Transposable elements: Self-seekers of the germline, team-players of the soma

David Haig

The germ track is the cellular path by which genes are transmitted to future generations whereas somatic cells die with their body and do not leave direct descendants. Transposable elements (TEs) evolve to be silent in somatic cells but active in the germ track. Thus, the performance of most bodily functions by a sequestered soma reduces organismal costs of TEs. Flexible forms of gene regulation are permissible in the soma because of the self-imposed silence of TEs, but strict licensing of transcription and translation is maintained in the germ track to control proliferation of TEs. Delayed zygotic genome activation (ZGA) and maternally inherited germ granules are adaptations that enhance germ-track security. Mammalian embryos exhibit very early ZGA associated with extensive mobilization of retroelements. This window of vulnerability to retrotransposition in early embryos is an indirect consequence of evolutionary conflicts within the mammalian genome over postzygotic maternal provisioning.

Keywords:
embryonic stem cells; germ granule; germline; pluripotency; transposable elements; trophectoderm; zygotic genome activation

DOI 10.1002/bies.201600125

Department of Organismic and Evolutionary Biology, Harvard University, Cambridge, MA, USA

Corresponding author:
David Haig
E-mail: dhaig@oeb.harvard.edu

Abbreviations:
BEG, biparentally expressed gene; **MEG,** maternally expressed gene; **PEG,** paternally expressed gene; **PGC,** primordial germ cell; **SS,** sedentary sequence; **TE,** transposable element; **ZGA,** zygotic genome activation.

Introduction

August Weismann distinguished an immortal hereditary substance from the succession of mortal bodies in which the substance temporarily resided [1]. His mature theory of continuity of the germplasm was *not* based on early segregation of germ cells from somatic cells [2]. Germplasm (*Keimplasma*) resided in nuclei of a germ track (*Keimbahn*) that was the cellular path by which germplasm was passed, unchanged, from parents to progeny. Weismann recognised that many organisms derived their germ cells from somatic cells, and that these somatic cells therefore belonged on the germ track and possessed intact germplasm, but he also believed that some somatic cells did not inherit a complete set of determinants, and therefore could not produce functional germ cells. Such cell lineages were cul-de-sacs off the germ thoroughfare [1].

Weismann's arguments are frequently misunderstood because his terms have acquired other meanings. His *Keimbahn* consisted of cells not irrevocably committed to somatic fates, but germline (an alternative translation of *Keimbahn*) now commonly refers to cells committed to production of gametes. Weismann's *Keimplasma* was a *nuclear* substance that contained 'determinants' for all cells of the body, whereas 'germ plasm' now refers to *cytoplasmic* materials that contain 'determinants' of germ cells. Weismann, if he were alive today, would probably recognise the nuclear genome as his germplasm and genes as his determinants.

'Germ track' in this essay will refer to cells that have been ancestors of gametes and can have gametes as descendants. 'Soma' will refer to cells not on the germ track and 'body' to soma plus germ track. Retrospectively, the germ track consists of all cells in which ancestral gene copies have resided as a gene lineage is traced backward through time from a zygote. Prospectively, the germ track consists of all cells derived from a zygote that can produce descendent germ cells. Thus, the planarian germ track includes adult stem cells (neoblasts) that can differentiate as germ cells [3], and the mammalian germ track includes totipotent and pluripotent progenitors of primordial germ cells (PGCs) [4]. The germ track has two segments that alternate each generation: a 'germ-stem' with both somatic and gametic descendants, and a 'germline'

committed to gametes alone (Fig. 1). This concept of the germ track is synonymous with Weismann's *Keimbahn* and with the 'totipotent cycle', 'germline cycle' and 'primordial stem cell hypothesis' of recent authors [5–7].

The partition of the body into germ track and soma marks a key distinction in evolutionary theory. Mutation, selection and genetic drift in the germ track directly affect the genetic constitution of future generations, but equivalent processes in the soma do not. As a consequence, intragenomic conflicts are focused on the germ track. Regulatory networks of the germ track are expected to diverge rapidly between species because of antagonistic coevolution between mobile genetic elements and the rest of the genome. Somatic gene expression is insulated from these conflicts, and evolves to maximise bodily fitness. The soma functions as a locus of calm amid germinal strife.

Somatic cells are sheltered from intragenomic conflicts

Chromosomes are the home of sedentary sequences (SSs) that are long-term residents at their current address, and transposable elements (TEs) that are recent occupants, arrived from elsewhere in the genome. SSs and TEs have a shared interest in their body's somatic survival and germline reproduction, and have been co-residents of a long series of past bodies. As such, they have been important parts of each other's environment, and have adapted to each other's presence but, despite their shared dependence on shared bodies, SSs and TEs propagate by different paths. SSs and TEs replicate when their chromosome replicates and, by this means, transmit their copies to half of a body's gametes. But TEs also disperse copies to new addresses, gaining extra representation amongst gametes (Fig. 2A).

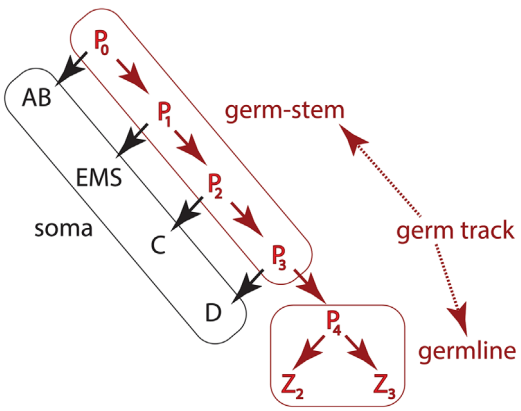

Figure 1. The early divisions of *Caenorhabditis elegans* embryos illustrate concepts used in this paper. The zygote (P_0) gives rise to all the cells of the body. Cells that have germ cells as descendants belong to the *germ track* (represented in dull red). The germ track has two segments: a *germ-stem* that contains cells that also have somatic cells as descendants and a *germline* that produces germ cells alone. Four asymmetric divisions occur in the germ-stem of *C. elegans*. One of the daughter cells from each of these divisions is the progenitor of somatic cells (AB, EMS, C, D) and the other daughter cell remains on the germ track (P_1, P_2, P_3, P_4). P_4 is the first cell of the germline because both of its daughter cells (Z_2, Z_3) are progenitors of germ cells alone.

A TE that inserts a copy at a new address in the germ track, whilst continuing to occupy its old address, increases its representation in the next generation provided that the doubling of copy number within its cell lineage more than compensates for any reduction in cellular or bodily fitness caused by the insertion. Transposition is more likely to reduce than increase the fitnesses of cell lineages in which an insertion occurs, and of bodies that inherit the insertion. All sequences suffer the negative effects of an insertion, but only the inserted sequence gains an advantage. Thus, a TE can spread through a sexual population despite reducing the fitness of the bodies in which it temporarily resides [8].

More formally, a sequence's fitness can be conceptualised as the product of n (the number of successful gametes produced by a body) and p (the sequence's average number of descendent copies per gamete). The fitness of a SS is determined solely by variation in n, because $p = \frac{1}{2}$ is constant, whereas the fitness of a TE is determined by a trade-off in which transposition increases p but decreases n. Roughly speaking, the lineage of a TE benefits from transposition provided that its increment in p is greater than half the proportional decrement in n [9]. By contrast, sedentary lineages experience only the cost from decrements of n. Natural selection can thus simultaneously favour SSs that suppress transposition and TEs that evade these controls.

