

REVIEW

Non-conflict theories for the evolution of genomic imprinting

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Theories focused on kinship and the genetic conflict it induces are widely considered to be the primary explanations for the evolution of genomic imprinting. However, there have appeared many competing ideas that do not involve kinship/conflict. These ideas are often overlooked because kinship/conflict is entrenched in the literature, especially outside evolutionary biology. Here we provide a critical overview of these non-conflict theories, providing an accessible perspective into this literature. We suggest that some of these alternative hypotheses may, in fact, provide tenable explanations of the evolution of imprinting for at least some loci.

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INTRODUCTION

Genomic imprinting violates the usual rules of Mendelian expression in a diploid individual by privileging the expression of one of the two copies of a gene, depending on its parental origin. The degree of unequal expression, usually but not always manifested as the complete silencing of one copy, often varies among tissues and different stages of development, and even among individuals. Moreover, although the direction of imprinting at a particular locus (that is, whether the maternal or paternal copy's expression is downregulated) is consistent within a species, there is significant discordance among species, with the majority of loci that are imprinted in the mouse, for example, not imprinted in humans (and vice versa; Morison *et al.*, 2005). The phylogenetic distribution of imprinting, too, is of interest, with unequivocal cases restricted to therian mammals (Suzuki *et al.*, 2011) and angiosperms (Hsieh *et al.*, 2011); the case in insects remains equivocal (for example, Coolon *et al.*, 2012). (We consider the myriad of cases of whole-genome silencing or elimination in insects and mites to be a different phenomenon, requiring completely different evolutionary explanations.) Finally, imprinted genes generally have appeared to occur in clusters on chromosomes (Morison *et al.*, 2005), but as more exhaustive lists of imprinted genes are compiled, the newly discovered genes more often appear to be singletons (Wang *et al.*, 2013).

All these features demand an evolutionary explanation. For example, the apparent restriction of imprinting in vertebrates to therian mammals suggests that it confers some advantage peculiar to mammals, and the numerous differences in the imprinting status of some loci among mammal species suggest that imprinting status evolves relatively easily, presumably in response to selection. In addition, the functional haploidy at loci with complete silencing means that recessive deleterious mutations cannot be masked whenever they are passed on by the non-inactivating parent.

The most frequently invoked selective explanation for the evolution of imprinting is David Haig's conflict or kinship hypothesis (see Haig, 2002), and, indeed, on reading the closing paragraphs of some of the empirical papers on imprinting that discuss the evolutionary context of their findings (for example, Varrault *et al.*, 2006) one could be forgiven for thinking it were the only one. Nevertheless, there are alternatives, a few of which invoke other forms of genetic conflict and many with evocative names dating back to before the proposing of Haig's conflict hypothesis. Additional new hypotheses are also being put forward regularly, to the chagrin of Haig's supporters (Moore and Mills, 2008). Here we survey these other hypotheses for the evolution of imprinting (which, for brevity and in accord with the prevailing terminology, we label 'non-conflict hypotheses'), briefly outlining each idea, discussing the evidence for and against, before giving our view on its current tenability. Of course more than one molecular mechanism for the conversion of an unimprinted gene to an imprinted gene exists, and it is equally plausible that different genes may have acquired an imprinted status through distinct evolutionary pathways. Note that we omit a number of other hypotheses that do not include an evolutionary rationale for imprinting's essential features. For example, we do not include the novel placenta hypothesis (Hall, 1990; Kaneko-Ishino *et al.*, 2003), which recognizes the importance of imprinted genes in the placenta and holds that imprinting arose to control their placental expression, because it does not predict any degree of differential expression.

