Epigenetic control of mobile DNA as an interface between experience and genome change

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Mobile DNA in the genome is subject to RNA-targeted epigenetic control. This control regulates the activity of transposons, retrotransposons and genomic proviruses. Many different life history experiences alter the activities of mobile DNA and the expression of genetic loci regulated by nearby insertions. The same experiences induce alterations in epigenetic formatting and lead to trans-generational modifications of genome expression and stability. These observations lead to the hypothesis that epigenetic formatting directed by non-coding RNA provides a molecular interface between life history events and genome alteration.

Keywords: mutation, evolution, natural genetic engineering, mobile DNA, viruses, mobile genetic elements, non-coding RNA

INTRODUCTION

Understanding the functional organization of the genome and its evolutionary history are key goals of modern molecular biology. The task has become more interesting and complex as we learn more the details of cell processes involving the genome. Recent applications of high resolution technologies to genome expression in animals reveal a dynamic four-dimensional interactive control architecture incompatible with prior notions that genomes contain discrete functional segments of DNA (“genes”) (Mercer and Mattick, 2013). This review will focus on the role of epigenetic regulation of viruses and mobile genetic elements as a key interface between the activities of these agents of evolutionary change and inputs from cell and organism life histories. The hypothesis developed as a result of the review is that disruption of epigenetic silencing constitutes a major target for life history activation of cellular functions for genome change. This likely occurs after genome replication, possibly by changes in small non-coding (snc) RNAs, typically on the order of 20–50 nucleotides long.

MOBILE DNA IS A MAJOR AND FUNCTIONALLY SIGNIFICANT COMPONENT OF GENOMES

One of the major surprises to come from the initial sequencing of the human genome was the high abundance of dispersed mobile repeat elements (Consortium, 2001). Today, we estimate that at least two-thirds of our genomes is composed of mobile DNA (De Koning et al., 2011). The human genome is not exceptional in its high content of mobile DNA (http://shapiro.bsd.uchicago.edu/TableII.1.shtml).

We increasingly recognize that viruses contribute to cell genomes (Kokosar and Kordis, 2013). They provide sequences for non-coding ncRNAs (Frias-Lasserre, 2012), sites for transcriptional control (Peaston et al., 2004; Dunn et al., 2005; Maksakova et al., 2006; Conley et al., 2008), and elements important in epigenetic regulation (Brunmeir et al., 2010; Conley and Jordan, 2012). Similar transcriptional and epigenetic regulatory contributions are made by mobile genetic elements (http://shapiro.bsd.uchicago.edu/Table5C-1.MobileElementsFoundtobeExaptedascis-RegulatoryControlSitesinAnimals.html) (Youngson et al., 2005; Kinoshita et al., 2007; Suzuki et al., 2007; Fujimoto et al., 2008; Gehring et al., 2009; Pask et al., 2009; Nakayashiki, 2011).

Mobile DNA is a major source of novel coding information. One mechanism is the process known as “exonization,” when splice signals are utilized in newly inserted DNA segments (http://shapiro.bsd.uchicago.edu/Origin_of_New_Protein_Domains.html). New coding sequences also form by reverse transcription of processed RNAs and genome insertion of the cDNAs, sometimes producing chimeric fusions with existing exons (http://shapiro.bsd.uchicago.edu/Table5B. Reports of retrogenes in plant and animal genomes.html) (Long, 2001; Betrán et al., 2002; Fu et al., 2010).

It is now clear that mobile genetic elements play a key role in establishing and rewiring genomic networks (http://shapiro.bsd.uchicago.edu/Table5C-1.MobileElementsFoundtobeExaptedascis-RegulatoryControlSitesinAnimals.html) (Feschotte, 2008; Lindblad-Toh et al., 2011; Lowe et al., 2011; Testori et al., 2012; Kokosar and Kordis, 2013). Moreover, mobile element proliferation is a key factor in the formation of very large genomes (http://shapiro.bsd.uchicago.edu/Genome_Size.html).