Transposition in somatic cells does not increase p, but decreases n via deleterious somatic mutations. Once a cell is committed to a somatic fate, all of its genetic residents, both SSs and TEs, have a shared interest in maximizing n and minimizing transposition, because all somatic sequences benefit from bodily survival and germline reproduction, and none gains a benefit, beyond the death of the body, from faster replication than its fellows [10]. The germ track is a congested freeway on which TEs change lanes and cut into the orderly flow of the sedentary genome whilst evading the attention of ubiquitous traffic police. But the quiet byways of the soma can be lightly policed because there are no through roads.

Transposition in the germ track must keep one step ahead of inactivating mutations

TEs have peculiar evolutionary properties. More-active TEs leave more descendants at new addresses (because transposition increases p) but fewer descendants at old addresses (because transposition reduces n). Therefore, adaptations of a mobile lineage must be distinguished from adaptations of the lineage's members (where individual members are defined by chromosomal address).

A mobile lineage jumps from site to site whilst leaving resident copies at each step along the way. Each sedentary copy suffers organismal costs associated with further transposition, but the lineage benefits from colonization of new sites. Natural selection at each site favours eviction (elimination of chromosomes with the TE) or domestication (loss of a TE's ability to transpose). For a mobile lineage to

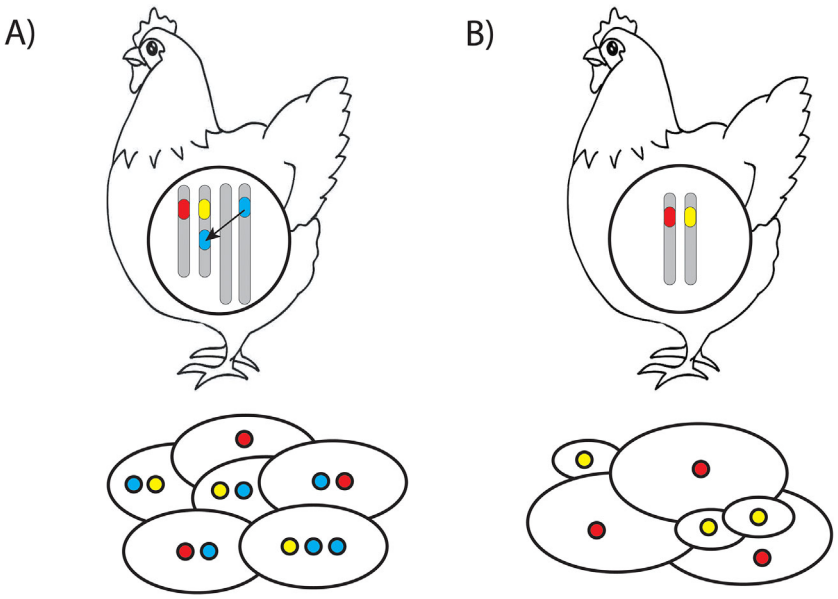

Figure 2. Two ways for a gene to obtain more than its 'fair' share. The two alleles at a parental locus are each transmitted to half of the eggs in a clutch (red and yellow dots). (**A**) A transposable element (blue dot) inserts a copy of itself at a new locus and is transmitted to more than half of the clutch. (**B**) If resources are transmitted to offspring after meiosis, then the red allele can obtain extra resources at the expense of the yellow allele. For simplicity, genes of paternal origin are not represented.

spread through the genome, its copies must transpose to new sites faster than active copies are evicted or domesticated at old sites. During such an expansion, most genomes will possess multiple active TEs that are rare variants at every site they occupy. Mutations that enhance transposition will accumulate along lineages of constantly changing address, whilst mutations that suppress transposition accumulate at every address where a TE resides long-term [11].

Every germ-track insertion creates a new heritable sequence, on a single chromosome in a single cell, subject to the same evolutionary forces as the flanking sequences within which it resides. If an insertion is to spread to most bodies of a population, then it must either provide a selective advantage to its chromosomal segment (perform a bodily function) or be the lucky beneficiary of drift (random sampling of nearly neutral variants) or draft (hitchhiking with a nearby positively selected site) [12]. Despite the odds, substantial proportions of many genomes are descended from formerly mobile TEs. Some of these sequences may perform organismal functions, but most are probably there by chance. The marginal effect on organismal fitness of each slightly deleterious (nearly neutral) insertion may be small – the smaller the marginal effect the greater the chance of fixation – but the cumulative costs of many fixed insertions may be substantial.

If a TE is found at the same chromosomal address in many individuals, then it is unlikely to be active and unlikely to have strongly deleterious effects on bodily fitness. If, in addition, its sequence is conserved over evolutionary time, then the presumption should be that it performs an organismal function. TEs that are common at a chromosomal address have almost universally lost the ability to transpose. Active TEs in inbred model organisms, such as mice, are a possible exception, because rare active elements may have been fixed by chance during close inbreeding [13, 14].

A TE's family tree contains a few vagabonds of no fixed abode, and their bourgeois relatives who have adopted sedentary life styles whilst retaining superficial trappings of a bohemian past (Fig. 3). Transposition is maintained and perfected as an adaptation of the vagabonds, whilst their settled kin degenerate or promote the interests of the sedentary genome. Every recent insert has a claim to membership on both sides of this divide, as a recent migrant who might move again and as a new resident who might settle down. The key evolutionary distinction is between sedentary and currently mobile sequences. Once a sequence has lost the ability to transpose, it is subject to the same desiderata as the rest of the sedentary genome.

Maternal control of early development restricts embryonic transposition

Early embryogenesis often proceeds without zygotic transcription, using stored maternal gene products [15]. Maternal control of embryonic cleavage has been interpreted as an adaptation for rapid development to minimise predation of immobile yolk-filled embryos [16–19]. In this view, oocytes transcribe RNAs and translate proteins in the safety of the ovary, and store them for later use, rather than have these time-consuming processes occur in the vulnerable embryo. Selection for speedy development probably contributed to heavy reliance on maternal stockpiles, but this hypothesis does not explain why zygotic transcription should be repressed, nor why repression should be maintained in the germline after somatic genome activation [20].

Transposition requires transcription and translation. Tight controls are therefore expected over which sequences are transcribed and which proteins translated in the germ track, but strict licensing can be relaxed in somatic cells. Transposition in early embryos is particularly costly because it is a source of both somatic and germline mutations. The absence of transcription during early embryogenesis tightly constrains transposition. For a TE to transpose before zygotic genome activation (ZGA), transposases or reverse transcriptases must be loaded into maternal oocytes or enter eggs via sperm. Stored maternal products will be marshalled against sperm-borne TEs because neither maternal SSs nor TEs benefit from transposition of paternal interlopers. In this contest, maternal SSs and TEs have the strategic advantage of control of the egg cytoplasm and the expected collaboration of paternal SSs in suppressing paternal TEs.