In our view some—but not all—of the hypotheses discussed below warrant closer examination: they appear to have solid theoretical underpinnings and could explain the evolution of imprinting in some subset of cases. These 'better' hypotheses are likely to be general (that is, apply to a number of cases) and make clear predictions (for example, in explaining the phylogenetic pattern or clustering). Satisfying hypotheses also provide an understanding of the origin of the molecular regulation that gives rise to genomic imprinting, and

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they provide a means for an increase in frequency in a population that is transiently polymorphic for the imprinting state. Interestingly, some theories may explain some aspects of the evolution of imprinting almost in passing. For example, in the context of the conflict theory, Úbeda and Wilkins (2008) have argued that loci at which imprinting may be expected to evolve are those for which mutations are unlikely to be recessive, perhaps because they are sensitive to dosage effects, and so the loss of masking inherent in imprinting is not an issue that needs explanation. Whether this argument applies to other hypotheses is not clear, however.

In brief, we suggest that both theorists and empiricists would benefit from considering whether or not one of these alternative, non-conflict hypotheses may apply to the cases in which they are interested.

HYPOTHESES

Prevention of parthenogenesis

Possibly the oldest proposed explanation for the evolution of imprinting begins by noting the absence of naturally occurring parthenogenesis in mammals, uniquely among the classes of jawed vertebrates (Solter, 1988). This observation extends to extensive laboratory experiments attempting to generate viable mice from endoreduplication of the chromosomes of a single sperm or a single egg. Such experiments had universally failed until normal oocytes fused with oocytes doubly deleted in the *H19* differentially methylated region and the *Dlk1–Dio3* differentially methylated region were fused and brought to term (Kawahara *et al.*, 2007). This absence implies that both maternal and paternal contributions are essential to the developing mammalian zygote, which would obtain if one or more essential genes were expressed from only the maternal copy and others only from the paternal. Thus, imprinting may have been selected to prevent the establishment of parthenogenetic lineages, which are often thought to be an evolutionary dead end because they lack the apparent selective benefits of recombination that occurs during sexual reproduction.

The central problem with this argument is that the selection pressure invoked is at the level of the group. An individual that was able to reproduce parthenogenetically would likely have a strong selective advantage. Thus, as with the case of many group-selectionist pressures, it is easily subverted by individual-level selection. As a consequence, this hypothesis is seldom cited in the scientific literature today. Nevertheless, although the evolutionary rationale for imprinting may not be the prevention of parthenogenesis, imprinting is no doubt one factor in the developmental failure of mammalian parthenogens.

Ovarian time-bomb

The ovarian time-bomb hypothesis is similar to the prevention of parthenogenesis hypothesis but posits an individual-level advantage for both paternal and maternal genetic contributions to the zygote. Varmuza and Mann (1994) argued that imprinting evolved to prevent ovarian trophoblastic disease arising from a parthenogenetically developing (unfertilized) egg in the ovary of a female mammal. If the maternal copy of an essential gene were inactivated and hence a paternal contribution necessary for correct development, this 'ovarian time-bomb' could be defused. Moreover, the sorts of genes subject to such maternal inactivation would be growth enhancing (and so their inactivation would impede growth until after fertilization) and expressed in early embryogenesis. The first examples of imprinted loci, notably *Igf2*, fitted well with these predictions.

This hypothesis was initially criticized as failing to account for paternal inactivation of genes such as the mouse *Igf2r* (Haig, 1994; Moore, 1994). Iwasa (1998) pointed out, however, that increased expression of maternal growth inhibitors should also help avert development of an unfertilized egg still in the ovary. Moreover, if the level of gene product in a zygote were critical, maternal upregulation might need to be balanced by downregulation of the paternal copy, a situation that is effectively imprinting. Iwasa's (1998) mathematical modelling backed this verbal adumbration.

Other criticisms still seem valid, however. The ovarian time-bomb does not explain imprinting of genes not involved in trophoblast development (except as 'innocent bystanders,' that is, genes also targeted by the imprinting mechanisms only because they share imprinting recognition sites), nor does it explain why imprinted expression persists long after fertilization, in fetal and even in adult tissues (Wilkins and Haig, 2003). Hurst (1997) also argued that ovarian trophoblastic disease is less of a problem in taxa with non-invasive placentas (let alone angiosperms) and yet imprinting occurs in such groups. It is also unclear why so many genes appear to be imprinted: it would seem that the hypothesized protective effect would occur with just a few imprinted genes. Finally, the differences among species in the loci that are imprinted (Wang *et al.*, 2013) would also appear to be inconsistent with this hypothesis: one might expect genes of similar function to have evolved their imprinting status early on in mammalian evolution and for this ancient pattern to have been largely conserved. Many of these criticisms are against the argument that all genes acquired imprinting by the ovarian time-bomb mechanism, and these arguments pale if instead imprinting were initiated in a few genes to neutralize the ovarian time-bomb, and then subsequent addition of imprinting arose by other means.

