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ScienceDirect
Frontiers in Neuroendocrinology 29 (2008) 428–444
Frontiers in Neuroendocrinology
www.elsevier.com/locate/yfrne

Review

The EDGE hypothesis: Epigenetically directed genetic errors in repeat-containing proteins (RCPs) involved in evolution, neuroendocrine signaling, and cancer

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Available online 8 January 2008

Abstract

Trans-generational epigenetic phenomena, such as contamination with endocrine-disrupting chemicals (EDCs) that decrease fertility and the global methylation status of DNA in the offspring, are of great concern because they may affect health, particularly the health of children. However, of even greater concern is the possibility that trans-generational changes in the methylation status of the DNA might lead to permanent changes in the DNA sequence itself. By contaminating the environment with EDCs, mankind might be permanently affecting the health of future generations. In this section, we present evidence from our laboratory and others that trans-generational epigenetic changes in DNA might lead to mutations directed to genes encoding amino acid repeat-containing proteins (RCPs) that are important for adaptive evolution or cancer progression. Such epigenetic changes can be induced "naturally" by hormones or "unnaturally" by EDCs or environmental stress. To illustrate the phenomenon, we present new bioinformatic evidence that the only RCP ontological categories conserved from *Drosophila* to humans are "regulation of splicing," "regulation of transcription," and "regulation of synaptogenesis," which are classes of genes likely to be important for evolutionary processes. Based on that and other evidence, we propose a model for evolution that we call the EDGE (Epigenetically Directed Genetic Errors) hypothesis for the mechanism by which mutations are targeted at epigenetically modified "contingency genes" encoding RCPs. In the model, "epigenetic assimilation" of metastable epialleles of RCPs over many generations can lead to mutations directed to those genes, thereby permanently stabilizing the adaptive phenotype.

Keywords: Repeat-containing proteins (RCPs); Neuroendocrine signaling; Evolution; Cancer; Epigenetics; Trans-generational epigenetics; Endocrine disruptors; Hsp90; Trinucleotide repeats

1. Introduction

> Nothing in biology makes sense except in the light of evolution [14].

Theodosius Dobzhansky (1900–1975), who had a long, distinguished career as an evolutionary geneticist, wrote a short paper with the above title near the end of his life to emphasize the central role of evolution in understanding biological processes. The title is a paraphrase of a statement in his classic 1955 textbook on evolutionary biology [13]. In 1937 he had published a model of evolution called the "modern synthesis", which links Darwinian evolutionary biology with Mendelian–Morganist genetics [12]. Also in 1937, he had published *Genetics and the Origin of*

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doi:10.1016/j.yfrne.2007.12.004

Species, a book in which he summarized many aspects of the "modern synthesis" model of evolution as "a change in the frequency of an allele within a gene pool" [15].

Dobzhansky's training and initial research in Russia emphasized the role of the environment in influencing phenotypic traits. The role of the environment in shaping evolution is an area that his most illustrious student, Lewontin continued, as illustrated in Lewontin's book, *The Triple Helix* [33]. However, most other practitioners of the modern synthesis minimized non-Mendelian ideas such as the role of the environment or the inheritance of acquired characteristics. The latter idea was first popularized in 1809 by Jean Baptiste Lamarck [30]. The classic Lamarckian example (although he did not actually use it himself) is that a giraffe has a long neck because successive generations have stretched their necks to eat the leaves on the tops of the trees.

We note that Darwin himself believed in Lamarckian-type inheritance [10]. That is succinctly stated in the last paragraph of *Origin of the Species*, where Darwin proposed that heritable variation stems from "use and disuse" [10]. In Darwin's Lamarck-inspired "pangenesis" hypothesis, he proposed that any environmental phenomenon that affects a parent also affects "gemmules" that transfer through the blood (neuroendocrine hormones?) and accumulate in the male and female reproductive organs [10]. The modified "gemmules" then modify the phenotypes of the progeny in the same manner that the parents' phenotype was modified by the environment [10].

Ironically, it was Darwin's cousin, Francis Galton, who helped "disprove" (at least according to popular sentiment) the "pangenesis" hypothesis. In 1871, Galton transferred massive amounts of blood between two rabbits of different colors and failed to find donor coat color inherited in the progeny [22]. For that and other reasons, Darwin's "pangenesis" hypothesis went quickly out of favor. However, as noted above, one could loosely translate "gemmules" as blood-borne "neuroendocrine hormones," which had not yet been discovered in Darwin's time. Therefore, the "pangenesis" hypothesis can be construed as an 18th century version of a neuroendocrine-mediated evolutionary hypothesis lacking 21st century molecular knowledge.

Despite the ridicule and scorn that such non-genetic ideas still generate in many biologists, recent studies in epigenetic inheritance of traits that are induced by environmental agents has necessitated reconsideration of the controversial ideas of Lamarckian-type inheritance mechanisms. For example, as described in Section 2, much has been learned about the role of epigenetics in cancer initiation and development. Based on the cancer studies, we wish to turn Dobzhansky's quotation on its head and argue that some aspects of evolution make sense only in the light of cancer biology.

2. The role of epigenetics in cancer initiation

Feinberg and colleagues have proposed that cancer has an epigenetic origin [20]. Their hypothesis is summarized in the following quotation:

> [T]umour cell heterogeneity is due in part to epigenetic variation in progenitor cells, and epigenetic plasticity together with genetic lesions drives tumor progression. This crucial early role for epigenetic alterations in cancer is in addition to epigenetic alterations that can substitute for genetic variation later in tumor progression [20].

Feinberg et al. recently proposed an "epigenetic progenitor origin" hypothesis for the development of cancer [20]. They proposed that crucial events in cancer initiation are epigenetic and that further genetic or epigenetic alterations in the DNA or histones can lead to the progression of cancer to more aggressive states. The insight that cancer may be an initially epigenetic disease suggests that morphological evolution, or evolution in general, might also be an initially epigenetic process.

Cancer epigenetics is an active and well-accepted area of research, but the role of epigenetics in evolutionary processes remains controversial. In this section, we attempt to incorporate recent ideas on the epigenetic basis of cancer into a novel "neo-Larmackian" mechanism for rapid morphological evolution. Our model, which we term EDGE (Epigenetically Directed Genetic Error), proposes that heritable epigenetic changes can lead to directed mutations in DNA to stabilize an environmentally induced phenotype. That is, we propose that epigenetic modifications of the DNA or chromatin, such as methylation of the DNA or acetylation or methylation of histones, can lead to mutations in precisely the classes of genes that govern the phenotype during development and consequently increase survival of the organism. The idea is that survival-based selection of "epigenetic marks" on the DNA can lead to cancer progression within the lifespan of an individual or can accelerate changes in morphology or behavior over several generations via "epigenetic assimilation" of a novel phenotype.

In the following sections, we review literature evidence and present new evidence to support the EDGE hypothesis. In the process, we show how the hypothesis can explain aspects of cancer progression within an individual and rapid morphological evolution within a population.

3. The beginning of the EDGE

Barbara McClintock's research on transposon mobilization in maize predated studies on DNA methylation or histone modifications. Nevertheless, she was an early pioneer in suggesting that the environment can affect genome structure. She said:

> 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 [37].