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An epigenetic toolkit allows for diverse genome architectures in eukaryotes

Xyrus X. Maurer-Alcalá[1,2] and **Laura A. Katz**[1,2,*]

[1]Department of Biological Sciences, Smith College, Northampton, Massachusetts 01063, USA

[2]Program in Organismic and Evolutionary Biology, University of Massachusetts, Amherst, Massachusetts 01003, USA

Abstract

Genome architecture varies considerably among eukaryotes in terms of both size and structure (e.g. distribution of sequences within the genome, elimination of DNA during formation of somatic nuclei). The diversity in eukaryotic genome architectures and the dynamic processes that they undergo are only possible due to the well-developed nature of an epigenetic toolkit, which likely existed in the Last Eukaryotic Common Ancestor (LECA). This toolkit may have arisen as a means of navigating the genomic conflict that arose from the expansion of transposable elements within the ancestral eukaryotic genome. This toolkit has been coopted to support the dynamic nature of genomes in lineages across the eukaryotic tree of life. Here we highlight how the changes in genome architecture in diverse eukaryotes are regulated by epigenetic processes by focusing on DNA elimination, genome rearrangements, and adaptive changes to genome architecture. The ability to epigenetically modify and regulate genomes has contributed greatly to the diversity of eukaryotes observed today.

Epigenetic mechanisms regulate gene expression, modify genome structures, silence mobile genetic elements, and are widespread among eukaryotes, suggesting that at least some were present in the last eukaryotic common ancestor [LECA; 1,2–4]. For example, the RNAi pathway that is involved in the post-transcriptional regulation of transposable elements (TEs) also plays a role in guiding large-scale chromatin remodeling processes such as *de novo* DNA methylation in plants [5,6] and diatoms [7], as well as in modifying histones [8,9]. Evidence for transgenerational epigenetic inheritance, a concept the emerged from Barbara McClintock's discovery of the impact of transposable elements (TEs) on phenotypes in corn, is now well established in plants and animals where it often involves chromatin modifications [10]. While less is known about microeukaryotic lineages, there is a growing body of literature suggesting that epigenetic processes underlie the structure and function of genomes in diverse lineages.

*Corresponding author: Laura A. KATZ, Department of Biological Sciences, Smith College, 44 College Lane, Northampton, Massachusetts 01063, USA, Phone: +1 (413) 585-3825, Fax: +1 (413) 585-3786, lkatz@smith.edu.

One hypothesis for the proliferation of epigenetic mechanisms in eukaryotes is that they evolved first to manage genome conflict that resulted from the expansion of TEs and then became coopted for other uses [11]. Silencing of TEs can be done post-transcriptionally or through heterochromatin formation targeting mobile elements [12,13], and both require epigenetic mechanisms that are now deployed more generally throughout the genome. As described below, several eukaryotic lineages have managed to reduce the negative impact of TEs through developmentally regulated genome rearrangements, which include the loss of 'germline-specific' genome sequences during the generation of somatic nuclei [14]. Other lineages have coopted epigenetic mechanisms to regulate gene expression and nuclear architecture [15,16].

Here we describe the links between epigenetic mechanisms and the diversity of genome architectures in lineages from across the eukaryotic tree of life. Available data are most abundant for plants, animals and fungi, and we discuss only select data from these multicellular lineages as reviews exist to cover many topics within these clades [17–19]. Data from the rest of the eukaryotic tree of life are patchy, and come largely from model lineages (e.g. ciliates), and parasites and pathogens (e.g. *Entamoeba, Plasmodium, Phytophthora)*. We are confident that examples of the roles of epigenetic processes in shaping genomes will only expand as poorly-sampled lineages receive greater scrutiny. We also believe that the value of this review includes highlighting the exceptions to biological principles (e.g. the concept of a static genome within species) that emerge from studies of diverse eukaryotic lineages.