Dominance modification

Imprinting is effectively parentally specific dominance, and it is possible that imprinting has evolved in a similar way to genetic dominance (Sapienza, 1989). The evolution of dominance is a long-standing question in evolutionary biology (see Otto and Bourguet, 1999 for a brief review), with much controversy about the role of selection. The scenario most often investigated envisages a neutral modifier locus determining the dominance of alleles at the locus of interest. Theoretical work has shown that, unless there is allelic variation at this latter locus at a level greater than that under mutation-selection balance, dominance modifiers evolve at a rate proportional to the mutation rate, which is considered too slow (Feldman and Karlin, 1971; Otto and Bourguet, 1999). Hence, in the absence of standing genetic variation, either dominant alleles are selected directly or they arise as an inherent property of the biochemistry of the locus in question. Spencer and Williams (1997) found that neutral modifiers of imprinting evolved at a similarly slow rate. This result means that, in order to explain the evolution of imprinting, we have to invoke selection directly on imprinting status (which implies that some other model applies).

Variance minimization/complementation

Solter (1988) suggested that imprinting may have evolved to regulate the expression level of a gene, minimizing the variation in the mean level of demand-controlled expression and reducing the chance of stochastically expressed genes with low transcription probabilities both being silent (see also Hurst, 1997). A possible metaphor here is that it may be easier to keep one faucet dripping at a very slow rate than two faucets dripping at half that rate. The risk is that one or both of the latter faucets will not drip at all. We note, too, that in a number

of developmental contexts genomic imprinting appears to be used as a switch to control gene dosage (for example, Ferrón *et al.*, 2011; Charalambous *et al.*, 2012).

Mathematical modelling suggests, however, that such selection is likely to be insufficient for origin of imprinting but could maintain it (Weisstein and Spencer, 2003). Moreover, as noted by Hurst (1997), the hypothesis only requires inactivation of genes inherited from one parent, which would be more likely to be the father in species with multiple paternity (as half sibs on average differ less in their maternally derived genes and so their maternal genes are more likely to be consistently expressed). Maternal inactivation should thus be rather improbable under this hypothesis.

Weisstein and Spencer (2003) pointed out that their mathematical model applied to a wide range of verbal models, in addition to the variance minimization hypothesis. In brief, it held for any other situations that hypothesized an intrinsic imprinting advantage in both sexes opposed by the cost of loss of masking. The complementation hypothesis outlined in Kaneko-Ishino *et al.* (2003) is one possibility. This idea holds that imprinting has evolved in order to ensure the expression of at least one copy of each gene in a cluster of imprinted genes. It is motivated by the observation of complementary expression of imprinted genes in a cluster (for example, the paternal expression of the murine *Air* gene causes the suppression of the paternal *Igf2r*, whereas the maternal expression of *Igf2r* occurs only when *Air* is maternally suppressed by methylation of the differentially methylated region in its promoter), which ensures that both genes are expressed. Any failure to imprint would lead to one of the genes being completely silenced, with consequent detrimental effects on the organism. Such circumstances could lock an organism into having to maintain imprinting, although it is not so obvious that imprinting could invade.

