people have different things in mind when they use the term (see Gissis and Jablonka 2011). Furthermore, it is not always clear precisely what Koonin has in

mind, as he moves between 'Lamarckian' and '(quasi)Lamarckian' throughout his paper.

We can think of at least three possible relevant senses of 'Lamarckian' with respect to IAC. The first sense (*L*1) could involve *any* inheritance of acquired characteristics. A good example of this is horizontal gene transfer, where the transferred "gene" is understood as responsible for some phenotypic change of the new host. The second sense (*L*2) is the inheritance of acquisred *adaptive* characteristics, where acquired characteristics *turn out to be* adaptive, in the context of a given organism and environment, regardless of how or why they were acquired. The third sense (*L*3) is the inheritance of acquired adaptive characteristics, where characteristics are acquired *because* they are adaptive; in other words, there is some goal-directedness to their acquisition. This need not involve an organism "deciding" to acquire them because they are adaptive; only that they be acquired as a result of an organism acting to become better adapted to its environment, as in the classic example of the giraffe stretching its neck as it "strives" to get previously out-of-reach leaves.

Koonin posits that the CRISPR-Cas system's DNA acquisition mechanism meets the criteria for IAC: it involves specific, heritable changes in the CRISPR-Cas array caused by an external factor—the pathogen—and results in a specific adaptive phenotypic effect, namely an immunological defence against similar pathogens. Therefore, particularly in pathogen-rich conditions, the claim is that the CRISPR-Cas DNA acquisition mechanism is working in an *L*2 Lamarckian sense, according to our characterization. This appears to be what Koonin is arguing, as he emphasizes there are no new elementary mechanisms involved, only an unusual combination of mechanisms (Koonin 2018). Furthermore, Koonin denies that, by calling CRISPR-Cas Lamarckian, he is claiming that the evolution is teleologically directed as in *L*3—that the bacteria are selecting an aspect of their environment to adapt to through phenotypic changes, with these changes inherited by offspring (Koonin 2018).

Calling the CRISPR-Cas mechanism Lamarckian in the sense of *L*2 invites confusion, given that 'Lamarckism' is often understood to be associated with our sense *L*3, where evolution is goal-directed. More importantly, though, it is unclear what conceptual work is being done by calling it Lamarckian at all. First, the uptake of exogenous pieces of DNA (i.e., horizontal gene transfer), of which the CRISPR-Cas mechanism is just a special case, is already well-described without appeal to Lamarckism (see Thomas and Nielsen 2005). Of course, the CRISPR-Cas mechanism does more than simply uptake exogenous DNA, but it is far from clear that any of its further features call for explanation in non-Darwinian terms. Further, the conventional understanding of random mutation allows for changes to prokaryote DNA, caused by exposure to harmful events (for example, mutations induced by UV light), that *may* result in heritable characteristics adaptive to that event. This meets Koonin's definition of IAC but, presumably, Koonin would not call these happenstance mutations "Lamarckian". In the case of CRISPR-Cas, it could be argued that the uptake of DNA is *more likely* to involve *useful* DNA (i.e., DNA from pathogens) than random DNA. Nevertheless, as far as we know, the uptake of DNA by CRISPR-Cas systems is still random in the sense that the system has no way of "knowing" whether the DNA it uptakes will be useful or not. The only distinction that Koonin raises is that the probability may be higher because the concentration

of pathogen-derived DNA may be locally higher during an infection. Thus, heightened rates of adaptive acquisitions are not due to "preference", but a side-effect of concentration.

As acquisition cannot be controlled, routine Darwinian selection, based on environmental circumstances (e.g., presence of a pathogen) will then winnow down to those bacteria who happen to have taken up useful DNA. Thus, the adaptive nature of this system is directly related to the DNA a bacterium encounters in its environment. It is easy to imagine a scenario where DNA acquisition might not often be adaptive, such as where pathogens are insufficiently frequent; in these cases, the CRISPR-Cas mechanism would qualify as "Lamarckian" only in the sense of *L*1. Indeed, the mechanism could here be maladaptive, for example if it incorporated DNA from itself, or a mutualist partner rather than a pathogen. Such strong dependency on the environmental context in determining whether the CRISPR-Cas mechanism is "Lamarckian" is far from the teleological connotations the term is commonly taken to have. Therefore, we feel that labelling the CRISPR-Cas DNA acquisition mechanism "Lamarckian" serves only to confuse, rather than clarify or enlighten, discussion of the underlying evolutionary processes.

CRISPR as a gene-editing tool: genuinely non-Darwinian evolution?

Lastly, we think there *is* something interesting to say about CRISPR as a mechanism for the inheritance of acquired adaptive characteristics whose acquisition is goal-directed, in the strong sense of what we called *L*3. This is the closest way we can see to treating CRISPR as the "best known case in point for Lamarckian evolution," as Koonin put it (Koonin 2018). This lies in its potential (mis)use as a human gene-editing tool. CRISPR-Cas systems greatly enhance our ability to genetically modify gametes or embryos in a way that leads to heritable changes. Imagine a situation where genetic manipulation of certain traits is seen as desirable, such as increased intelligence, enhanced longevity, or protection from dementia. There are obviously serious ethical implications of these manipulations, and we should not be read as endorsing them. But if they were to become widespread in the human population, this would be the kind of directedness of evolution that could be considered "Lamarckian". To qualify as "Lamarckian" in our *L*3 sense, however, such changes would need to be adaptive and invoked by a conscious decision by parents to furnish their offspring with the desired trait. We can further speculate as to how we might deliberately alter our genome in response to selection pressures. For example, in response to looming existential threats we may alter our genome to thrive on other planets, enabling us to endure harsher climates or cope with varying oxygen levels and gravitational effects. Still, we question whether there is value in referring to this kind of "directed evolution" as "Lamarckian". To do so might be, in Gould's words, to "cast aside the guts" of Lamarck (Gould 1979, 38), given that his primary contribution was the first coherent description of a theory of evolution rather than the intellectual development of IAC (Burkhardt 2013). Nonetheless, this CRISPR-assisted gene-editing would certainly qualify as a "non-Darwinian" process that is distinct from all previous evolution on Earth.

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