The potential functional importance of distributed mobile DNA in genomes grows rapidly as evidence accumulates for pervasive genome transcription (http://shapiro.bsd.uchicago.edu/PervasiveGenomeTranscription.html) and for the regulatory role of non-coding RNAs (ncRNAs) in genome expression, including the functional juxtaposition of distant genome regions to activate transcription (http://shapiro.bsd.uchicago.edu/NonCodingRNAinGenomeExpression.html). Mobile elements participate in this long-range genomic communication and provide the sequences of many ncRNAs (Kapusta et al., 2013).
CELLS USE RNA-TARGETED EPGENETIC CONTROL TO INHIBIT THE ACTIVITY OF MOBILE DNA

Given the high content of mobile DNA in many genomes, an important question is: what prevents all the mobility systems from destroying genome integrity? In eukaryotic cells, a major control mechanism is sncRNA-directed epigenetic formatting into silent chromatin (Law and Jacobsen, 2010; Castel and Martienssen, 2013).

Both prokaryotes and eukaryotes have systems for capturing fragments from invading DNA molecules and placing the fragments into special loci encoding sncRNAs (Dumesic and Madhani, 2014). In prokaryotes, these loci are called CRISPRs (clustered regularly interspersed palindromic repeats) (http://shapiro.bsd.uchicago.edu/CRISPRs.html) (Marraffini and Sontheimer, 2010; Garrett et al., 2011; Bikard and Marraffini, 2013; Watanabe et al., 2013). The RNA transcripts from CRISPRs are processed into sncRNAs that target cleavage of homologous invading DNA and also inactivation of complementary mRNA (Djordjevic et al., 2012). The details of the RNA processing and interference activities are well-characterized, but the acquisition of DNA fragments is poorly understood. The process must be very rapid, because viral infection yields cells that survive the initial infection with appropriate fragments added to their CRISPR repertoire (Barrangou et al., 2007).

Virtually all eukaryotes investigated, with the notable exception of budding yeast, have mechanisms for sncRNA-directed chromatin silencing. They are based on members of the Argonaute family of sncRNA-processing proteins (http://shapiro.bsd.uchicago.edu/microRNA-directedchromatininsilencing.html). Plants and animals have independently evolved distinct mechanisms of processing the sncRNAs for the Argonaute family systems, but both groups use targeted epigenetic regulatory processes to defend against virus infection (Ding and Voinnet, 2013; Watanabe et al., 2013). The RNA transcripts from CRISPRs are processed into sncRNAs that target cleavage of homologous invading DNA and also inactivation of complementary mRNA (Djordjevic et al., 2012). The details of the RNA processing and interference activities are well-characterized, but the acquisition of DNA fragments is poorly understood. The process must be very rapid, because viral infection yields cells that survive the initial infection with appropriate fragments added to their CRISPR repertoire (Barrangou et al., 2007).

LIFE HISTORY EVENTS DESTABILIZE GENOMES AND ACTIVATE MOBILE DNA

Anyone who has studied real-time genome changes quantitatively knows that mutation frequencies depend upon the treatment of the experimental organism prior to measurement. A wide variety of life history events influence the natural genetic engineering (NGE) functions that generate mutations, especially mobile elements (Table 2; Shapiro, 2011). In some cases, the genome instabilities are large scale and last multiple cell or organismal generations.

Many observations demonstrate responses of the circuits controlling NGE functions to biological and abiotic inputs. It is particularly significant that many such responses occur following exceptional cell interactions with viruses or with other cells, either by infection or by hybridization (Table 2). As we might expect, the introduction of alien DNA or chromatin into a cell often has disruptive effects on genome homeostasis (Shapiro, 2014).

