OPINION: Genetic conflict with mobile elements drives eukaryotic genome evolution, and perhaps also eukaryogenesis.

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Abstract:

Through analyses of diverse microeukaryotes, we have previously argued that eukaryotic genomes are dynamic systems that rely on epigenetic mechanisms to distinguish germline (i.e. DNA to be inherited) from soma (i.e. DNA that undergoes polyploidization, genome rearrangement, etc.), even in the context of a single nucleus. Here, we extend these arguments by including two well-documented observations: 1) eukaryotic genomes interact frequently with mobile genetic elements (MGEs) like viruses and transposable elements (TEs), creating genetic conflict and 2) epigenetic mechanisms regulate MGEs. Synthesis of these ideas leads to the hypothesis that genetic conflict with MGEs contributed to the evolution of a dynamic eukaryotic genome in the last eukaryotic common ancestor (LECA), and may have contributed to eukaryogenesis (i.e. may have been a driver in the creation of FECA, the first eukaryotic common ancestor). Sex (i.e. meiosis) may have evolved within the context of the development of germline-soma distinctions in LECA, as this process resets the germline genome by regulating/eliminating somatic (i.e. polyploid, rearranged) genetic material. Our synthesis of these ideas expands on hypotheses of the origin of eukaryotes by integrating the roles of mobile genetic elements and epigenetics.

Keywords: transposable elements, viruses, epigenetics, eukaryotic diversity, LECA, meiosis

Overview

Based on observations of dynamic genomes (i.e. cyclical polyploidy, genome rearrangements) in diverse eukaryotic lineages, we have previously argued that LECA used epigenetic mechanisms to distinguish germline from somatic DNA, even in the context of a single nucleus (Maurer-Alcala and Katz, 2015; McGrath and Katz, 2004; Parfrey and Katz, 2010; Parfrey, Lahr and Katz, 2008; Weiner*, et al.*, 2020; Zufall, Robinson and Katz, 2005). As discussed in this series of papers from our lab, examples of such germline/soma distinctions include: sequestered germline nuclei in animals, ciliates, and some foraminifera; cyclical polyploidization throughout life cycles of apicomplexans such as *Plasmodium* (the causative agent of malaria); generation of extrachromosomal DNA, including amplification of ribosomal RNA loci in many eukaryotes; developmentally-regulated genome rearrangements, for example trypanosomes and immune cells of vertebrates (i.e. V(D)J recombination); and even the mis-regulation of DNA through polyploidization in cancer cells (Erenpreisa*, et al.*, 2017). Despite this long list, examples of genome dynamics in diverse lineages of eukaryotic microbes are still limited as the bulk of life cycle data come from a small number of model lineages (e.g. *Tetrahymena*, *Plasmodium*). However, promising recent evidence of chromatin extrusion and depolyploidization in *Amoeba proteus* (Goodkov*, et al.*, 2020) suggests that more examples of such dynamics are on the horizon.

We have also argued that germline/soma distinctions in eukaryotes are regulated by epigenetic tools including histone modification, DNA methylation, and scanning by small non-protein-coding RNAs (Maurer-Alcala and Katz, 2015; Parfrey and Katz, 2010; Parfrey*, et al.*, 2008; Weiner*, et al.*, 2020; Zufall*, et al.*, 2005). Here, we extend this hypothesis by combining it with two observations: 1) the widespread occurrence of MGEs (e.g. transposable elements (TEs), viruses) and 2) data on the epigenetic regulation of MGEs within eukaryotes. Synthesis of these observations leads to the hypothesis that genetic conflict has shaped the evolution of eukaryotic genomes and, as others have also argued (e.g. Aravind*, et al.*, 2012; Havird*, et al.*,

2019; Koonin, 2017; Massey and Mishra, 2018), perhaps the evolution of eukaryotes themselves.

Mobile Genetic Elements are Widespread

The function and abundance of mobile genetic elements such as viruses and TEs has been extensively reviewed, and we provide only a few highlights here. Transposable elements are present in genomes across the tree of life (e.g. Campbell, Aswadl and Katzourakis, 2017; Kejnovsky, Hawkins and Feschotte, 2012; Kidwell and Lisch, 2001; Suzuki and Bird, 2008) and can constitute more than half the genome of many eukaryotic lineages (e.g. Fedoroff, 2012; Kazazian, 2004; Song and Schaack, 2018). Viruses are the most abundant biological entities on Earth (e.g. Edwards and Rohwer, 2005; Koonin, 2017), and, like TEs, they are able to integrate into eukaryotic genomes (Chalker and Yao, 2011; Koonin, 2017; Song and Schaack, 2018).