Diversity of eukaryotic genome contents

Understanding the impact of epigenetic processes in eukaryotes requires an appreciation of the tremendous variation in size and content of eukaryotic genomes [11]. This is perhaps best exemplified by the C-value paradox whereby genome size is highly variable and does not obviously correlate with any measure of complexity, particularly in eukaryotes [11,20,21]. Among eukaryotes, size variation can be extreme with genomes ranging from only 2.3 Mbp in the microsporidian fungus *Encephalitozoon intestinalis* (Opisthokonta; Fungi) [22], 3 Gbp in *Homo sapiens* (Opisthokonta; Metazoa) [23], to over 20 Gbp in the gymnosperm *Pinus taeda* (Loblolly pine; Plantae [24]) and an estimated 670 Gbp in the *Amoeba dubia* (Amoebozoa) [25]. Variation in the number of TEs is one factor that contributes to variation in genome sizes, with the proportion of transposable elements comprising more than 50% of the genome content in some lineages [11]. Transposable elements are rare in other lineages including the ancient-asexual Bdelloid rotifers (Opisthokonta; Metazoa) [26] and the somatic macronuclei of ciliates (SAR) [27] where they comprise less than 10% of the genome.

DNA elimination in establishing somatic genomes

One example of epigenetic control of eukaryotic genome structure can be seen in the purging of portions of the genome during the development of somatic nuclei. This distinction between germline and somatic nuclei defines both animals and ciliates, and is also found in a subset of foraminifera (Figure 1) [28].

Distinct germline and somatic genomes in animals

Beyond simply differing between haploid and diploid, multiple non-sister animal lineages generate somatic genomes with distinct contents that often includes reduced levels of TEs and other repetitive elements (Figure 1)[14]. During early animal development, the germline genome is physically sequestered into specialized tissues where it often remains heavily heterochromatinized for much of the life cycle [29,30]. The loss of germline-specific DNA, also described as chromatin diminution, has been documented in a diversity of non-monophyletic animal lineages [14] and molecular details have been worked out in ascarid worms [31], copepods [32], and in early-diverging vertebrates (i.e. hagfish and lampreys) [33–35]. In copepods, for example, the zygotic genome expands through successive rounds of endoreplication and/or TE proliferation [32,36,37], which is then followed by large-scale elimination of germline-limited sequences [37]. In *Cyclops kolensis* (Opisthokonta), the genome is amplified from ~ 1 Gbp up to ~75 Gbp [37]. Recently, Sun et al. [36] sequenced portions of both the somatic and germline genomes of *Mesocyclops edax* (Opisthokotna) revealing that TEs are rare in the somatic genome, and younger (i.e. less degenerate) TEs appear to be more effectively eliminated (absent) from the somatic genome [36]. Given the broad distribution of examples of DNA elimination during the formation of somatic nuclei in lineages across the animal tree of life [14], we suspect that this process may be even more widespread and may have evolved as a means of managing the genome conflict introduced by the invasion of TEs.

Distinct germline and somatic genomes in ciliates

Ciliates are marked by the presence of distinct germline and somatic genomes within a shared cytoplasm. Because of mechanistic similarities in some elements of chromosome processing, Klobutcher and Herrick [38] argued that nuclear dualism in ciliates arose as a means of eliminating TEs from the somatic genome (Figure 1; SAR). The somatic macronucleus harbors gene-rich chromosomes that are the result from developmentally regulated genome processing following conjugation (i.e. sex). These processes include DNA elimination, genome rearrangements and genome amplification [39,40]. In contrast, the germline micronucleus is enriched in repetitive regions that interrupt gene-coding regions [27,39]. Many of these repetitive regions harbor signatures of TEs, suggesting that an ancient proliferation of TEs was counterbalanced by the evolution/cooption of mechanisms for DNA elimination of germline-limited sequences during somatic development [38,41]. For example, a domesticated PiggyBac transposase (i.e. PiggyMAC) is responsible for excision of germline-limited DNA, effectively deleting TEs from the somatic genome.

The molecular mechanisms behind genome reduction have been worked out in some ciliate lineages and involve a suite of epigenetic players [42–44]. In the model ciliate *Tetrahymena thermophila* (SAR), which only eliminates ~30% of its germline genome, small RNAs are enriched in germline specific sequences and are believed to serve as scan RNAs during the development of the somatic nucleus [45]. In contrast, the ciliate *Stylonychia lemnae* (SAR), which eliminates >90% of its germline genome, small RNAs appear to target somatic sequences to be kept [46]. These same small RNAs also contribute to heterochromatin formation, by guiding repressive histone modifications [44] and DNA methylation [47] in regions to be eliminated.