Development of *Caenorhabditis* illustrates differential timing of ZGA in soma and germ track. The germ track

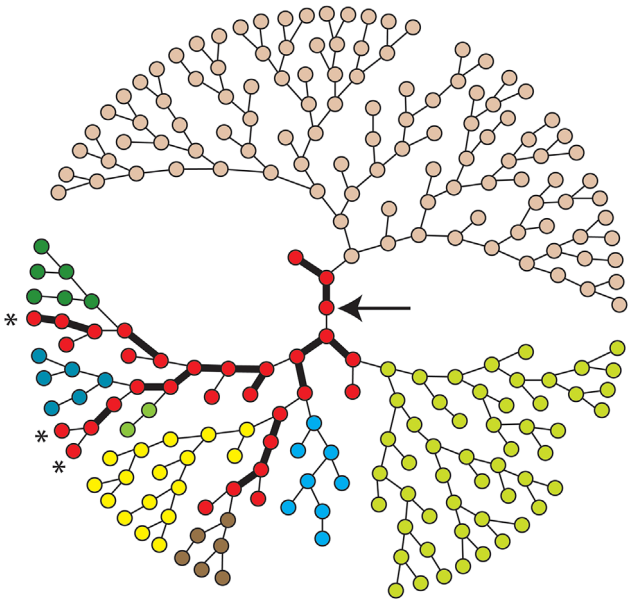

Figure 3. Family tree of transposable elements. The outer circle represents present-day descendants of an ancestral TE (indicated by arrow). Active elements (red circles) mutate to inactive elements (other colours, each representing a different chromosomal location). Active elements replicate faster than inactive elements because of their ability to transpose (changes of chromosomal location represented by thicker connecting lines) but have a survival disadvantage. Active and inactive elements are replicated when their chromosome replicates (replication at the same address represented by thinner connecting lines). The current population contains three active elements (indicated by asterisks) and many inactive elements. Transposition selects for active elements whereas natural selection at each chromosomal address favours inactive elements. A TE lineage must continually change chromosomal location to remain active.

consists of P_0 (the zygote), P_1 (a daughter of P_0), P_2 (a daughter of P_1), P_3 (a daughter of P_2), P_4 (a daughter of P_3) and the descendants of P_4, whereas the soma descends from the sisters of P_1, P_2 and P_3 (Fig. 1). After each of the asymmetric divisions, zygotic transcription is activated in somatic cells but remains repressed in the germ track [21]. *Caenorhabditis* embryos can develop to a hundred cells using maternal transcripts alone [22], despite early activation of the somatic genome. Thus, the timing of ZGA and the transfer of control from the maternal to embryonic genome are evolutionarily separable.

Early embryonic divisions of *Drosophila* occur rapidly within a syncytial cytoplasm. Nuclei migrate to the periphery of the egg after the eighth division, at which stage a few nuclei bud off as 'pole cells' that are the progenitors of the germline. ZGA occurs prior to cellularization of somatic nuclei at the thirteenth division [23, 24], but is delayed in pole cells [25, 26]. *Xenopus* embryos divide rapidly 12 times using stored maternal products before the somatic genome is activated at the 'midblastula transition' [27, 28]. Transcription is repressed in the germ-stem until the germline separates from endoderm in late gastrulas [29, 30]. ZGA in zebrafish occurs after ten embryonic divisions in both somatic and germline cells [31, 32].

Transcriptional quiescence in the germ track is usually interpreted as a mechanism for suppressing somatic gene programs [33–35]. But why should suppression of somatic programs in germ cells be different in kind from suppression of muscle programs in bone or neural programs in kidney? An alternative hypothesis should be considered: transcription and translation are tightly controlled in the germ track to control the activity of TEs, a process in which somatic differentiation is a fail-safe option when repressive mechanisms are themselves repressed. A division of labour between a transcriptionally silent germ track (micronucleus) and a transcriptionally active soma (macronucleus) has evolved independently in ciliates [36]. The mammalian germ-stem is transcriptionally active, and will be discussed in a subsequent section.

All SSs have a common interest in suppressing transposition in the germ track, but each TE benefits from its own transposition and suffers the costs of transposition by other TEs. Thus, the sedentary genome can mount a coordinated defense against 'disunited' TEs [37, 38]. Despite this strategic advantage, SSs are not expected to prevent all transposition, because the strength of selection to maintain defenses weakens as threats become less frequent. Germ-track defenses, like any other security system, are not expected to be perfect, because vigilance diminishes once threats are rare, creating vulnerabilities to be exploited by the next generation of 'hackers'. Moreover, the load of inherited mutations caused by security lapses of some SSs are shared, via sexual reproduction, with other SSs that maintain germline security. For these reasons, the germ track is predicted to be an arena of unresolved conflict between SSs and TEs.

Specification of germ cells is evolutionarily labile

Whenever the egg cytoplasm contains markers of the location of future PGCs, natural selection favours maternal TEs whose transposases (or reverse transcriptases and RNA genomes) segregate with the markers, and maternal SSs that target defensive countermeasures to the same locations. Oocytes of *Caenorhabditis*, *Drosophila*, *Xenopus* and zebrafish contain cytoplasmic granules that are inherited by PGCs. Other animals lack 'preformed' determinants, and induce PGCs by 'epigenetic' interactions amongst embryonic cells [39]. Preformation has evolved several times from epigenesis [40–42]. Evolutionary lability of the mechanisms of germ-cell differentiation has puzzled embryologists [43, 44], but it makes sense in the context of a long history of move and countermove by TEs and SSs: preformation creates targets at which TEs can aim; epigenesis risks widespread activation of TEs in early embryos for the chance that a few insertions will be inherited by PGCs.

Germ granules contain diverse RNAs and RNA-binding proteins with important roles in transcriptional silencing and control of TEs [45–47]. Germ granules or similar structures are associated with nuclear pores [45, 48] and can be considered gatekeepers of RNA exit from, and entry to, germline nuclei [49, 50]. Germline security, including the exclusion

of infectious retroelements from the nucleus, may be the primary function of germ granules [50]. We are now all familiar with security checkpoints at which everyone who attempts to enter a restricted area is searched, in an effort to prevent prohibited entries of disguised malefactors.

Both SSs and TEs may have evolutionary incentives to upset the status quo of germ cell specification. A TE could, for example, increase its representation amongst gametes by causing its cell to adopt a germinal, rather than somatic, fate after transposition or to divide faster than other cells of the germ track. Because TEs rarely transpose in somatic cells, natural selection may sometimes have favoured SSs that induced germ cells in new locations, creating detours of the germ track through previously somatic cells. A body that produced some or all of its PGCs at a 'hidden site', distant from established markers of germ cell fate, would thereby produce gametes with a lower load of deleterious mutations until TEs adapted to the new location. Interesting questions for future research are whether animals with different mechanisms of germ cell specification have different rates of TE insertion, whether they are vulnerable to different classes of TEs and whether preformation versus epigenesis has implications for genome size.