Maternal–fetal co-adaptation

Wolf and Hager (2006) observed that interacting maternal and offspring traits are often selected to facilitate offspring development and hence to increase offspring fitness. As a consequence, they reasoned, co-adaptation of these traits, especially those involved in close maternal–offspring interactions, should result and they modelled the evolution of imprinting from this standpoint. By way of example, in their single-locus model (in which offspring fitness was greatest for those expressing the same allele as their homozygous mother) they found that increasingly biased maternal expression would increase the mean fitness of a population. These authors then argued that this directional bias was consistent with data from the mouse, in which all genes known to be imprinted in the placenta but not elsewhere are maternally expressed (Ferguson-Smith *et al.*, 2006; Wagschal and Feil, 2006). More recent data from horse–donkey hybrids, however, show an overabundance of paternally expressed imprinted genes in the equine placenta (Wang *et al.*, 2013), which clearly does not fit with this prediction. Moreover, the model implies that imprinting should be found outside mammals, in taxa with strong parent–offspring interactions, and that in taxa where paternal care was important paternal expression would be favoured for the genes involved in this interaction.

A second possible concern arises from the details of Wolf and Hager's models. Their single-locus model is effectively one of heterozygote disadvantage and, as pointed out by the authors, the elimination of genetic variation would also increase fitness and, indeed, is predicted by the model's dynamics. (Similar concerns apply to their two-locus model as well.) Wolf and Hager (2006) argued that genetic variation is ubiquitous, however, and should thus be present

at these imprinted loci. The issue of simple population-genetic models of selection depleting variation is by no means confined to models for the evolution of imprinting, but the maintenance of variation would seem to be critical here when its elimination is a potential solution to the problem being investigated (see also Haig, 2014).

One variant on this theme is Wolf and Hager's (2009) suggestion that imprinting acts as a 'cloak', shielding an unfavoured allele in the fetus from selective abortion by the mother. As above, paternal inactivation would evolve when matching between the mother and fetus is favoured, but if mismatching were favoured (as it might be for immunity genes) maternal inactivation would evolve. They went on to describe a mathematical model that corroborated these ideas. The horse–donkey hybrid data in Wang *et al.* (2013) may fit better with this version of the hypothesis.

Maternal–fetal coordination/mother knows best

In a similar vein, Keverne and Curley (2008) argued that the molecular machinery for imprinting was primarily under maternal control. It is noteworthy that the maternal and paternal pronuclei behave very differently after fertilization: the maternal genome is ready to begin development, whereas the paternal contribution is condensed and soon undergoes extensive remodelling (including global demethylation) (Sanz *et al.*, 2010). As a consequence Keverne and Curley (2008) suggested that imprinting evolved to coordinate fetal development with the availability of maternal resources. Moreover, such maternal control would be expected in mammals given that mothers usually invest significantly more in fetal development than do fathers. Keverne and Curley (2008) maintained that, in addition to many traits important in pregnancy, imprinting would likely affect feeding, suckling and sexual behaviour.

Miri and Varmuza (2009) agreed that imprinting was (at least in mammals) largely a maternal effect and suggested that the methylation patterns in the paternal pronucleus are reset by remodelling components (for example, demethylases) entering from the oocyte cytoplasm. Crucially, these enzymes do not affect the maternal pronucleus, which, as the oocyte matures, is protected. Like Keverne and Curley (2008), Miri and Varmuza (2009) saw this maternal control as primarily benefitting the mother, in contrast to the emphasis on mutual benefits to mother and offspring envisaged by Wolf and Hager (2006). This mechanism raises the question of why there should be any gene that shows excess paternal expression in extra-embryonic tissues, let alone a majority of imprinted genes with this paternal bias (Wang *et al.*, 2013).

Moreover, being motivated by the fact that many mammalian genes manifest imprinted expression only in the extraembryonic tissues (that is, the placenta and the yolk sac), Miri and Varmuza (2009) suggested that a maternal mechanism (such as imprinting) can efficiently enhance the survival of the mother (and indeed the fetus as well) by regulating gene expression in those tissues. Thus, the evolutionary rationale for imprinting under this 'Mother Knows Best' hypothesis is the protection of the mother from rogue pregnancies (reminiscent of that under the ovarian time-bomb).