| Organisms | sncRNA targets | References |
|-----------|---------------|------------|
| Plants    | Transposable elements | Rigal and Mathieu, 2011; Ng et al., 2012; Nuthikattu et al., 2013 |
| Arabidopsis | Retrotransposons | Mrouze et al., 2009; Slottkin, 2010 |
| Rice      | Retrotransposons | Tian et al., 2011 |
| Brassica  | Retrotransposons | Zhang et al., 2013 |
| Arabidopsis | Transposable elements | Mccue et al., 2012 |
| Maize     | Transposable elements | Barber et al., 2012; He et al., 2013 |
| Plants    | Viruses and viroids | Navarro et al., 2009; Pantaleo, 2011; Zhu and Guo, 2012; Ramesh et al., 2014 |
| Rice, tobacco and Laodelphax striatellus insect vector | Rice stripe virus | Xu et al., 2012b |
| Arabidopsis | Geminiviruses | Vanitharani et al., 2005; Raja et al., 2014 |
| Caenorhabditis elegans germ-line | Transposons | Sijen and Plasterk, 2003; Buckley et al., 2012; Lee et al., 2012 |
| Drosophila | Viruses | Van Rij et al., 2006 |
| Drosophila somatic cells | Retrotransposons | Kawamura et al., 2008 |
| Drosophila male germ-line | Retrotransposons | Kalmykova et al., 2005 |
| Drosophila female germ-line | Transposons, retrotransposons and retroviruses | Brennecke et al., 2007, 2008 |
| Drosophila female germ-line | Telomeric retrotransposons | Shpiz et al., 2009 |
| Drosophila gonads | Transposons | Sienski et al., 2012 |
| Drosophila somatic and germ-line cells | Transposons, retrotransposons and retroviruses | Handler et al., 2013 |
| Drosophila tissue culture cells | Transposons | Chung et al., 2008 |
| Shrimp    | White spot syndrome DNA virus | Huang and Zhang, 2013; Sabin and Cherry, 2013 |
| Mammalian cells | EMCV and NoV RNA viruses | Maillard et al., 2013 |
| Human tissue culture cells | LINE retrotransposons | Yang and Kazazian, 2006 |

EPigenetic changes in response to life history events

One of the most active research areas in the second decade of the 21st century is analyzing the impact of life history events on the epigenetic layers of cell regulatory architecture (Table 3) (Chinnusamy and Zhu, 2009a; Vandegehuchte and Janssen,
Table 2 | Life history events that lead to genome destabilization (see also http://shapiro.bsd.uchicago.edu/TableII.8.shtml for earlier references).

| Organism       | Life history event                                      | Genome instability                                                                                       | References                                                                 |
|----------------|---------------------------------------------------------|---------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Plant          | Polyploidization                                        | Transposon and retrotransposon activation                                                              | Bento et al., 2013                                                        |
| Rice           | Introgression from wild rice (Zizania)                  | Genome-wide variation of all kinds, including transposon reactivation and transgenerational mobile element activation | Wang et al., 2009, 2010, 2013b                                              |
| Apple          | Polyploidization                                        | Aneuploidy                                                                                              | Considine et al., 2012                                                     |
| Brassica       | Intergenetic hybridization; genome triplication; allopolyploidization | Retrotransposition; loss of tandem arrays; Homoeologous shuffling and chromosome compensation        | Xiong et al., 2011; Fang et al., 2012; Zhang et al., 2013                  |
| Wheat, rye     | Allopolyploidization                                    | Loss of repetitive and non-coding DNA, including chromosome-specific sequences; transposon and retrotransposon activity | Bento et al., 2008, 2010, 2013; Kraitshtein et al., 2010; Yaakov and Kashkush, 2011b, 2012; Feldman and Levy, 2012; Tomas et al., 2012; Luo et al., 2012; Martis et al., 2013 |
| Sunflower      | Polyploidization                                        | Chromosome rearrangements                                                                                | Lim et al., 2008; Chester et al., 2012                                    |
| Plants         | Polyploidization                                        | Rapid genome reshuffling                                                                                 | Tayale and Parisod, 2013                                                   |
| Plants         | Polyploidization                                        | Meiotic and fertilization abnormalities                                                                  | Grandont et al., 2013                                                     |
| Animals        | Polyploidization                                        | Meiotic and fertilization abnormalities                                                                  | Bogart and Bi, 2013; Choleva and Janko, 2013; Stenberg and Saura, 2013    |
| Squalius albumoides (Cyprinid fish) | Polyploidization | Rapid genome reshuffling; mobile element activity                                                      | Collares-Pereira et al., 2013                                              |
| Arabidopsis    | Oilseed rape mosaic virus infection                     | Increased homologous recombination                                                                       | Yao et al., 2013                                                           |
| Arabidopsis    | Heat shock                                              | Transgenerational ONSEN retrotransposon activation                                                       | Matsunaga et al., 2012                                                    |
| Arabidopsis    | Volatiles from UV-irradiated Arabidopsis or tobacco plants | Increased homologous recombination                                                                       | Yao et al., 2011                                                           |
| Arabidopsis    | Abiotic stresses (ionizing radiation, heavy metals, chlorine, temperature and water) | Somatic and heritable changes in homologous recombination, strand breakage                               | Boyko et al., 2010; Rahavi et al., 2011; Yao and Kovalchuk, 2011           |
| Tobacco        | Tobacco mosaic virus infection                          | Increased homologous recombination                                                                       | Kathiria et al., 2010                                                      |
| Rice           | Tissue culture cultivation                              | Genomic DNA fragment length polymorphisms                                                               | Wang et al., 2013a                                                        |
| Rice           | Etoposide exposure                                      | Increased transposon activity                                                                            | Yang et al., 2012                                                         |
| Human          | Human papillomavirus (HPV) integration                  | Extensive rearrangements, often focused on insertion site                                               | Korzeniewski et al., 2011; Akagi et al., 2014                              |