Transposable elements evolve to be inactive in somatic cells

The expression of somatic TEs is subject to natural selection for its effects on organismal fitness. Because somatic transposition is usually detrimental for organismal fitness, SSs and TEs are predicted to collaborate to suppress somatic transposition. Conserved sequences of active TEs play a role in the somatic inhibition of transposition, and are thus candidate adaptations for the long-term persistence of mobile lineages. For example, mRNAs of *Drosophila* P elements retain an intron in somatic cells that prevents translation of the transposase but that is spliced out in nuclei of the germ track [51]; many retrotransposons are transcribed from sense and antisense promoters to produce double-stranded RNAs, which are processed into siRNAs that block somatic transposition [52]; somatic transcription of other TEs is inhibited by methylation of conserved CpG dinucleotides [53, 54]; and Tc1 transposons of *Caenorhabditis* are excised from somatic nuclei [55]. Diverse organisms eliminate large quantities of repetitive DNA from somatic nuclei [56–58]. SSs and TEs should both benefit from somatic elimination of TEs [10]. Indeed, transposases of active and domesticated TEs participate in the elimination of germline TEs from somatic macronuclei of ciliates [59, 60].

A well-adapted TE should possess internal regulatory elements that either activate transposition in the germ track or inhibit transposition in the soma (or both). Many mammalian TEs possess binding sites for factors – such as Nanog and Oct4 – that activate transcription in early embryos [61–65]. Many TEs also possess binding sites for p53 [66–71], a factor that is active in differentiated somatic cells and formerly proliferating cells that have exited the cell cycle [72, 73]. Consistent with expectations, binding of p53 usually inhibits TE activity [74–76]. Multiple families of TEs probably evolved negative regulation by p53 because binding by p53 was a reliable cue of somatic exit from the germ-stem.

Although most TEs are inactive in somatic cells, there are exceptions. Somatic transposition, in these cases, may serve organismal functions [77–79]. In particular, active transposition in neural tissues [80–82] has been proposed to generate adaptive neural diversity [78, 83], although other studies suggest that the frequency of neural transposition has been grossly overestimated [84, 85]. Alternative explanations of somatic transposition should also be considered. First, all adaptations are subject to sporadic malfunction due to mutation. Second, occasional transposition in somatic cells might be a maladaptive side-effect of adaptations to evade repression in the germ track. Under this scenario, somatic transposition would be most frequent in tissues where it does the least damage rather than in tissues where it confers the greatest benefit. Third, somatic transposition of TEs that are not exclusively vertically transmitted could be maintained by natural selection if TEs that are transcribed in somatic cells infect more new hosts than TEs that are expressed solely in the germ track. If somatic copies of TEs are able to infect germline cells or other bodies via viral particles or exosomes, then somatic cells form part of a TE's germ track [86]. *Mariner* elements, for example, are expressed in somatic cells and undergo frequent horizontal transmission between species (and presumably within species) [87].

Postzygotic provisioning of mammalian embryos is a cause of intragenomic conflict

Mammalian embryogenesis differs in fundamental respects from that of other animals considered in this essay. First, ZGA occurs during the first few cell cycles, long before differentiation of PGCs [15, 88]. As an accompaniment of precocious ZGA, retroelements are prolifically transcribed in early embryos [89–94] and different families are active at different stages of development [95, 96]. Second, preimplantation embryos undergo genome-wide DNA demethylation [97] followed by remethylation of nuclei in the germ track, necessitating a second wave of demethylation in PGCs [98]. Neither *Xenopus* nor zebrafish embryos undergo extensive demethylation during early cleavage [99, 100]. Third, extraembryonic cell lineages diverge very early from the germ track: trophectoderm in 32-cell embryos or earlier and primitive endoderm in 64-cell embryos [101, 102].

The unusual features of mammalian development are undoubtedly related to the replacement of yolk-based oviparity by placental viviparity [17, 19]. Development within the safety of the uterus eliminates the selective premium on speed and the need to package massive nutrient reserves into a single cell. But postzygotic maternal provisioning also fundamentally changes the nature of the relationship between mother and embryo by creating intergenerational conflict over the level of maternal care [103, 104]. Embryos of oviparous mothers can do nothing to increase maternal investment, because eggs are fully provisioned before fertilisation.

Therefore, embryos do not contest maternal control of development because of the advantages of rapid cleavage and suppression of transposition. Mammalian mothers, by contrast, provision their embryos after, rather than before, fertilization. Equal transmission of the two alleles at a parental locus is ensured by the fairness of meiosis, but parental alleles compete for maternal resources after they segregate amongst offspring (Fig. 2B). Mammalian embryos do not simply accept what is given, but take for themselves [105, 106]. From this perspective, mammalian embryos wrested control of transcription from their mothers to develop feeding structures and circumvent maternal restraints.

Postzygotic provisioning not only created conflict between genes of mothers and embryos but also disrupted the alignment of interests within embryonic genomes. Paternally expressed imprinted genes (PEGs) of embryos favour greater extraction of resources from mothers than maternally expressed imprinted genes (MEGs), a context in which biparentally expressed genes (BEGs) favour intermediate extraction. Thus, early mammalian development has been shaped by adaptations of multiple genetic factions with distinct desiderata of fitness. At least four SS factions can be identified: MEGs, PEGs and BEGs of embryos, plus genes of mothers, the latter represented by maternal factors inherited with the egg cytoplasm [107–109]. Epigenetic reprogramming in preimplantation embryos may reflect an evolutionary history of struggles for control amongst the different genetic factions with a stake in early cell fates [110–112]. Imprinted genes resist the first wave of demethylation in preimplantation embryos because imprints need to be passed to somatic cells, but not the second wave in PGCs, because imprints need to be reset for the next generation [113].

Allocation of blastomeres to precursors of the future placenta is a focus of intragenomic conflict under the presupposition that larger placentas – other things being equal – are associated with greater resource transfer. PEGs are predicted to favour greater contribution to trophectoderm and primitive endoderm, and MEGs greater contribution to inner cell mass and epiblast, BEGs favouring a compromise. The segregation of trophectoderm, primitive endoderm and epiblast in mammalian blastocysts is characterised by cellular heterogeneity within embryos and stochastic variation amongst embryos [114, 115]. Strict choreography of development may have been lost because lineage specification in blastocysts resembles more the messy resolution of a 'political' dispute, in which different factions advocate different fates, than an elegant solution to an engineering problem.

Some mammalian TEs promote pluripotency of cells in which they are active [95, 116–119]. SSs may incorporate TEs into core regulatory networks because TE activity is an ever-present backdrop of pluripotent cells, but promotion of pluripotency may also be an adaptation of TEs. A TE that has transposed in an early blastomere could increase its representation amongst gametes by causing the blastomere to adopt a germinal, rather than somatic, fate. From a TE's perspective, jostling amongst blastomeres for internal positions [120] makes adaptive sense only if the cell that joins the inner cell mass rather than trophectoderm, thereby ~~increasing~~ increases the TE's average number of copies per gamete. TEs might also benefit from simply prolonging pluripotency [121].

Precocious ZGA in mammals created an opportunity for TE proliferation in the germ-stem that is absent in taxa with delayed ZGA. This security flaw was exacerbated by the breakdown of cooperation between maternal and embryonic genomes, and between egg-derived and sperm-derived genomes of embryos, occasioned by placental development. New security measures evolved to silence TEs [122, 123], but a fully coordinated defense was precluded by disunity amongst the germ track's defenders. Postzygotic maternal provisioning of embryos created dissent amongst somatic SSs. Conflicts between genes of maternal and paternal origin over cellular proliferation of trophoblast and other tissues may have contributed to unique mammalian vulnerabilities to cancer [124].