Transposable elements, epigenetics, and the potential for adaptation

The idea that epigenetic mechanisms evolved at least in part as a means of silencing transposable elements is well-established and has been reviewed elsewhere [19,48,49]. Some well documented examples of epigenetic silencing of transposable elements include: RNA-directed *de novo* DNA methylation in plants and diatoms [50,51], repeat-induced point mutations in fungi [52], and small RNA guided transposon silencing in animals [53]. Despite the ability of diverse eukaryotes to effectively 'purge' or silence TEs throughout development, TEs and their associated processing/silencing in genomes can also play an adaptive role [10,11,54] and perhaps even influence patterns of speciation [55]. For example, cell-to-cell heterogeneity and life stage specific control of gene expression – both of which are categorized as stochastic developmental variation –are underlain by epigenetic modifications to chromatin and have been argued to be adaptive in lineages as diverse as bacteria, yeast, animals, plants, apicomplexa, ciliates, green algae, slime molds, and choanoflagellates [56–59]. The broad distribution of stochastic developmental variation among lineages of bacteria, archaea and eukaryotes suggests that this phenomenon may have been present in the last universal common ancestor [LUCA; 58].

Epigenetic mechanisms and expansive TE burden in plants

The prevalence of TEs in plants led to the concept that a diverse epigenetic toolkit evolved for genome defense from TEs and viruses [60], and that this toolkit has become part of an adaptive, TE-mediated response to stress [61,62]. The diverse suite of epigenetic mechanisms in plants can been attributed to the large portion of genomes comprised of both functional TEs and repetitive elements (i.e. degraded TEs; >80% in some plants such as *Zea mays*; Plantae [63]). Silencing of TEs in plants occurs through RNA-directed DNA methylation, where transcribed TEs are processed into the small RNAs that guide their own *de novo* methylation [64,65]. During non-stressed growth, epigenetic proteins ensure the maintenance of heterochromatin and genomic stability in the vast TE rich chromosomal regions [66,67].

Evidence for the adaptive impact of TEs in adaptive responses in plants has emerged in recent decades. Upon abiotic stress in *Arabidopsis* (Plantae), TE activity increases measurably, leading to distinct changes in genome organization through both homologous recombination and copy number variation of TEs and protein coding genes [62,68]. Interestingly, these effects are heritable through multiple generations of progeny, suggesting the possibility that this response is adaptive [62,68,69]. For example, increased rates of homologous recombination are heritable in *Nicotiana tabacum* (tobacco; Plantae), where stress induces global changes in hypermethylation of DNA and loci-specific hypomethylation that allows for recombination [70]. It is possible that the impacts of genome rearrangement are adaptive to some individuals due to beneficial changes in gene regulation or even gene copy number (Figure 1).

Epigenetic modifications of genome structures in eukaryotic parasites

We focus on the role of epigenetics in parasites to exemplify processes in eukaryotic microbes, largely due to the lack of data in non-parasitic lineages; we do recognize that data

are beginning to emerge from lineages such as dinoflagellates, stramenopiles and other marine algae [71–73]. Epigenetic mechanisms play a role in phenotypic plasticity and in the ability of parasites to modify host physiology and behavior [74–77]. Moreover, mechanisms like pathogen-induced chromatin modifications also play a role in bacterial disease [74], suggesting that they may be very ancient.

The apicomplexan parasite *Plasmodium falciparum* (Figure 1; SAR), the causative agent of malaria, relies on epigenetic mechanisms to regulate the transcription of genes necessary for its varying life cycle stages [56,74,78–80]. Transitions between life cycle stages in *Plasmodium* is in part driven by post-translational modifications of histones [56] and in part by large scale reorganization of nuclear architecture [79]. *Plasmodium falciparum* also differentially modifies the expression of the *var* genes that underlie antigenic variation through epigenetic modification of histones in small chromatin domains; the *var* genes are located in subtelomeric regions and their expression is regulated both by localized modification of chromatin and position within the nucleus [56]. Epigenetic mechanisms in the apicomplexan *Toxoplasma gondii* (Figure 1; SAR) have evolved to alter the behavior of one of their hosts, the rat, to make it less fearful of cats, which are the final hosts for the parasite [77].

Life cycle variation is also epigenetically regulated in the parasite *Giardia intestinalis* (Figure 1; Excavata) [81]. Changes in histone acetylation correspond to transition from free-living to encysted states [81]. Another interesting feature about the structure of the *G. intestinalis* genome is the restriction of active retrotransposons to subtelomeric regions [82]. The variation in the number of retrotransposons (and their recombination) may contribute to the variable karyotypes observed among strains of *Giardia* [82–84]. These homologous regions could allow for recombination in the absence of traditional meiosis, providing *Giardia* with an alternative means to generate genomic diversity after the fusion of its two nuclei [84,85].