The observed epigenetic responses include alterations to cytosine methylation in DNA (Chinnusamy and Zhu, 2009b), histone modifications in nucleosomes, and snRNAs (Ruiz-Ferrer and Voinnet, 2009; Ng et al., 2012) as well as transgenerational inheritance of complex novel phenotypes (Zucchi et al., 2012), frequently induced by stress (Boyko and Kovalchuk, 2010). The phenomenon of hybrid vigor, or heterosis, is increasingly viewed as an alteration in snRNA-targeted epigenetic formatting stimulated by the encounter of two distinct genome control regimes (Groszmann et al., 2011; Miller et al., 2012; Shivaprasad et al., 2012). Many of the studies demonstrating induced epigenetic modifications also document accompanying genome instabilities and emphasize their evolutionary potential (Madlung and Wendel, 2013). It is noteworthy that many of the same stimuli are involved in both genomic and epigenetic responses in plants (Hegarty et al., 2013) and animals (Arkhipova and Rodriguez, 2013). The common stimuli include infection and symbiosis (Hamon and Cossart, 2008; Bierne et al., 2012; Takahashi, 2014), hybridization and changes in ploidy.

**DIRECT INTERACTIONS BETWEEN NGE ACTIVITIES AND EPIGENETIC REGULATORY FUNCTIONS**

In addition to disruption of snRNA-targeted inhibition, there is limited but growing evidence that NGE functions acting on DNA molecules interact directly with epigenetic control factors. There is convincing evidence of the connection between NGE and the epigenome in DNA damage repair and retroviral or retrotransposon insertions into chromosomes.

**EPIGENETIC INVOLVEMENT IN DNA PROOFREADING AND REPAIR**

There are recent reports that a specific histone modification (H3K36me3) primes DNA mismatch repair (Schmidt and Jackson, 2013), that H3K56 acetylation affects mismatch repair (Kadyrova et al., 2013), that hypoacetylation of H3K56 by HDACs 1 and 2 facilitates recruitment of non-homologous end-joining mechanisms.
### Table 3 | Life history events that induce epigenetic changes (see also http://shapiro.bsd.uchicago.edu/TableII.10.shtml for earlier references).