Transposable elements rewire some, but not all, regulatory networks

Transposition disperses regulatory elements to sites throughout the genome, but these will not be a random sample of enhancers and binding sites. Successful mobile lineages transpose in the germ track but not in the soma. TEs are therefore expected to be a rich source of regulatory elements for activating transcription in the germ track [125, 126]. For example, a substantial proportion of all binding sites for Oct4 and Nanog in the mouse and human genomes are derived from TEs although only 5% of these sites are conserved [65].

Each insertion of a regulatory sequence is subject to genetic drift and draft, and to natural selection for its effects on organismal fitness. By these processes, TE-derived sequences can be incorporated into gene regulatory networks of the germ track [62, 126]. These networks are expected to diverge rapidly between species. No data exist on how often a new node in a network is beneficial for organismal fitness and how often it is merely tolerated as nearly neutral. Are mice and humans better beasts because their germ tracks have been 'rewired'?

Extensive regulatory rewiring by retroelements has been reported in the placenta [127, 128] and endometrium [129, 130], but not in the neocortex [131]. For what adaptive reason would retroelements possess regulatory elements that drive transcription in some somatic tissues but not others? The placenta was an evolutionarily novel interface for viral transmission [132], with embryonic trophoblast on one side and maternal endometrium on the other. Retroviruses may have evolved expression in these tissues as way-stations for transmission of exogenous retroviruses from mothers to offspring or endogenous retroviruses from offspring to mothers [11, 133]. In this interpretation, regulatory networks of trophoblast and endometrium have been rewired because these tissues were sites of infectious transmission [134]. Future studies should address whether rewiring of regulatory networks by retroviruses, and by TEs more generally, shows predictable variation amongst tissues and whether these patterns provide clues about routes of retroviral transmission.

Conclusion

Bodies are the constructed niches of communities of genes [135]. SSs form the cohesive core of these communities because they possess no private good apart from the communal good. Relations between SSs and TEs in the germ track are fraught by a tension between transposition (a 'private' good of individual TEs) and bodily fitness (a 'public' good of all sequences). Transposition in somatic cells, by contrast, serves no-gene's interests, and will usually be suppressed by cooperation between TEs and SSs. As a consequence, regulatory mechanisms in the germ track are dominated by security 'concerns' of how to prevent unlicensed transcription and translation, but less restrictive modes of control can evolve in somatic cells. Antagonistic coevolution of defenses of SSs and evasive responses of TEs may have contributed to evolutionary instability of regulatory networks in the germ track and to the lack of evolutionary conservation of mechanisms of germline specification.

The ancient and protracted struggle between sedentary and mobile residents of the genome for relative advantage in transmission to gametes is central to an understanding of germ–soma differentiation. Because SSs and TEs cooperate in somatic cells, the performance of most bodily functions by a sequestered soma mitigates costs of intragenomic conflicts and facilitates gains from cooperation. Moreover, the migration of PGCs to the somatic gonad greatly diminishes the risk of nepotistic collusion between cells that share recent TE insertions because it eliminates genetic correlations between germ cells and their somatic supporting cells. This *pax somatica* exists only in cells without germline descendants, and it is most effective when somatic cells diverge early from the germ track. The evolution of postzygotic provisioning of embryos in mammals disrupted the symmetry of selective forces acting on SSs of maternal and paternal origin and thereby destabilised cooperation amongst SSs for the collective good.

Acknowledgements

The manuscript benefited from the comments of Holly Elmore, Marc Kirschner, Andrew Murray and the anonymous reviewers.

The author has declared no conflict of interest.

References

1. **Weismann A**. 1892. *Das Keimplasma. Eine Theorie der Vererbung*. Jena: Gustav Fischer. Translated by Parker WN, Rönnfeldt N. 1902. *The germ-plasm. A theory of heredity*. New York: Charles Scribner.
2. **Nieuwkoop PD**. 1949. The present state of the problem of the "Keimbahn" in the vertebrates. *Experientia* **5**: 308–12.
3. **Rink JC**. 2016. Stem cell systems and regeneration in planaria. *Dev Genes Evol* **223**: 67–84.
4. **Crichton JH, Dunican DS, MacLennan M, Meehan RR**, et al. 2014. Defending the genome from the enemy within: mechanisms of retrotransposon suppression in the mouse germline. *Cell Mol Life Sci* **71**: 1581–605.
5. **Yeom YI, Fuhrmann G, Ovitt CE, Brehm A**, et al. 1996. Germline regulatory element of Oct-4 specific for the totipotent cycle of embryonal cells. *Development* **120**: 881–94.
6. **Leitch HG, Smith A**. 2013. The mammalian germline as a pluripotency cycle. *Development* **140**: 2495–501.
7. **Solana J**. 2013. Closing the circle of germline and stem cells: the Primordial Stem Cell hypothesis. *EvoDevo* **4**: 2.
8. **Hickey DA**. 1982. Selfish DNA: a sexually transmitted nuclear parasite. *Genetics* **101**: 519–31.
9. **Burt A, Trivers R**. 2006. *Genes in conflict*. Cambridge, Massachusetts: Harvard University Press.
10. **Charlesworth B, Langley CH**. 1986. The evolution of self-regulated transposition of transposable elements. *Genetics* **112**: 359–83.
11. **Haig D**. 2012. Retroviruses and the placenta. *Curr Biol* **22**: R609–13.
12. **Haig D**. 2013. Genomic vagabonds: endogenous retroviruses and placental evolution. *BioEssays* **35**: 845–6.
13. **Maksakova IA, Romanish MT, Gagnier L, Dunn CA**, et al. 2006. Retroviral elements and their hosts: insertional mutagenesis in the mouse germ line. *PLoS Genet* **2**: e2.
14. **Nellåker C, Keane TM, Yalcin B, Wong K**, et al. 2012. The genomic landscape shaped by selection on transposable elements across 18 mouse strains. *Genome Biol* **13**: R45.
15. **Lee MT, Bonneau AR, Giraldez AJ**. 2014. Zygotic genome activation during the maternal-to-zygotic transition. *Annu Rev Cell Dev Biol* **30**: 581–613.
16. **Woodland H**. 1982. The translational control phase of early development. *Biosci Rep* **2**: 471–91.
17. **Evsikov SV, Morozova LM, Solomko AP**. 1994. Role of ooplasmic segregation in mammalian development. *Roux Arch Dev Biol* **203**: 199–204.
18. **Strathmann RR, Staver JM, Hoffman JR**. 2002. Risk and the evolution of cell-cycle durations of embryos. *Evolution* **56**: 708–20.
19. **O'Farrell PH**. 2015. Growing an embryo from a single cell: a hurdle in animal life. *Cold Spring Harb Perspect Biol* **7**: a019042.
20. **Robert VJ, Garvis S, Palladino F**. 2015. Repression of somatic cell fate in the germline. *Cell Mol Life Sci* **72**: 3599–620.
21. **Robertson S, Lin R**. 2015. The maternal-to-zygotic transition in *C. elegans*. *Curr Top Dev Biol* **113**: 1–42.
22. **Edgar LG, Wolf N, Wood WB**. 1994. Early transcription in *Caenorhabditis elegans* embryos. *Development* **120**: 443–51.
23. **Williamson A, Lehmann R**. 1996. Germ cell development in *Drosophila*. *Annu Rev Cell Dev Biol* **12**: 365–91.
24. **Blythe SA, Wieschaus EF**. 2015. Coordinating cell cycle remodeling with transcriptional activation at the *Drosophila* MBT. *Curr Top Dev Biol* **113**: 113–48.
25. **van Doren M, Williamson AL, Lehmann R**. 1998. Regulation of zygotic gene expression in *Drosophila* primordial germ cells. *Curr Biol* **8**: 243–6.
26. **Siddiqui NU, Li X, Luo H, Karaiskakis A**, et al. 2012. Genome-wide analysis of the maternal-to-zygotic transition in *Drosophila* primordial germ cells. *Genome Biol* **13**: R11.
27. **Newport J, Kirschner M**. 1981. A major developmental transition in early *Xenopus* embryos: I. Characterization and timing of cellular changes at the midblastula stage. *Cell* **30**: 675–86.
28. **Sheets MD**. 2015. Building the future: post-transcriptional regulation of cell fate decisions prior to the *Xenopus* midblastula transition. *Curr Top Dev Biol* **113**: 233–70.
29. **Venkatarama T, Lai F, Luo X, Zhou Y**, et al. 2010. Repression of zygotic gene expression in *Xenopus* germline. *Development* **137**: 651–60.
30. **Yang J, Aguero T, King ML**. 2015. The *Xenopus* maternal-to-zygotic transition from the perspective of the germ line. *Curr Top Dev Biol* **113**: 271–303.
31. **Kane DA, Kimmel CB**. 1993. The zebrafish midblastula transition. *Development* **119**: 447–56.
32. **Knaut H, Pelegri F, Bohmann K, Schwarz H**, et al. 2000. Zebrafish *vasa* RNA but not its protein is a component of the germ plasm and segregates asymmetrically before germline specification. *J Cell Biol* **149**: 875–88.
33. **Matova N, Cooley L**. 2001. Comparative aspects of animal oogenesis. *Dev Biol* **231**: 291–320.
34. **Strome S, Lehmann R**. 2007. Germ versus soma decisions: lessons from flies and worms. *Science* **316**: 392–3.
35. **Nakamura A, Seydoux G**. 2008. Less is more: specification of the germline by transcriptional repression. *Development* **135**: 3817–27.
36. **Prescott DM**. 1994. The DNA of ciliated protozoa. *Microbiol Rev* **58**: 233–67.