What is not clear under these hypotheses is why imprinting should be the best way to evolve efficient maternal control of fetal gene expression, as well as why certain genes important in placental development but not others should be imprinted. Moreover, it should be recognized that cooperation and co-adaptation can arise from genetic conflict (see also Haig, 2014); the metaphor of genetic conflict does not mean that maternal–fetal conflict is the outcome. As far as we are aware, there has been no mathematical modelling in this area,

although it is possible that some extension of the approach of Weisstein and Spencer (2003) that incorporates the benefits to the mother may be applicable.

Genome defence

The idea that imprinting has evolved as a by-product of the defence of the genome against transposable elements and retroviruses was inspired by the observation that foreign DNA inserts are often silenced by methylation, the same mechanism underlying much of the silencing involved in imprinting (Barlow, 1993; McDonald, 1999; McDonald *et al.*, 2005). Moreover, a number of imprinted genes contain or are near such insertions, which suggests that these insertions could have had a direct role in the differential methylation controlling expression of these genes. The non-random clustering of imprinted genes in parts of the genome near retroviruses and transposable elements also backs up this suggestion.

Given that host defence would presumably work best if expression of both copies of the foreign genes were silenced, the central question here is what has led to the sexual asymmetry inherent in imprinting? Intriguingly, transcription of human endogenous retroviruses is elevated in both reproductive tissues and the placenta (Seifarth *et al.*, 2005), and, indeed, Haig (2012) has suggested that the latter may set up heightened selection for silencing in female germlines, which could explain the asymmetry. However, perhaps the greatest weakness of the genome defence argument is that it ignores the molecular details of piRNA pathways for control of retrotransposable elements, and siRNAs for control of viral transcription in the germline (Aravin *et al.*, 2007). To our knowledge, none of the genes in these pathways are imprinted. Moreover, given the plausibility that methylation has been co-opted during mammalian evolution to implement imprinting, these observations appear insufficient to explain the evolution of imprinting without some further selective pressures to generate differential expression, such as genetic conflict (Spencer *et al.*, 1999; Haig, 2012). It might be argued that some intrinsic difference in male and female gametogenesis sets up various asymmetries in methylation, which are simply propagated during development and result in differential expression. This explanation would appear to work better for recently evolved cases arising, presumably, in response to the insertion of novel retroviruses than it would for evolutionarily conserved cases such as *Igf2* where evolution would have had ample opportunity for a more efficient method of silencing foreign DNA.

X-linked sex-specific selection

The apparent failure of the genetic-conflict hypothesis to predict the retarded development of X^{PO} mice compared with X^{mO} and (standard) $X^{\text{mX}^{\text{P}}}$ mice led Iwasa and Pomiankowski (1999) to propose that imprinting evolved under differential selection on males and females to enhance sex-linked expression. Noting that eutherian females are a mosaic of cells with one of X^{m} or X^{P} inactivated, whereas cells of eutherian males contain just X^{m} , they inferred that changes to X^{P} expression affect only females but changes to X^{m} expression affect both sexes, although males more than females. Consequently, X-linked traits with different male and female optima should be selected to be imprinted to take advantage of this mechanism for differential male/female expression and, moreover, X-linked growth enhancers should be maternally active in most eutherians as males are generally larger than females. This prediction, the opposite of that of the genetic conflict model (even as applied to X-chromosome inactivation; see Spencer *et al.*, 2004), explains the monosomic mouse data (Iwasa and Pomiankowski, 1999).

Mathematical modelling (Iwasa and Pomiankowski, 2001) bears out these verbal predictions. Nevertheless, although imprinting can ameliorate some of the conflict wrought by the differential selection pressures on males and females, it does not remove it all, and there are more efficient solutions (for example, sex-specific expression) that do. The obvious downsides to this hypothesis, clearly, are that it applies only to X-linked loci, few of which have been shown to be imprinted, and it would predict imprinting on sex chromosomes in non-mammalian taxa (for example, the Z chromosome of birds).