Though early studies characterized MGEs as 'parasitic' and/or 'selfish' because of the harm they can cause to host genomes, it is now clear that MGEs also generate novel genetic variation that can be the source of adaptation (e.g. Fedoroff, 2012; Koonin and Krupovic, 2018). Some of the damage TEs can cause include mutations, DNA breaks, and rearrangement of chromosomes as they move through host genomes (e.g. Fedoroff, 2012; Kazazian, 2004; Parhad and Theurkauf, 2019). Similarly, rapid evolution and replication of viruses creates an 'arms race' with host genomes evolved to eliminate them (e.g. Bruscella*, et al.*, 2017; Koonin and Krupovic, 2018). Consequently, replication and mobilization of MGEs is a substantial source of genetic variation in eukaryotes, and these abilities allow MGEs to both resist elimination and create an immediate and lasting impact on host evolution (e.g. Campbell*, et al.*, 2017; Kidwell and Lisch, 2001; Koonin and Krupovic, 2018; Schaack, Gilbert and Feschotte, 2010).

Mobile Genetic Elements are Regulated by Epigenetics

Epigenetic mechanisms are key for eukaryotic responses to MGEs (e.g. Campbell*, et al.*, 2017; Levine*, et al.*, 2016; Parhad and Theurkauf, 2019; Song and Schaack, 2018). In many cases, epigenetic responses protect the host's germline by limiting TE mobilization (Chung*, et al.*, 2008; Parhad and Theurkauf, 2019; Suzuki and Bird, 2008). *Drosophila* exemplify this through expansion of the *HP1D* gene family, which silences TEs in the female germline (Levine*, et al.*, 2016). While under epigenetic regulation, TEs display a spectrum of fitness effects within host genomes from parasitism to mutualism (Cosby, Chang and Feschotte, 2019; Kidwell and Lisch, 2001; Vogt*, et al.*, 2013). This relationship can also change over time as the epigenetic systems that regulate them evolve such that transposons may ultimately become domesticated (e.g. neutral or used for host function, Cosby*, et al.*, 2019; Doyle and Coate, 2019; Kidwell and Lisch, 2001; Piegu*, et al.*, 2015; Vogt*, et al.*, 2013).

Epigenetic mechanisms can also regulate viruses within eukaryotic genomes. Endogenous retroviruses, like transposable elements, occur at various levels of mobility and can be epigenetically regulated *via* processes like histone methylation (Collins*, et al.*, 2015; Manghera and Douville, 2013; Meyer*, et al.*, 2017). Viruses have also been observed to regulate their replication cycles through epigenetic mechanisms of their own (Balakrishnan and Milavetz, 2017; Bruscella*, et al.*, 2017; Woellmer and Hammerschmidt, 2013). The human Epstein–Barr herpesvirus represents one such intimate relationship, as the latent virus is restrained by Polycomb proteins, but in the lytic replication stage, when Polycomb repression is erased, the virus escapes from the methylation network of the host (Woellmer and Hammerschmidt, 2013). This type of multilayered epigenetic relationship reflects the complexity of interactions between viral replication systems and eukaryotic hosts.

Genetic Conflict is Foundational to Eukaryotic Genome Evolution, and Perhaps Eukaryogenesis

The widespread occurrence and epigenetic regulation of MGEs engenders the hypothesis that genetic conflict between host and MGEs led to the evolution of a dynamic eukaryotic genome that distinguishes germline and soma (Fig 1). Genetic conflict, the competitive relationship between MGEs and host genomes, has been well-described as a driving force of evolutionary change (e.g. Hurst, Atlan and Bengtsson, 1996; Massey and Mishra, 2018; McLaughlin and Malik, 2017; Song and Schaack, 2018; Werren, 2011). Hurst et al. (1996) argued for a "gene's-eye view" of such conflict to describe the strategies MGEs and hosts deploy in the struggle over inheritance and proliferation. Nearly two decades later, Song and Schaack (2018) provide an extensive review on the nature of genetic conflict between hosts and MGEs, and the possible mechanisms of resolution. In light of this conflict, we and others (e.g. Aravind*, et al.*, 2012; Fedoroff, 2012; Koonin, 2017) propose that epigenetic mechanisms resulting from interactions with MGEs were likely fundamental to eukaryotic evolution. Indeed, the genetic mechanisms that underlie epigenetic regulation (i.e. the epigenetic toolkit) clearly predate the evolution of eukaryotes (e.g.Oliverio and Katz, 2014; Weiner*, et al.*, 2020), though the specific machinery may have been replaced and/or elaborated over time (Maurer-Alcala and Katz, 2015). Here, we extend on these ideas by linking them explicitly to the origin of germline-soma distinctions during eukaryogenesis.