37. **Dumesic PA, Madhani HD**. 2014. Recognizing the enemy within: licensing RNA-guided genome defense. *Trends Biochem Sci* **39**: 25–34.
38. **Wolf G, Greenberg D, Macfarlan TS**. 2015. Spotting the enemy within: targeted silencing of foreign DNA in mammalian genomes by the Krüppel-associated box zinc finger protein family. *Mobile DNA* **6**: 17.
39. **Extavour CGM**. 2009. Evolution of the bilaterian germ line: lineage origin and modulation of specification mechanisms. *Integ Comp Biol* **47**: 770–85.
40. **Extavour CG, Akam M**. 2003. Mechanisms of germ cell specification across the metazoans: epigenesis and preformation. *Development* **130**: 5869–84.
41. **Johnson AD, Richardson E, Bachvarova RF, Crother BI**. 2011. Evolution of the germ line-soma relationship in vertebrate embryos. *Reproduction* **141**: 291–300.
42. **Kumano G**. 2015. Evolution of germline segregation processes in animal development. *Dev Growth Differ* **57**: 324–32.
43. **Lai F, Zhou Y, Luo X, Fox J**, et al. 2011. Xenopus Xpat protein is a major component of germ plasm and may function in its organisation and positioning. *Dev Biol* **287**: 289–300.
44. **Chatfield J, O'Reilly MA, Bachvarova RF, Ferjentsik Z**, et al. 2014. Stochastic specification of primordial germ cells from mesoderm precursors in axolotl embryos. *Development* **141**: 2429–40.
45. **Voronina E, Seydoux G, Sassone-Corsi P, Nagamori I**. 2011. RNA granules in germ cells. *Cold Spring Harb Perspect Biol* **3**: a002744.
46. **Siomi MC, Sato K, Pezic D, Aravin AA**. 2011. PIWI-interacting small RNAs: the vanguard of genome defence. *Nat Rev Mol Cell Biol* **12**: 246–58.
47. **Strome S, Updike D**. 2015. Specifying and protecting germ cell fate. *Nat Rev Mol Cell Biol* **16**: 406–16.
48. **Pitt JN, Schisa JA, Priess JR**. 2000. P granules in the germ cells of *Caenorhabditis elegans* adults are associated with clusters of nuclear pores and contain RNA. *Dev Biol* **219**: 315–33.
49. **Sheth U, Pitt J, Dennis S, Priess JR**. 2010. Perinuclear P granules are the principal sites of mRNA export in adult *C. elegans* germ cells. *Development* **137**: 1305–14.
50. **Dennis S, Sheth U, Feldman JL, English KA**, et al. 2012. *C. elegans* germ cells show temperature and age-dependent expression of Cer1, a Gypsy/Ty3-related retrotransposon. *PLoS Pathog* **8**: e1002591.
51. **Chain AC, Zollman S, Tseng JC, Laski FA**. 1991. Identification of a *cis*-acting sequence required for germ line-specific splicing of the P element ORF2-ORF3 intron. *Mol Cell Biol* **11**: 1538–46.
52. **Russo J, Harrington AW, Steiniger M**. 2016. Antisense transcription of retrotransposons in *Drosophila*: an origin of endogenous small interfering RNA precursors. *Genetics* **202**: 107–21.
53. **Hata K, Sakaki Y**. 1997. Identification of critical CpG sites for repression of L1 transcription by DNA methylation. *Gene* **189**: 227–34.
54. **Glass JL, Fazzari MJ, Ferguson-Smith AC, Greally JM**. 2009. CG dinucleotide periodicities recognized by the Dnmt3a-Dnmt3L complex are distinctive at retroelements and imprinted domains. *Mammal Genome* **20**: 633–43.
55. **Emmons SW, Yesner L**. 1984. High-frequency excision of transposable element Tc1 in the nematode *Caenorhabditis elegans* is limited to somatic cells. *Cell* **36**: 599–605.
56. **Boveri T**. 1887. Über Differenzierung der Zellkerne während der Furchung des Eies von *Ascaris megalocephala*. *Anatomischer Anzeiger* **2**: 688–93.
57. **Smith JJ, Stuart AB, Sauka-Spengler T, Clifton SW**, et al. 2010. Development and analysis of a germline BAC resource for the sea lamprey, a vertebrate that undergoes substantial chromatin diminution. *Chromosoma* **119**: 381–9.
58. **Sun C, Wyngaard G, Walton DB, Wichman HA**, et al. 2014. Billions of basepairs of recently expanded, repetitive sequences are eliminated from the somatic genome during copepod development. *BMC Genomics* **15**: 186.
59. **Nowacki M, Higgins BP, Maquilan GM, Swart EC**, et al. 2009. A functional role for transposases in a large eukaryotic genome. *Science* **324**: 935–8.
60. **Arnaiz O, Mathy N, Baudry C, Malinsky S**, et al. 2012. The Paramecium germline genome provides a niche for intragenic parasitic DNA: evolutionary dynamics of internal eliminated sequences. *PLoS Genet* **8**: e1002984.
61. **Bourque G, Leong B, Vega VB, Chen X**, et al. 2008. Evolution of the mammalian transcription factor binding repertoire via transposable elements. *Genome Res* **18**: 1752–62.