Sexually antagonistic selection (intra-locus sexual conflict)

In what could be seen as an extension of the previous hypothesis to autosomes, Day and Bonduriansky (2004) argued that imprinting may arise as a result of sexually antagonistic selection, whereby different alleles at a single locus are favoured in males and females. This 'intra-locus sexual conflict' can be at least partially resolved by the evolution of sex-specific imprinting, in which whether or not a gene is expressed depends not only on the sex of the parent passing on the gene but also on the sex of the recipient offspring. Because of the sexually antagonistic selection, fathers will transmit alleles with higher than average fitness when expressed in males and so selection would favour (paternal) inactivation of those alleles in daughters. Similarly, maternal inactivation of high female-fitness alleles in sons would also be favoured.

Once again, mathematical modelling confirms the verbal reasoning, but the hypothesis has been criticized as predicting sexually dimorphic imprinting, for which we are yet to discover a completely convincing example (but see Hager *et al.*, 2008; Gregg *et al.*, 2010). Nevertheless, gene expression differs between males and females for many organisms (Ellegren and Parsch, 2007) and it would be surprising if such differences did not apply to at least some loci subject to imprinting. Certainly, molecular biologists should be alert to this possibility when examining their data. Moreover, in the absence of genetic variation for sexually dimorphic imprinting or when selection is stronger on one sex than on the other, the model predicts the evolution of standard imprinting (that is, where all offspring are imprinted, regardless of sex). A second criticism is that this hypothesis would appear to apply to most groups of organisms, not just to the phylogenetically select groups of therian mammals and angiosperms. Finally, the argument given against X-linked sex-specific selection, that sex-specific expression is a more efficient way of eliminating conflict, also applies to this hypothesis.

Chip off the old block (selection for parental similarity)

Also emphasizing the centrality of sexual dimorphism, Spencer and Clark (2006) pointed out that, if there were selection for similarity with the parent of one sex, imprinting would be favoured. In circumstances where one sex has higher fitness for some trait than the other, selection will favour the expression of alleles inherited from that sex. For example, in a mammalian species exhibiting male-biased dispersal, females should exhibit greater local adaptation, and silencing of paternal alleles would be favoured. They modelled this scenario and found that high migration rates and high values of recombination were required for imprinting to evolve, conditions that, they argued, were rather restrictive. Moreover, even when imprinting was predicted to evolve, they noted that selection pressure for imprinting was rather weak, arising as a by-product of local adaptation. Other scenarios in which there is selection for parental similarity have not been modelled, but it seems imprinting is probably an unlikely evolutionary outcome. Moreover, this hypothesis requires separate selective explanations for similarity to one parent for each

imprinted locus, which again suggests that this hypothesis is not a general explanation. Once again, this hypothesis does not predict the phylogenetic pattern of observed imprinting cases.

Cytonuclear interactions

Another arena of sexual asymmetry is that of the inheritance of cytoplasmic organelles, which are transmitted uniparentally in mammals and most angiosperms. Wolf (2009) suggested that this asymmetry may lead to imprinting through the co-adaptation of organelle and nuclear genes, which would favour inactivation of nuclear copy inherited from the parent not transmitting the organelle. Thus, in mammals, which inherit their mitochondria maternally, selection should favour maternal expression and we should observe an excess of paternal inactivation of imprinted loci. Wolf (2009) modelled this scenario and confirmed the verbal plausibility of the hypothesis; imprinting evolved whenever there was cytonuclear epistasis affecting fitness, which in turn generated linkage disequilibrium between the cytoplasmic and nuclear alleles. The obvious downside to this idea is that it cannot explain maternal silencing of mammalian genes. Nevertheless, if different selection pressures have led to imprinting at different loci, it may explain some cases. Wolf (2009) also pointed out that any costs associated with imprinting might (depending on their size) prevent its evolutionary success. Finally, we know of no current examples of imprinted genes that interact with mitochondria, although, again, we suggest that empiricists be alert to this possibility.