| Organism | Life history event | Epigenetic change | References |
|----------|-------------------|-------------------|------------|
| Plants  | Hybridization, polyploidization | sncRNA changes | Ng et al., 2012 |
| Maize   | Hybridization | rasRNA variation | Barber et al., 2012 |
| Cotton  | Allotetraploidization | Changes in mi- and siRNA content and levels | Pang et al., 2009 |
| Brassica napus | Intertribal hybridization and introgression | Changes in cytosine methylation | Zhang et al., 2013 |
| Wheat   | Allopolyploidization | Multigenerational transposon methylation changes | Kraitshtein et al., 2010; Yaakov and Kashkush, 2011a,b |
| Wheat   | Hybridization and polyploidization | Deregulation of sncRNAs | Kenan-Eichler et al., 2011 |
| Solanaceae | Interspecific grafting | DNA methylation changes | Wu et al., 2013 |
| Tobacco | Geminivirus and geminivirus-beta satellite infection | Suppression of DNA methylation-base silencing | Vanitharani et al., 2005; Buchmann et al., 2009; Yang et al., 2011 |
| Tobacco | Tobacco mosaic virus infection | Heritable resistance to viral, bacterial and fungal pathogens | Kathiria et al., 2010 |
| Rice    | Drought exposure | Multigenerational DNA methylation changes | Zheng et al., 2013 |
| Rice    | Nitrogen deprivation | Heritable stress tolerance | Kou et al., 2011 |
| Rice    | Tissue culture cultivation | DNA methylation changes | Fukai et al., 2010; Wang et al., 2013a |
| Rice    | Etoxoside exposure | Multigenerational DNA methylation changes | Yang et al., 2012 |
| Rice    | Salt exposure | DNA methylation changes | Karan et al., 2012 |
| Rice    | Heavy metal exposure | Multigenerational DNA methylation changes | Ou et al., 2012 |
| Rice    | Abiotic stresses | Novel sncRNAs in the inflorescences | Barrera-Figueroa et al., 2012 |
| Pear seeds | Desiccation | DNA methylation changes | Michalak et al., 2013 |
| Arabidopsis | Interspecific hybridization | Polycomb response complex changes | Burkart-Waco et al., 2013 |
| Arabidopsis | Geminivirus (Cabbage leaf curl virus, CaLCuV) infection | Epigenetic silencing | Aregger et al., 2012 |
| Arabidopsis | Stress response | Alteration of Athila family retrotransposon sncRNA | McCue et al., 2012 |
| Arabidopsis | Biotic stresses (bacteria, hormones) | Increased DNA methylation | Down et al., 2012 |
| Arabidopsis | β-amino-butyric acid | Imprinted resistance (multigenational) to Psuedomonas syringae and Hyaloperonospora arabidopsis fungus | Slaughter et al., 2012 |
| Arabidopsis | Salt exposure | DNA methylation, nucleosome composition | Bilichak et al., 2012 |
| Arabidopsis | Hyperosmotic priming | Shortening and fractionation of H3K27me3 islands | Sani et al., 2013 |
| Wild rye | Abiotic stresses | DNA methylation | Yu et al., 2013b |
| Neptune grass | Cadmium | DNA methylation and chromatin patterning | Greco et al., 2012 |
| Plant and mammalian cells | Cadmium | DNA methylation and histone modification | Wang et al., 2012 |
| Nematode (Caenorhabditis elegans) | Flock house virus expression | Transgenerational resistance transmitted by sncRNAs | Rechavi et al., 2011 |
| Mosquito (Aedes aegypti) | Wolbachia infection | Disruption of cytosine methylation | Ye et al., 2013 |
| Carp | Allotetraploidization | Localized hypermethylation | Xiao et al., 2013 |
| Squalius albomoides (fish) | Polyploidization | Alterations in sncRNA patterns | Inacio et al., 2012 |
| Rats | Exposure to dioxin and endocrine disruptors of F0 generation | Transgenerational inheritance of adult onset diseases and sperm epimutations | Manikkam et al., 2012, 2013 |
| Rats | Vinclozolin fungicide exposure of F0 males | Transgeneration changes to physiology, behavior, metabolic activity, and transcriptome in discrete brain nuclei, altered restraint stress responses | Creus et al., 2012 |
| Pigs | Diet supplementation of F0 with methylating micronutrients | Transgenerational inheritance of extra fat and DNA methylation changes | Braunschweig et al., 2012 |
| Mouse neuronal cells | Short-term hypoxia | DNA methylation changes | Hartley et al., 2013 |
| Humans | High fat diet | DNA methylation changes | Jacobsen et al., 2012 |
| Humans | Early life trauma | DNA methylation changes | Labonte et al., 2012 |

(Continued)
phosphorylated form (Rogakou et al., 1998; Kinner et al., 2008).

A key feature of genome repair is that H2AX-marked damaged DNA mobilizes to subnuclear “repair centers” where homologous recombination and NHEJ proteins also localize (Lisby and Rothstein, 2005; Plate et al., 2008; Bekker-Jensen and Maitland, 2010). A role for chromatin in mobilization of damaged DNA has been proposed (Seeber et al., 2013), but multiple sources of evidence are lacking.

**RETROVIRAL AND RETROTRANSPOSON INTEGRASES**

A more extensive case for NG-E-chromatin interactions comes from analysis of retroviral and retrotransposon insertion specificities (Zhang and Mager, 2012). Each type of retrovirus displays a characteristic insertion specificity for its provirus (Leswini et al., 2006). A number of targeting mechanisms involve epigenetic formatting molecules.