62. **Santoni F, Guerra J, Luban J**. 2012. HERV-H RNA is abundant in human embryonic stem cells and a precise marker for pluripotency. *Retrovirology* **9**: 111.
63. **Boyer LA, Lee TI, Cole MF, Johnstone SE**, et al. 2005. Core transcriptional regulatory circuitry in human embryonic stem cells. *Cell* **122**: 947–56.
64. **Loh YH, Wu Q, Chew JL, Vega VB**, et al. 2006. The Oct4 and Nanog transcription network regulates pluripotency in mouse embryonic stem cells. *Nat Genet* **24**: 431–40.
65. **Kunarso G, Chia NY, Jeyakani J, Hwang C**, et al. 2010. Transposable elements have rewired the core regulatory network of human embryonic stem cells. *Nat Genet* **42**: 631–4.
66. **Harris CR, Dewan A, Zupnick A, Normart R**, et al. 2009. P53 responsive elements in human retrotransposons. *Oncogene* **28**: 3857–65.
67. **Wang T, Zeng J, Lowe CB, Sellers RG**, et al. 2007. Species-specific endogenous retroviruses shape the transcriptional network of the human tumor suppressor protein p53. *Proc Natl Acad Sci USA* **104**: 18613–18.
68. **Cui F, Sirotin MV, Zhurkin VB**. 2010. Impact of Alu repeats on the evolution of p53 binding sites. *Biol Direct* **6**: 2.
69. **Micali L, Loviglio MN, Manzoni M, Fusco C**, et al. 2016. A fish-specific transposable element shapes the repertoire of p53 target genes in zebrafish. *PLoS ONE* **7**: e46642.
70. **Chesnokov I, Chu WM, Botchan MR, Schmid CW**. 1996. P53 inhibits RNA polymerase III-directed transcription in a promoter-dependent manner. *Mol Cell Biol* **16**: 7084–8.
71. **Hagan CR, Rudin CM**. 2007. DNA cleavage and Trp53 differentially affect SINE transcription. *Genes Chrom Cancer* **46**: 248–60.
72. **Aloni-Grinstein R, Shetzer Y, Kaufman T, Rotter V**. 2014. P53: the barrier to cancer stem cell formation. *FEBS Lett* **588**: 2580–9.
73. **Levine AJ, Ting DT, Greenbaum BD**. 2016. P53 and the defenses against genome instability caused by transposons and repetitive elements. *Bioessays* **38**: 508–13.
74. **Chang NT, Yang WK, Huang HC, Yeh KW**, et al. 2007. The transcriptional activity of HERV-I LTR is negatively regulated by its cis-elements and wild type p53 tumor suppressor protein. *J Biomed Sci* **14**: 211–22.
75. **Leonova KI, Brosky L, Lipchick B, Pal M**, et al. 2012. P53 cooperates with DNA methylation and a suicidal interferon response to maintain epigenetic silencing of repeats and noncoding RNAs. *Proc Natl Acad Sci USA* **110**: E89.
76. **Wylie A, Jones AE, D'Brot A, WJ Lu**, et al. 2016. P53 genes function to restrain mobile elements. *Genes Dev* **30**: 64–77.
77. **Kazazian HH**. 2011. Mobile DNA transposition in somatic cells. *BMC Biol* **9**: 62.
78. **Erwin JA, Marchetto MC, Gage FH**. 2014. Mobile DNA elements in the generation of diversity and complexity in the brain. *Nat Rev Neurosci* **15**: 497–505.
79. **Ecco G, Cassano M, Kauzlaric A, Duc J**, et al. 2016. Transposable elements and their KRAB-ZFP controllers regulate gene expression in adult tissues. *Dev Cell* **36**: 611–23.
80. **Coufal NG, Garcia-Perez JL, Peng GE, Y Mu**, et al. 2009. L1 retrotransposition in human neural progenitor cells. *Nature* **460**: 1127–31.
81. **Baillie JK, Barnett MW, Upton KR, Gerhardt DJ**, et al. 2011. Somatic retrotransposition alters the genetic landscape of the human brain. *Nature* **479**: 534–7.
82. **Upton KR, Gerhardt DJ, Jesuadian JS, Richardson SR**, et al. 2015. Ubiquitous L1 mosaicism in hippocampal neurons. *Cell* **161**: 228–39.
83. **Richardson SR, Morell S, Faulkner GJ**. 2014. L1 retrotransposons and somatic mosaicism in the brain. *Annu Rev Genet* **48**: 1–27.
84. **Evrony GD, Cai X, Lee E, Hills EB**, et al. 2012. Single-neuron sequencing analysis of L1 retrotransposition and somatic mutation in the human brain. *Cell* **151**: 483–96.
85. **Evrony GD, Lee E, Park PJ, Walsh CA**. 2016. Resolving rates of mutation in the brain using single-neuron genomics. *Elife* **5**: e12966.
86. **Henriet S, Sumic S, Doufoundou-Guilengui C, Jensen MF**, et al. 2015. Embryonic expression of endogenous retroviral RNAs in somatic tissues adjacent to the *Oikopleura* germline. *Nucleic Acids Res* **43**: 3701–11.
87. **Hartl DL, Lozovskaya ER, Nurminsky DL, Lohe AR**. 1997. What restricts the activity of *mariner*-like transposable elements? *Trends Genet* **13**: 197–201.
88. **Svoboda P, Franke V, Schultz RM**. 2015. Sculpting the transcriptome during the oocyte-to-embryo transition in mouse. *Curr Top Dev Biol* **113**: 305–49.