Co-adaptation of gene expression

Inspired by the abundance of interactions observed among imprinted genes (for example, Varrault *et al.*, 2006), especially among those genes located in clusters on mammalian chromosomes, Wolf (2013) proposed that loci strongly interacting with a locus that is already imprinted subsequently evolve to be imprinted in the same direction and become more tightly linked. Consider a pair of genes, whose products (proteins, RNAs, etc.) interact in some way. Selection would favour co-adaptation and thus co-inheritance of positively interacting alleles at the two loci, much like the classical models of recombination modification, which favour tighter linkage among epistatically interacting genes (Otto and Feldman, 1997). If imprinting evolves at one locus, then selection will favour imprinting in the same direction at the second locus because it allows co-expression of alleles inherited from the same parent, which are more likely to interact positively than alleles from different parents. Moreover, tighter linkage raises the probability that the positively interacting alleles are co-inherited.

Wolf (2013) described a mathematical model that supported this verbal hypothesis. Clearly, the hypothesis does not explain the initial evolution of imprinting. However, intriguingly, it suggests that different hypotheses may explain the evolution of imprinting at different loci in a particular cluster. Moreover, it does well in predicting both the interactions among and the clustering of many imprinted loci, something that few other hypotheses do. Not all imprinted genes in clusters, however, are imprinted in the same direction, but just how they interact with other genes in their cluster should be examined in the light of this hypothesis.

Distinguishing chromosomal homologues

The hypotheses adumbrated the above posit that the target of selection leading to the evolution of imprinting is the level of expression of the maternally and paternally derived copies of the alleles at the imprinted locus. Pardo-Manuel de Villena *et al.* (2000) suggested, however, that the target is the chromatin structure of the

maternally and paternally derived chromosomes. They argued that differences between the homologous copies of chromosomes assist meiotic pairing and recombination, as well as DNA repair. Mono-allelic expression arises either as a by-product or by subsequent selection for other reasons.

One clear problem with this view is that it fails to predict the phylogenetic distribution of imprinting. Pardo-Manuel de Villena *et al.* (2000) view imprinting as part of a suite of parent-of-origin effects and see the apparent restriction of differential gene expression in animals to therian mammals as a consequence of selection (for other reasons that may be peculiar to mammals) at targets already modified by the fact that maternal and paternal alleles have distinguishable chromatin structure. They suggest that recognition of the origin of homologues may be beneficial in mediating pairing of homologous chromosomes, and that differential parent-of-origin expression may be a by-product of maintenance and exaggeration of the parent-specific chromatin marks. It seems to us, however, that this argument avoids the question motivating the other models: what selection pressures have led to differential expression?

DISCUSSION

At least 13 different models for the evolution of imprinting have been articulated that do not rely on a conflict between parents or between parents and offspring. Most of these models have some problems, as do the conflict theories for that matter, and often the problem centres on the implausibility that any given model could explain all instances of genomic imprinting. On first principles, and because of this plausibility argument, we suggest that it seems most likely that genomic imprinting exists and is maintained in mammalian genomes for several different reasons, and that the imprinting status of different genes might have quite different mechanisms of origin. It is clear, for instance, that the differentially methylated domain of *Rasgrfl* was introduced by a transposable element, and its imprinting may be associated with co-option of the mechanism to silence the element (Watanabe *et al.*, 2011). Contrasts of imprinting status of genes across different mammalian species also show acquisition of novel imprinted genes brought about by a genome rearrangement, bringing a formerly non-imprinted gene into the proximity of an imprinted gene cluster where it acquires allele-specific methylation and imprinting. An excellent example of this is the retinoblastoma gene *RBI*, which is not imprinted in rodents, but after insertion of a transposed pseudogene bearing a differentially methylated CpG island in an ancestral primate it has become imprinted through acquisition of maternally biased methylation producing maternally biased expression in humans and chimpanzee (Kamber *et al.*, 2009).