In budding yeast, Ty1 retrotransposon integrase contacts an H2A/H2B interface upstream of RNA polymerase III initiation sites (Ball et al., 2012; Bridier-Nahmias and Lesage, 2012; Mularoni et al., 2012). Histone deacetylase Hos2 and Trithorax group protein Set3 stimulate this nucleosome-targeted integration (Mou et al., 2006), and chromatin remodeling factor Isw2p is also implicated (Bachman et al., 2005). In contrast, the Ty5 retrotransposon inserts in silent chromatin, targeted by binding of its integrase to the Sir4 heterochromatin nucleating factor (Xie et al., 2001; Dai et al., 2007; Brady et al., 2008; Baller et al., 2011).

HIV and other lentiviral targeted integration into actively transcribed regions of the genome is associated with transcription-associated histone modifications, including H3 acetylation, H4 acetylation, and H3 K4 methylation, but is disfavored in regions rich in transcription-inhibiting modifications, which include H3K27me3 and DNA CpG methylation (Wang et al., 2007). The specificity results from integrase tethering by the LEDGF/p75 chromatin-binding growth factor (Vanegas et al., 2005; Llano et al., 2006; Ciuffi, 2008; Meehan and Poeschla, 2010; Zheng et al., 2010; Christ and Debyser, 2013). Replacing the LEDGF/p75 domain that interacts with expressed chromatin by the CBX1 domain, which binds histones H3K9me2 or H3K9me3 found in pericentric heterochromatin, targets HIV insertions to silent chromatin regions (Gijbers et al., 2010).

Murine leukemia virus (MuLV) insertion targeting to initiation sites upstream of actively transcribed regions involves integrase interactions with bromodomain proteins BRD2, BRD3, and BRD4 (De Rijck et al., 2013; Gupta et al., 2013; Sharma et al., 2013a). Interestingly, chromatin recognition bromodomain

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**Table 3 | Continued**

| Organism          | Life History Event             | Epigenetic change                          | References                  |
|-------------------|--------------------------------|--------------------------------------------|-----------------------------|
| Humans lymphocytes| Cadmium                        | DNA hypo-methylation                       | Hossain et al., 2012        |
| Human liver cells | Epstein-Bar virus (EBV) infection | Hypermethylation of tumor suppressor loci, DNA methylation changes | Leonard et al., 2011; Kaneda et al., 2012; Queen et al., 2013 |
| Gastric epithelium| Helicobacter pylori infection | DNA methylation, histone and snRNA changes | Tian et al., 2013; Rongrui et al., 2014 |
| Schwann cells     | Mycobacterium leprae infection | Reprogramming to stem cell-like state      | Ding et al., 2010; Alvarez et al., 2013; Chianotti et al., 2013 |

Nucleosome disassembly is probably necessary for certain repair processes (Linger and Tyler, 2007; Amouroux et al., 2010; Gospodinov and Herceg, 2013), and histone modifications affect damage-induced checkpoint signaling (Chen and Tyler, 2008). Once repair is complete, nucleosome modifications are reversed, and H2AX∼P is eliminated from chromatin (Svetlova et al., 2010). So-called “bystander” cells, which are not subjected to DNA damage but are in the same culture as irradiated cells, also display H2AX phosphorylation (Sokolov et al., 2007; Dickey et al., 2009a, 2011).
protein BRD4 antagonizes HIV provirus reactivation (Zhu et al., 2012).

Certain retrotransposons are specifically targeted to centromeres (Wolfrubger et al., 2009; Birchler and Presting, 2012; Tsukahara et al., 2012; Sharma et al., 2013b), which have a special chromatin configuration characterized by centromeric versions of H3 (Henikoff and Dalal, 2005; Vos et al., 2006; Partridge, 2008; Zhang et al., 2008a). Centromeric retrotransposons in rice are highly associated with H3K9me2, a hallmark for heterochromatin (Neumann et al., 2007). Some centromeric retrotransposons encode integrase proteins with histone-binding chromodomains at their carboxy-termini (Neumann et al., 2011). Chromodomains recognize lysine methylation (Blus et al., 2011; Yap and Zhou, 2011; Eisenberg, 2012).

It is probably not coincidental that the most widely distributed group of retrotransposons among all eukaryotic clades are the “chromoviruses,” which are so named because they have chromodomains in their integrase proteins (Gorinsek et al., 2004; Kordis, 2005; Novikov et al., 2012; Weber et al., 2013). A chromodomain has been reported to target fungal chromovirus MAGGY insertions to heterochromatin marked by H3K9me2/methyl (Gao et al., 2008). An integrase chromodomain also participates in activator protein-targeted insertion of fusion yeast retrotransposon TFI upstream of RNA polymerase II transcription start sites (Hizi and Levin, 2005; Chatterjee et al., 2009).