89. **Packer AI, Manova K, Bachvarova RF**. 1993. A discrete LINE-1 transcript in mouse blastocysts. *Dev Biol* **157**: 281–3.
90. **Peaston AE, Evsikov AV, Graber JH, de Vries WN**, et al. 2004. Retrotransposons regulate host genes in mouse oocytes and preimplantation embryos. *Dev Cell* **7**: 597–606.
91. **Evsikov AV, de Vries WN, Peaston AE, Radford EE**, et al. 2004. Systems biology of the 2-cell mouse embryo. *Cytogenet Genome Res* **105**: 240–50.
92. **Kano H, Godoy I, Courtney C, Vetter MR**, et al. 2009. L1 retrotransposition occurs mainly in embryogenesis and creates somatic mosaicism. *Genes Dev* **23**: 1303–12.
93. **Macia A, Muñoz-Lopez M, Cortes JL, Hastings RK**, et al. 2011. Epigenetic control of retrotransposon expression in human embryonic stem cells. *Mol Cell Biol* **31**: 300–16.
94. **Grow EJ, Flynn RA, Chavez SL, Bayless NL**, et al. 2015. Intrinsic retrovirus reactivation in human preimplantation embryos and pluripotent cells. *Nature* **522**: 221–5.
95. **Macfarlan TS, Gifford WD, Driscoll S, Lettieri K**, et al. 2012. Embryonic stem cell potency fluctuates with endogenous retrovirus activity. *Nature* **487**: 57–63.
96. **Göke J, Lu X, Chan YS, HH Ng**, et al. 2015. Dynamic transcription of distinct classes of endogenous retroviral element marks specific populations of early human embryonic stem cells. *Cell Stem Cell* **16**: 135–41.
97. **Smith ZD, Chan MM, Mikkelsen TS, H Gu**, et al. 2012. A unique regulatory phase of DNA methylation in the early mammalian embryo. *Nature* **484**: 339–44.
98. **Seisenberger S, Peat JR, Hore TA, Santos F**, et al. 2013. Reprogramming DNA methylation in the mammalian life cycle: building and breaking epigenetic barriers. *Phil Trans R Soc B* **368**: 20110330.
99. **Bogdanovic O, Long SW, van Heeringen SJ, Brinkman AB**, et al. 2011. Temporal uncoupling of the DNA methylome and transcriptional repression during embryogenesis. *Genome Res* **21**: 1313–27.
100. **Potok ME, Nix DA, Parnell TJ, Cairns BR**. 2013. Reprogramming the maternal zebrafish genome after fertilization to match the paternal methylation pattern. *Cell* **153**: 759–72.
101. **Johnson MH, McConnell JML**. 2004. Lineage allocation and cell polarity during mouse embryogenesis. *Semin Cell Dev Biol* **15**: 583–97.
102. **Frum T, Ralston A**. 2015. Cell signaling and transcription factors regulating cell fate during formation of the mouse blastocyst. *Trends Genet* **31**: 402–10.
103. **Trivers RL**. 1974. Parent-offspring conflict. *Am Zool* **14**: 249–64.
104. **Blick J**. 1977. Selection for traits which lower individual reproduction. *J Theor Biol* **67**: 597–601.
105. **Haig D**. 1993. Genetic conflicts in human pregnancy. *Q Rev Biol* **68**: 495–532.
106. **Haig D**. 2010. Fertile soil or no man's land: cooperation and conflict in the placental bed. In: Pijnenborg R, Brosens I, Romero R, eds; *Placental Bed Disorders*. Cambridge, England: University Press. p. 165–73.
107. **Haig D**. 1992. Genomic imprinting and the theory of parent-offspring conflict. *Semin Dev Biol* **3**: 153–60.
108. **Haig D**. 2004. Genomic imprinting and kinship: how good is the evidence? *Annu Rev Genet* **38**: 553–85.
109. **Burt A, Trivers R**. 1998. Genetic conflicts in genomic imprinting. *Proc R Soc B* **265**: 2393–7.
110. **Reik W, Walter J**. 2001. Evolution of imprinting mechanisms: the battle of the sexes begins in the zygote. *Nat Genet* **27**: 255–6.
111. **Wilkins JF, Haig D**. 2002. Parental modifiers, antisense transcripts and loss of imprinting. *Proc R Soc B* **269**: 1841–6.
112. **Haig D**. 2015. Going retro: transposable elements, embryonic stem cells, and the mammalian placenta. *Bioessays* **37**: 1154.
113. **Voon HPJ, Gibbons RJ**. 2016. Maintaining memory of silencing at imprinted differentially methylated regions. *Cell Mol Life Sci* **73**: 1871–9.
114. **Wennekamp S, Mesecke S, Nédélec F, Hiiragi T**. 2013. A self-organization framework for symmetry breaking in the mammalian embryo. *Nat Rev Mol Cell Biol* **14**: 452–9.
115. **MacArthur BD, Lemischka IR**. 2013. Statistical mechanics of pluripotency. *Cell* **154**: 484–9.
116. **Beraldi R, Pittoggi C, Sciamanna I, Mattei E**, et al. 2006. Expression of LINE-1 retroposons is essential for murine preimplantation development. *Mol Reprod Dev* **73**: 279–87.
117. **Ohnuki M, Tanabe K, Sutou K, Teramoto I**, et al. 2014. Dynamic regulation of human endogenous retroviruses mediates factor-induced reprogramming and differentiation potential. *Proc Natl Acad Sci USA* **111**: 12426–31.
118. **Lu X, Sachs F, Ramsay L, Jacques PÉ**, et al. 2014. The retrovirus HERVH is a long noncoding RNA required for human embryonic stem cell identity. *Nat Struct Mol Biol* **21**: 423–5.
119. **Wang J, Xie G, Singh M, Ghanbarian AT**, et al. 2014. Primate-specific endogenous retrovirus-driven transcription defines naive-like stem cells. *Nature* **516**: 405–9.
120. **Samarage CR, White MD, Álvarez YD, Fierro-González JC**, et al. 2015. Cortical tension allocates the first inner cells of the mammalian embryo. *Dev Cell* **34**: 435–47.
121. **Izsvák Z, Wang J, Singh M, Mager DL**, et al. 2016. Pluripotency and the endogenous retrovirus HERVH: conflict or serendipity? *Bioessays* **38**: 109–17.
122. **Thomas JH, Schneider S**. 2011. Coevolution of retroelements and tandem zinc finger genes. *Genome Res* **21**: 1800–12.
123. **Molaro A, Malik HS**. 2016. Hide and seek: how chromatin-based pathways silence retroelements in the mammalian germline. *Curr Opin Genet Dev* **37**: 51–8.
124. **Haig D**. 2015. Maternal-fetal conflict, genomic imprinting, and mammalian vulnerabilities to cancer. *Phil Trans R Soc B* **370**: 20140178.
125. **Rebollo R, Romanish MT, Mager DL**. 2012. Transposable elements: an abundant and natural source of regulatory sequences for host genes. *Annu Rev Genet* **46**: 21–42.
126. **Xie D, Chen CC, Ptaszek LM, Xiao S**, et al. 2010. Rewirable gene regulatory networks in the preimplantation embryonic development of three mammalian species. *Genome Res* **20**: 804–15.
127. **Cohen CJ, Lock WM, Mager DL**. 2009. Endogenous retroviral LTRs as promoters for human genes: a critical assessment. *Gene* **448**: 105–14.
128. **Chuong EB, Rumi MAK, Soares MJ, Baker JC**. 2013. Endogenous retroviruses function as species-specific enhancer elements in the placenta. *Nat Genet* **45**: 325–9.
129. **Lynch VJ, LeClerc RD, May G, Wagner GP**. 2011. Transposon-mediated rewiring of gene regulatory networks contributed to the evolution of pregnancy in mammals. *Nat Genet* **43**: 1154–9.
130. **Lynch VJ, Nnamami M, Kapusta A, Brayer K**, et al. 2015. Ancient transposable elements transformed the uterine regulatory landscape and transcriptome during the evolution of mammalian pregnancy. *Cell Rep* **10**: 551–61.
131. **Emera D, Yin J, Reilly SK, Gockley J**, et al. 2016. Origin and evolution of developmental enhancers in the mammalian neocortex. *Proc Natl Acad Sci USA* **113**: E2617–26.
132. **Villarreal LP**. 2016. Viruses and the placenta: the essential virus first view. *APMIS* **124**: 20–30.
133. **Panem S**. 1979. C-type virus expression in the placenta. *Curr Top Path* **66**: 175–89.
134. **Haig D**. 2015. Sameness, novelty, and nominal kinds. *Biol Philos* **30**: 857–72.
135. **Haig D**. 1997. The social gene. In Krebs JR, Davies NB, eds; *Behavioural Ecology*. 4th Ed. Oxford: Blackwell Scientific. p. 284–304.