Consistent with the idea that genetic conflict between host and MGEs specifically led to distinction of germline and somatic genome material are observations on the differential epigenetic regulation of MGEs in extant lineages. For example, flowering plant pollen possesses the ability to epigenetically regulate and de-regulate transcription of TEs in a cyclical manner (Slotkin*, et al.*, 2009). In animals like *Drosophila,* TEs are silenced in the germline through female-specific RNA silencing mechanisms (Levine*, et al.*, 2016) while a different set of small interfering RNAs regulate TEs in the soma (Chung*, et al.*, 2008). In the nematode

Caenorhabditis elegans, piRNA epigenetic silencing networks suppress TE mobility in germline, and this silencing can be inherited across more than 20 generations (Ashe*, et al.*, 2012). In ciliates, epigenetic mechanisms including small non-protein-coding RNAs and transposases co-opted from transposons are used to shape somatic genomes following conjugation (e.g. Bracht*, et al.*, 2013; Chalker and Yao, 2011; Maurer-Alcala and Nowacki, 2019). The observation of differential epigenetic regulation of MGEs between germline and somatic nuclei in diverse extant eukaryotes raises the possibility that such a mechanism was present in LECA and perhaps even FECA.

A special case of conflict at the origin of eukaryotes stems from the acquisition of mitochondria, an event extensively reviewed in the literature (though there remain debates on the timing and physiology of the events; e.g. Gabaldon, 2018; Lopez-Garcia, Eme and Moreira, 2017; Lopez-Garcia and Moreira, 2019; Martin, 2017; Pittis and Gabaldon, 2016; Wein*, et al.*, 2019). At the time of the acquisition of mitochondria, the chimeric cell had to navigate two distinct genomes in a shared cytoplasm. Certainly, there is evidence of conflict between mitochondria and nuclei of extant organisms; for example, in humans, nucleocytoplasmic conflict can lead to disease (e.g. Cummins, 2001; Havird*, et al.*, 2019) and there are data indicating epigenetic interactions between mitochondria and nuclei (Harvey, 2019). Hence, it is possible that conflict from a single but significant 'mobile' event, the acquisition of an alphaproteobacterial symbiont in FECA, contributed to the invasion/expansion of MGEs (Krupovic and Koonin, 2015) and ultimately the evolution of eukaryotic genome structures.

We suggest that eukaryogenesis resulted in the evolution of a genome that distinguishes germline from soma, which was fueled by genetic conflict between MGEs and hosts (Fig. 1). Our hypothesis does not specify the timing of events between FECA and LECA, nor do we address the origin of the eukaryotic cytoskeleton, the synapomorphy of eukaryotes that allowed for the evolution of diverse morphologies and life histories. Instead, we suggest that germline-soma distinctions evolved as a response to genetic conflict with MGEs and contributed to the

second major epoch of evolution, the origin of eukaryotes with meiotic sex, as described in Bonner (2019). Under such a scenario, the nucleus may have evolved to 'protect' the genome from viruses (e.g. Aravind*, et al.*, 2012; Bell, 2009; Forterre and Gaia, 2016; Hendrickson and Poole, 2018) or may have resulted from selection to separate transcription from translation, allowing excision of mobile elements (Brunk and Martin, 2019; Martin and Koonin, 2006). It may also be the case that the nuclear envelope is just a byproduct of events at the time (i.e. resulting from the chaos of the acquisition of mitochondria with its genome (including its own MGEs), or some other autogenous event).

Sex (i.e. meiosis and syngamy) is argued to be ancestral in eukaryotes based on the widespread distribution of meiotic genes coupled with other evidence (i.e. cell fusion, cryptic sexual cycles) in lineages previously thought to be asexual (Hofstatter, Brown and Lahr, 2018; Lahr*, et al.*, 2011; Tekle*, et al.*, 2017) but see (Maciver, 2019). Kondrashov (1994; 1997) argued that meiosis evolved as a means to regulate polyploid cycles, which are part of what we refer to as somatic genome content (i.e. cyclical polyploidization,along with the generation of extrachromosomal DNA and developmental regulated rearrangements, all represented by the thin lines within the nucleus of LECA in Figure 1). In fact, Kondrashov (1994) suggested that sex may have evolved as a means for 'orderly genetic reduction', which would be required in novel eukaryotic lineages with complex genome dynamics (e.g. Goodkov*, et al.*, 2020; Maurer-Alcala and Katz, 2015; McGrath and Katz, 2004; Parfrey and Katz, 2010; Parfrey*, et al.*, 2008; Weiner*, et al.*, 2020; Zufall*, et al.*, 2005). Despite open questions (e.g. on the timing of events, the origin of nuclear envelope and cytoskeleton), we believe consideration of our hypothesis – that genetic conflict between host and MGEs at the time of the origin of eukaryotes led to dynamic genomes in which germline-soma distinctions are regulated by epigenetics and reset through meiosis – provides an important expansion on models of eukaryogenesis.