DNA TRANSPONSONS
In contrast with many transposons that interact with nucleosomes, the DNA transposon Hermes inserts preferentially in budding yeast into nucleosome-free regions of the genome (Gangadharan et al., 2010). The widely used P element DNA transposons in Drosophila show targeting (called “P element homing”) by incorporating binding sites for various regulatory factors, including chromatin insulators (Bender and Hudson, 2000; Fujioka et al., 2009) and Polycomb group response elements (Kassis, 2002; Cheng et al., 2012).

EPIGENETIC REFORMATTING AFTER DNA REPLICATION AND ncRNAs AS POTENTIAL AGENTS FOR TRANSMITTING EXPERIENCE TO THE GENOME
While the evidence is increasingly abundant for effects of different life history events on epigenetic states in particular, it is far from clear how those effects occur (Lim and Brunet, 2013). We know very little about the connections between cell sensors and epigenetic reformatting complexes (Erdel et al., 2011; Narlikar et al., 2013). Deciphering those connections is currently an important research goal.

DNA replication provides a key decision point for maintaining or changing chromatin configurations (Poot et al., 2005; Liu and Gong, 2011; Mermod et al., 2011). The replication apparatus must disassemble chromatin for polymerization and then reassemble chromatin once replication is complete. Replication takes place only in dividing cells, and transgenerational inheritance of epigenetic states must involve the proliferating cells that give rise to gametes. Transfer of outside information from somatic tissues to the germline has been reported in mammals (Sharma, 2013; Skinner et al., 2013). And epigenetic windows of susceptibility to environmental insults have been suggested during sperm development (Soubry et al., 2014). Since there is no segregated germ line in plants and eukaryotic microbes, the same cells that experience environmental inputs can also be the progenitors of gametes.

A number of different factors have been found or hypothesized to participate in post-replication chromatin restoration: histone chaperones (Budhavarapu et al., 2013), RNA editing and snRNAs (Savva et al., 2013), chromatin remodeler SMARCAD1 (Mermoud et al., 2011), chromatin assembly factor 1 (Huang and Jiao, 2012), histone chaperon FACT (Winkler and Lugger, 2011) and Swi/Snf complexes (Neves-Costa and Varga-Weisz, 2006; Ryan and Owen-Hughes, 2011; Zhu et al., 2013), and ISWI complexes (Erdel and Rippe, 2011).

One frequently overlooked feature of post-replication reestablishment of epigenetic formatting is where in the nucleus it might occur. Replication takes place in specialized “replication factories” (Vago et al., 2009; Guilhou et al., 2010). Does chromatin reestablishment occur in the same location or does it involve migration of newly replicated DNA segments to distinct subnuclear “chromatin factories,” like the ones that exist in the nucleolus for heterochromatin formation on rRNA-encoding DNA (Guett and Santoro, 2012)? If so, such post-replication relocalization would be guided by the nucleoskeleton and IncRNAs (Merce and Mattick, 2013; Mercer et al., 2013) and might present an attractive target for stress response and sensory input signaling (Weiner et al., 2012).

It is notable that changes to ncRNAs are frequently cited with regard to the impact of life history events on the genome (Sunkar et al., 2007; Khraiwesh et al., 2012; Lelandais-Briere et al., 2012; Nakaminami et al., 2012; Amaral et al., 2013). In the plant literature, there is documentation of numerous ncRNA changes in response to particular biotic and abiotic stress regimes (Table 4).

A number of observations about resistance to biotic and abiotic stresses are consistent with a key role for ncRNA changes in life history responses. Several viruses encode siRNA suppressors to overcome host defenses (Jiang et al., 2012; Omarov and Schlothof, 2012; Guo and Lu, 2013). Transgenic constructs encoding constitutive miRNA expression can lead to salt and drought tolerance in creeping bentgrass (Zhou et al., 2013), to immunity against blast fungus in rice (Li et al., 2014), and in Arabidopsis to greater salt and alkalinity sensitivity (Gao et al., 2011). Acquired aphid resistance in Arabidopsis involves snRNA changes (Kettles et al., 2013), and most acquired stress resistances in plants display transgenerational epigenetic inheritance (Holeski et al., 2012; Luna and Ton, 2012; Slaughter et al., 2012).