Another disease-causing group of Excavata, the kinetoplastids (e.g. *Leishmania* and *Trypanosoma;* Figure 1; Excavata), also deploy epigenetic mechanisms in causing disease (e.g. Leishmaniasis, African sleeping sickness) and evading host immune systems. The genus *Trypanosoma* relies on epigenetic modification of VSG (variable surface glycoprotein) genes to evade host immune systems [75], including inducing homologous recombination of VSG genes nestled in subtelomeric regions. Similar to the *var* genes in *Plasmodium*, changes in nuclear position of the active VSG gene initiate changes in chromatin structure (e.g. chromatin condensation) that lead to differential and mono-allelic VSG expression [15]. Beyond altering their own genome, the parasite *Leishmania donovani* (the causative agent of leishmaniasis) is able to induce epigenetic modifications in host macrophages that allow for the successful invasion by the parasite [76].

Epigenetics may also underlie karyotype variation in the genus *Entamoeba* (Figure 1; Amoebozoa), which includes *Entamoeba histolytica,* the causative agent of dysentery [86]. As in *Giardia*, karyotype variation may be generated by recombination between transposable elements within the genome, and may contribute to the ability of *Entamoeba* to escape host immune systems [86]. Adding a further layer of complexity, differential methylation of TEs

in *Entamoeba* has been linked to varying levels of virulence [75,87]. Together, these data indicate the role the epigenetic toolkit plays in virulence of this human pathogen.

Genome architecture also drives patterns of substitutions in the genomes of some eukaryotic lineages. Oomycetes and some filamentous fungi (Figure 1; SAR; Stramenopiles and Opisthokonta; Fungi respectively) have managed to physically partition their genomes into core regions with greater conservation that are interrupted by gene-poor plastic regions[88–90]. This is most apparent in *Phytophthora infestans*, the causative agent in the Irish potato famine, whose 240 Mbp genome is divided unevenly as the regions of conserved 'house-keeping' genes that comprise about 25% of the total genome size. The gene-poor regions that comprise the bulk of the *P. infestans* genome are rich in mobile and repetitive elements and are associated with pathogenicity and epigenetic silencing [89]. This division of function within the *P. infestans* genome behaves almost as two functionally and spatially distinct genomes, and is determined by epigenetic mechanisms. RNAi-mediated heterochromatin formation not only controls the activity of mobile elements but also has major impacts on the transcription of nearby effector genes (more than half of all effector genes in *P. infestans* are within <2kb of a TE) where increasing proximity can alter an effector gene's transcription due to the spreading of heterochromatin from targeted loci [91,92]. The combination of complex epigenetic silencing and the evolutionary impacts of the repetitive genome on gene evolution (e.g. copy number variation, and recombination) contribute to the incredible virulence of the pathogenic oomycetes.

Perspective

Epigenetic mechanisms that regulate transposable elements as part of genome defense have been coopted and contribute to the development of diversity across the eukaryotic tree of life. Eukaryotes share a core epigenetic toolkit (though individual components vary among lineages) comprised of proteins and RNAs that regulate histone and DNA modifications, and that enable RNA scanning mechanisms. These epigenetic processes have expanded among eukaryotic lineages and have enabled eukaryotes to explore diverse genomic landscapes. The resulting epigenetic toolkit provides the basis for the dynamic processes that have contributed to the overall diversity and success of eukaryotic lineages.

Glossary

Endoreplication	Replication of the genome without any following cell division that leads to changes in ploidy
Heterochromatin	Tightly packed chromatin that blocks transcription from occurring and is associated with histone modifications
Histone modification	Post-transcriptional modifications of the histone proteins at varying amino acid residues. The most well known are histone methylation and acetylation, which are often generalized to be repressive and activating modifications, respectively

Macronucleus	Somatic and transcriptionally active nucleus in ciliates. Contains streamlined chromosomes that leack centromeric sequences and are often gene-rich. In some ciliate lineages, processing of germline chromosomes leads to macronuclei with chromosomes coding for single-genes and that can be highly amplified
Micronucleus	The germline nucleus in ciliates that is heterochromatinized and has a more traditional genome architecture (e.g. long chromosomes with centromeric sequences). Micronuclear genomes also contain transposable element sequences that sometimes interrupt protein-coding genes
Stochastic developmental variation	Seemingly random changes in phenotype such as heterogeneity in gene expression among cells. Stochastic developmental variation provides populations with genetic diversity that may allow exploration of adaptive landscapes
Transposable elements	Regions of DNA that are capable of changing their position in the genome