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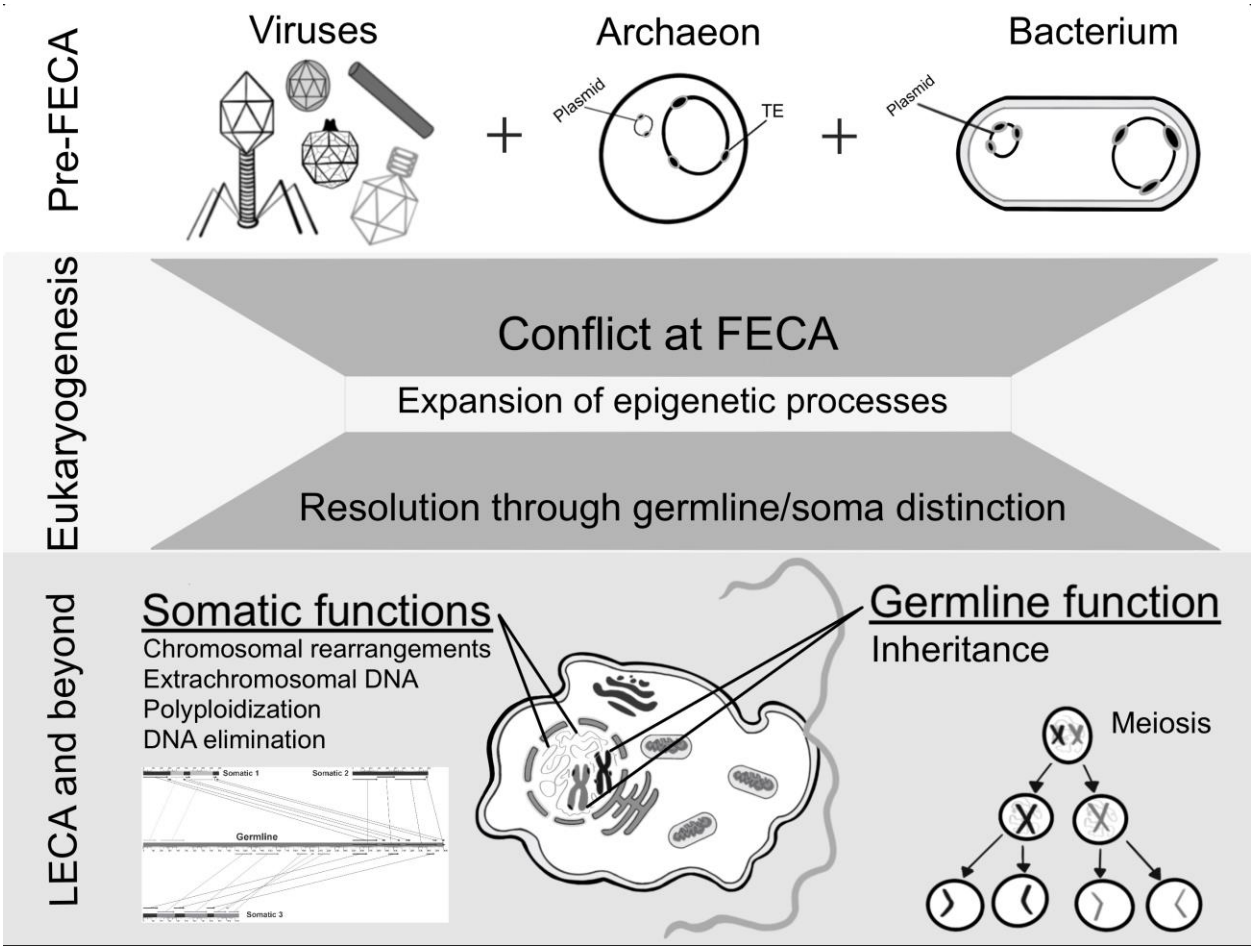

Figure 1. Genetic conflict during eukaryogenesis resulted in epigenetically-regulated germline-soma distinctions in eukaryotes. This figure depicts the players at the origin of eukaryotes, namely the diversity of viruses and the presence of TEs integrated within both bacteria, including the ancestor of mitochondria, and archaea, including the likely host cell of FECA (top panel). Conflict among these genomes and mobile genetic elements (MGEs; middle panel) resulted in eukaryotes that distinguish germline (i.e. marked for inheritance, capable of meiosis to reset genome, represented by the condensed chromosomes in LECA) and somatic (e.g. cyclical polyploidy, extrachromosomal DNA, developmentally-regulated genome rearrangements, DNA elimination, represented by the thinner lines within the nucleus of LECA) material (bottom panel). The inset under the somatic functions in LECA represents three somatic chromosomes generated from a single germline region in the ciliate *Chilodonella uncinata* (redrawn from Gao, Roy and Katz, 2015). Additional details and references can be found in the text.