SPECULATIVE CONCLUSIONS ABOUT AN EPIGENETIC INTERFACE BETWEEN EXPERIENCE AND GENOME CHANGE
Mobile DNA and other NGE functions are the key agents for adaptively significant changes in genome organization and DNA sequences. The data reviewed and tabulated above establish the importance of RNA-directed chromatin formatting in the regulation and operation of mobile elements, viruses and DNA repair.
functions. In addition, there is a remarkable correlation between the life history events that activate NGE functions to destabilize genomes and those that lead to alteration of chromatin states and DNA methylation patterns.

The preceding observations lead to the plausible hypothesis that epigenetic regulation serves as a key interface between organismal life history and the agents that restructure genomic DNA. This hypothesis is supported by the limited number of cases where empirical observations have established direct molecular connections between NGE functions and components of the epigenetic control system: histones, nucleosomes, and chromatin reformatting complexes.

If, as I expect, further research bolsters the epigenome-NGE correlations and connections documented above, then we need to ask: what components(s) of the epigenetic control apparatus communicate information about experience to NGE operators? We do not know the answer to this fundamental question. However, the data reported in Table 4 indicate that ncRNAs are good candidates for key intermediates in the experience-genome signal transduction process. If this is so, then ncRNAs are logical molecular targets for modulating genome change toward potentially adaptive outcomes. Let us hope that research aimed at examining this proposal deepens our understanding of how life history impacts both epigenetic and genome change operations (Tables 2–4), whether or not my speculation ultimately proves to be correct.

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Table 4 | Changes in non-coding RNAs in response to life history events.

| Stress or input                  | Organism(s)                | References                                                                 |
|----------------------------------|----------------------------|-----------------------------------------------------------------------------|
| Salt                             | Multiple plants            | Ding et al., 2009; Qin et al., 2011; Macovei and Tuteja, 2012; Carnavale    |
| Drought                          | Multiple plants            | Bottino et al., 2013; Li et al., 2013; Ren et al., 2013; Zhuang et al., 2014 |
| Waterlogging                     | Maize, poplar              | Zhang et al., 2008b; Liu et al., 2012; Ren et al., 2012; Zhai et al., 2013  |
| Cold stress                      | Wheat                      | Tang et al., 2012                                                           |
| Aluminum                         | Soybeans                   | Chen et al., 2012a; Zeng et al., 2012                                       |
| Cadmium                          | Radish                     | Xu et al., 2013                                                             |
| Boron                            | Barley                     | Ozhuner et al., 2013                                                       |
| ethylene                         | *Medicago truncatula*      | Chen et al., 2012b                                                          |
| Ozone                            | *Arabidopsis*              | Iyer et al., 2012                                                           |
| Hypoxia                          | *Arabidopsis*              | Moldovan et al., 2010                                                       |
| Low phosphorous                  | Maize                      | Zhang et al., 2012                                                          |
| Low nitrate                      | Maize                      | Xu et al., 2011                                                             |
| Sulfur deprivation               | *Chlamydomonas reinhardtii* | Shu and Hu, 2012                                                           |
| Abiotic stresses                 | Multiple plants            | Kulcheski et al., 2011; Li et al., 2011b; Barrera-Figueroa et al., 2012; Sun et al., 2012; Zhai et al., 2013; Ballen-Taborda et al., 2013 |
| Physiological stressors and invasive plant infection | Rice blast fungus, *Magnaporthe oryzae* | Raman et al., 2013 |
| Virus infection                  | Multiple plants, rice      | Du et al., 2011; Sha et al., 2014                                           |
| Viral and bacterial infections   | Multiple plants, cassava (*Xanthomonas infection*) | Perez-Quintero et al., 2012; Zvereva and Pooggin, 2012; Pelaez and Sanchez, 2013; Quintero et al., 2013 |
| Bacterial/phytoplasma infection  | Multiple plants, lime trees | Zhang et al., 2011; Ehya et al., 2013                                       |
| Powdery mildew infection         | Wheat                      | (Xin et al., 2011) miRNAs (Xin et al., 2010)                                |
| Verticillium wilt infection      | Cotton, eggplant           | Yin et al., 2012; Yang et al., 2013                                         |
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