In order to ease the summary of the salient features of the various non-conflict models, we assemble them in Table 1. Many of the models seem to be rather poorly supported, but some models (or combinations of models) could easily explain imprinting of some genes. For example, co-adaptation of gene expression would appear to do a better job of explaining the co-ordinated expression of clusters of imprinted genes than the kinship/conflict hypothesis, although it cannot explain the original evolution-of-imprinting event in the cluster. The variance-minimization model seems quite plausible for a subset of imprinted genes that are near or within imprinted clusters, especially in light of data showing the exquisite sensitivity of gene dosage at some imprinted loci (for example, Charalambous *et al.*, 2012). The idea that some maternally expressed imprinted genes might interact with the mitochondrion is especially attractive, even if it could only explain a minority of genes. Cases of transposable-element insertion impacting methylation status and likely giving rise

Table 1 Summary of the support and challenges for the non-conflict models of imprinting

Model	Supportive data	Math support?	Challenges
1. Prevention of parthenogenesis	No parthenogenesis in mammals	No	Requires group selection
2. Ovarian time-bomb	No parthenogenesis in mammals	Yes	Not clear why there are so many imprinted genes; Why are there not more conserved imprinted genes?
3. Dominance modification	Imprinting acts rather like dominance	Theory argues against it	Evolution of dominance modifiers is very slow
4. Variance minimization/ complementation	Clusters of alternatively imprinted genes	Yes, for maintenance but not origination	Not all imprinted genes are in clusters; Fails to predict phylogenetic pattern
5. Maternal–fetal co-adaptation	Imprinting could easily accomplish this coadaptation	Yes, but the model cannot maintain polymorphism	Many cases of placental imprinting express the paternal allele
6. Mother knows best	Maternally expressed imprinted genes can coevolve with maternal genome	No	Many cases of placental imprinting express the paternal allele
7. Genome defence	Many imprinted genes are near transposable element insertions	No	Only explains local presence of methylation, not parent-of-origin specificity; Does not predict phylogenetic pattern
8. X-linked sex-specific selection	X ^{PO} mice develop more slowly than X ^{MO} mice	Yes	Applies only to X-linked loci
9. Sexually antagonistic selection	There are male-favourable and female-favourable alleles, so why not imprint them?	Yes	No clear examples of sexually dimorphic imprinting; Fails to predict phylogenetic pattern
10. Chip off the old block	Selection to favour offspring matching one of their parents	Yes, but conditions restrictive	Requires separate selection scenario for each imprinted locus; Fails to predict phylogenetic pattern
11. Cytonuclear interaction	Expect expression of parental allele that transmits unisexually transmitted organelles	Yes, verbal	No examples of imprinted genes interacting with organelles; Fails to predict phylogenetic pattern
12. Co-adaptation of gene expression	Imprinted genes occur in clusters and are often imprinted in the same direction	Yes	Does not explain initial origin of imprinting; Not all genes in clusters are imprinted in the same direction
13. Distinguishing chromosomal homologues	Epigenetic differences occur between chromosomes of different parental origin	No	Does not explain differential gene expression being limited to mammals and angiosperms

to *de novo* imprinting have been cited; hence, TEs clearly can be involved in some cases; however, this observation does not mean that genomic defence of TE insertion is tied to the evolution of imprinting. Several models posit the existence of sex-specific genomic imprinting, but there have been no reports pinning down the quantitative-trait loci (QTLs) reported by Hager *et al.* (2008) or confirming the findings of Gregg *et al.* (2010), and efforts using RNA-seq in reciprocal F1 mouse brain and placenta find no cases of sex-specific genomic imprinting (Wang and Clark, unpublished). The maternal–fetal co-adaptation hypothesis is appealing because of the significant number of imprinted genes whose expression levels seem to be highly coordinated in the mother and fetus and seem to be crucial for placental function. In sum, for a substantial subset of imprinted genes, one or more of these non-conflict/ non-kinship models appear to offer plausible alternative explanations for the evolution of imprinting, challenging the hegemony of the conflict/kinship hypothesis. In our view, genomic imprinting appears to be yet another phenomenon where nature has opportunistically opted to exhibit parent-of-origin expression for many reasons tied to the functional constraints and context of each gene.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

The authors declare no conflict interest.

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