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Review

How life changes itself: The Read–Write (RW) genome

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Abstract

The genome has traditionally been treated as a Read-Only Memory (ROM) subject to change by copying errors and accidents. In this review, I propose that we need to change that perspective and understand the genome as an intricately formatted Read–Write (RW) data storage system constantly subject to cellular modifications and inscriptions. Cells operate under changing conditions and are continually modifying themselves by genome inscriptions. These inscriptions occur over three distinct time-scales (cell reproduction, multicellular development and evolutionary change) and involve a variety of different processes at each time scale (forming nucleoprotein complexes, epigenetic formatting and changes in DNA sequence structure). Research dating back to the 1930s has shown that genetic change is the result of cell-mediated processes, not simply accidents or damage to the DNA. This cell-active view of genome change applies to all scales of DNA sequence variation, from point mutations to large-scale genome rearrangements and whole genome duplications (WGDs). This conceptual change to active cell inscriptions controlling RW genome functions has profound implications for all areas of the life sciences.

Keywords: Epigenetics; Natural genetic engineering (NGE); Mobile genetic elements (MGEs); Genome inscriptions

Contents

Abbreviations: nc, non-coding; CDS, coding sequence; CRM, *cis*-regulatory module; TF, transcription factor; C, cytosine; U, uracil; A, adenine; I, inosine; G, guanine; T, thymine; RITS, RNA interference by transcriptional silencing; CRISPR, clustered regularly interspaced short palindromic repeats; WGD, whole genome duplication; MGE, mobile genetic element; TPRT, target-primed reverse transcription; LTR, long terminal repeat; DS, double-strand; CSR, class switch recombination; Rec, recombination; NHEJ, non-homologous end joining; NER, nucleotide excision repair; BER, base excision repair; NGE, natural genetic engineering; CNE, conserved nucleotide element; K, lysine; R, arginine; TIR, terminal inverted repeat; MB, mega-base-pairs.

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0. Introduction: Hereditary change – what have we learned in the last 60 years?

Understanding the proper role of the genome is a central issue in biology. The susceptibility of hereditary mechanisms to biological influences was a matter of intense debate in the late 18th and 19th centuries [1–3]. With the twin triumphs of Mechanism over Vitalism and Darwinism over Lamarckism in the first half of the 20th century, the Weismann idea of the segregated germ plasm directing the actions of the cell and organism in a hard-wired fashion has been the prevailing view. Ever since the formulation of the neo-Darwinist Modern Synthesis evolutionary theory in the 1930s and 1940s, it has been an article of faith that hereditary variation results from stochastic copying errors and unavoidable damage to the genome. In this perspective, the genome is a "read-only memory" (ROM) data storage system passed on from one generation to the next.[1]

In the past 60 years, since the structure of DNA was elucidated [5,6], molecular biologists have studied the basic mechanisms of long-term genome change. They have discovered a wide array of proofreading and damage repair biochemical systems that remove copying errors and correct DNA damage. At the same time, they have revealed an amazing and wholly unanticipated array of cellular and molecular systems that operate to generate genome variability, both temporary and structural. As we begin the second decade of the 21st century, accumulating empirical evidence has thus shifted the perspective on genome variation to that of an active inscription process changing the information passed on to future generations.[2]

In other words, we now have to reconsider the genome as a "read–write" (RW) information storage system highly sensitive to biological inputs. Although there are other cell structures that contain hereditary information [8,9], we know most about how susceptible genomic DNA is to biologically regulated modifications [10]. Indeed, I will argue that one of the main adaptive features of DNA-based heredity is that DNA is a highly malleable storage medium, permitting rapid and major changes to complex organisms without disrupting their functional integrity. Every time we do a molecular genetic intervention to work out the operation of some intricate cell control circuit, we make use of this malleability.

This review will summarize some of the molecular biology lessons acquired since 1953 about (1) genome structure, functions and organization, (2) the time scales for genome inscriptions, (3) proofreading and DNA damage repair, (4) cell action in restructuring genomic DNA (*i.e.*, natural genetic engineering or NGE), (5) the historical role of NGE processes as evidenced by the evolutionary DNA record, and (6) the conceptual and experimental challenges posed by the success of living cells in creating adaptive genomic novelties in the course of evolution.

As we shall see, the molecular lexicon and cellular writing methods are quite ample, at the levels of both temporary and permanent inscriptions on and in DNA. The references to the material in the tables will be available online in links at http://shapiro.bsd.uchicago.edu/PLREV.RWGenome.html. This format makes for ease of reading, keeps the review

[1] Sydney Brenner captured this view well from an informatics perspective in his Alan Turing Centennial tribute: "Turing's ideas were carried further in the 1940s by mathematician and engineer John von Neumann, who conceived of a 'constructor' machine capable of assembling another according to a description. A universal constructor with its own description would build a machine like itself. To complete the task, the universal constructor needs to copy its description and insert the copy into the offspring machine. Von Neumann noted that if the copying machine made errors, these 'mutations' would provide inheritable changes in the progeny." [4].

[2] Barbara McClintock most vividly expressed this view in her 1983 Nobel Prize lecture when she described her work analyzing the mutagenic effects of X-rays in maize: "The conclusion seems inescapable that cells are able to sense the presence in their nuclei of ruptured ends of chromosomes and then to activate a mechanism that will bring together and then unite these ends, one with another... The ability of a cell to sense these broken ends, to direct them toward each other, and then to unite them so that the union of the two DNA strands is correctly oriented, is a particularly revealing example of the sensitivity of cells to all that is going on within them... There must be numerous homeostatic adjustments required of cells. The sensing devices and the signals that initiate these adjustments are beyond our present ability to fathom. A goal for the future would be to determine the extent of knowledge the cell has of itself and how it utilizes this knowledge in a "thoughtful" manner when challenged... In the future, attention undoubtedly will be centered on the genome, with greater appreciation of its significance as a highly sensitive organ of the cell that monitors genomic activities and corrects common errors, senses unusual and unexpected events, and responds to them, often by restructuring the genome." [7].

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