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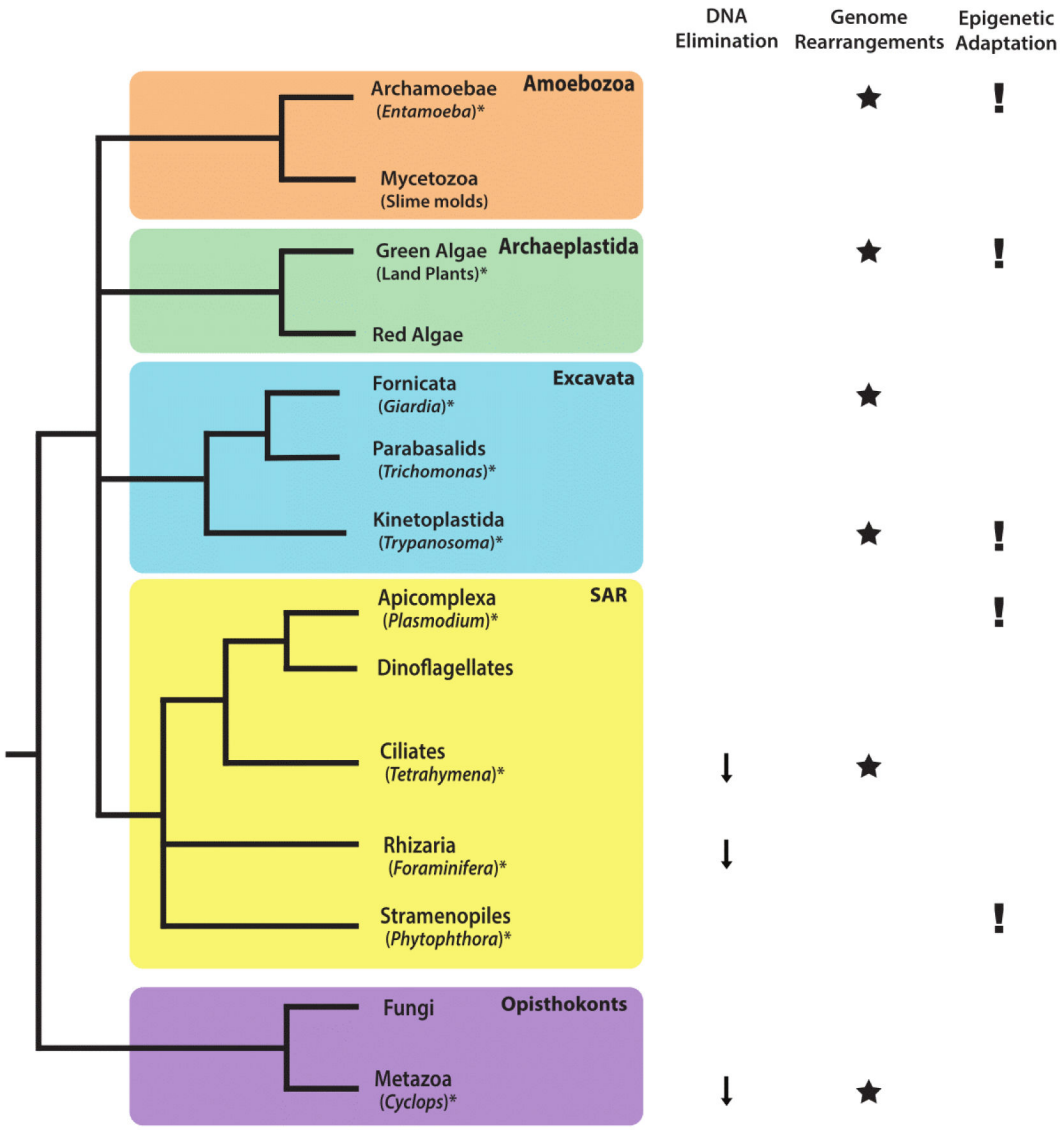

Figure 1.

Distribution of epigenetic processes across the eukaryotic tree of life. These exemplar epigenetically regulated processes are widespread across eukaryotes. Organisms denoted with '*' are discussed in this review.