Monoallelic Gene Expression in Mammals

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Abstract

Monoallelic expression not due to *cis*-regulatory sequence polymorphism poses an intriguing problem in epigenetics because it requires the unequal treatment of two segments of DNA that are present in the same nucleus and that can indeed have absolutely identical sequences. Here, I focus on a few recent developments in the field of monoallelic expression that are of particular interest and raise interesting questions for future work. One development is regarding analyses of imprinted genes, in which recent work suggests the possibility that intriguing networks of imprinted genes exist and are important for genetic and physiological studies. Another issue that has been raised in recent years by a number of publications is the question of how skewed allelic expression should be for it to be designated as monoallelic expression and, further, what methods are appropriate or inappropriate for analyzing genomic data to examine allele-specific expression. Perhaps the most exciting recent development in mammalian monoallelic expression is a clever and carefully executed analysis of genetic diversity of autosomal genes subject to random monoallelic expression (RMAE), which provides compelling evidence for distinct evolutionary forces acting on random monoallelically expressed genes.

INTRODUCTION

In diploid eukaryotic organisms, the maternally and paternally derived copies of each autosomal gene are usually assumed to be simultaneously expressed at similar levels. One type of violation of the assumption of similar levels of expression comes from polymorphisms in *cis*-regulatory elements close to or far away from a given gene. Such *cis*-regulation is an important driver of evolution and plays a large role in disease, but is not considered in this review. Another type of genetic variation that can impact allele-specific studies is the ever increasingly appreciated presence of copy number variation. See, for example, a recent study by the McCarroll group examining multiallelic copy number variation in humans (27).

Here, I focus on epigenetic mechanisms that allow even equally capable alleles to be differentially expressed, noting that such epigenetic mechanisms coexist with copy number variation and genetic polymorphism in *cis*-regulatory elements, and indeed such genetic mechanisms pose technical hurdles in accurately examining epigenetically determined allelic imbalance. Epigenetic mechanisms can lead, in some cases, to only one allele being transcribed while the other allele is transcriptionally silent, referred to as monoallelic expression.

Monoallelically expressed genes belong to three distinct classes (**Figure 1**). In parent-of-origin imprinting (usually referred to as imprinting), monoallelic expression is determined by marks placed during gametogenesis, which lead to imprinting either in specific tissues or throughout the entire organism (46). All cells in which a given gene is imprinted have the same active allele, which is determined solely by the parent of origin of the allele. The remaining two classes of genes both fall into the category of random monoallelic expression (RMAE) and include X-inactivated genes, for which there is coordination across the X chromosome (37), and autosomal RMAE (24). In both types of RMAE of genes, the initial random choice between alleles is followed by a stable mitotic transmission of monoallelic expression. A more fluid type of monoallelic expression that while random is not mitotically stable has also been described but is not considered further here (16).

IMPRINTING

Whether it is called parent-of-origin imprinting, genomic imprinting, or simply imprinting, this type of monoallelic expression is determined by different epigenetic marks placed during gametogenesis in the male and female germline. The fertilized egg thus has different marks on the copies of imprinted genes that came from the paternal and maternal contributions. The differential marking

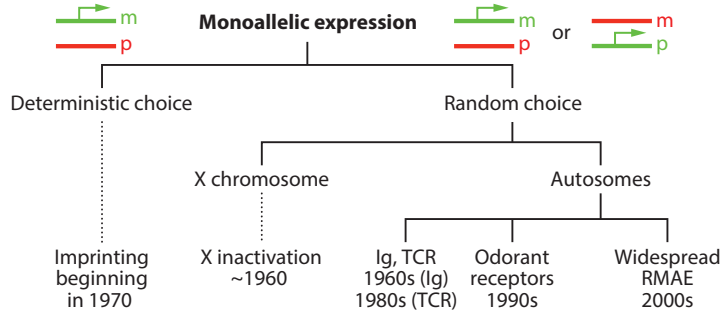

Figure 1

Types of epigenetically mediated monoallelic expression. The first division is between deterministic monoallelic expression and stochastic monoallelic expression. In deterministic monoallelic expression, one allele is always chosen, whereas in stochastic monoallelic expression, cells express either of the two alleles. Abbreviations: Ig, immunoglobulin; RMAE, random monoallelic expression; TCR, T-cell receptor.

leads to monoallelic expression, sometimes just in specific tissues but more commonly throughout the entire organism; some imprinted genes are expressed only from the maternal allele, whereas others are expressed only from the paternal allele. All cells in which a given gene is imprinted have the same active allele, which is determined solely by the parent of origin of the allele. Imprinted genes encode proteins whose functions are widely spread among cellular functions. It is notable that a variety of epigenetic marks, including DNA methylation and modifications of histones, have been associated with imprinted loci (22).

How many genes are subject to imprinting? Estimates of the number of imprinted genes are in the range of 100 in mice and approximately 50 in humans. Most imprinted human genes are also imprinted in the mouse, but because there are more imprinted genes in the mouse not all of them are imprinted in humans. Some recent controversies regarding the best way to assess imprinting using new mRNA sequencing technologies are addressed below.

History of Searches for Imprinted Genes

The term imprinting was first used in biology in 1960 by Helen Crouse (13) to describe the programmed elimination of paternally derived X chromosomes in sciarid flies. Early use of the term imprinting to refer to the loss of genetic information notwithstanding, imprinting is now commonly accepted as describing parent-of-origin–dependent monoallelic expression. The first described case was a plant example, wherein it was shown that the R locus involved in maize kernel coloration has allele-specific expression determined by the parent of origin of the allele rather than the DNA sequence (36).

Mouse experiments published in the 1970s also revealed parent-of-origin effects. One study analyzed a deletion at the Tme (T-associated maternal effect) locus that showed early lethality when maternally inherited but not when paternally inherited (35). Other studies analyzed Robertsonian translocations (reciprocal translocations), which allowed manipulation of the parent of origin of distinct chromosomal regions. Areas of uniparental disomy were created, and it was shown that for certain chromosomal regions, or entire chromosomes, even though the dosage of all areas of the genome was diploid, there were phenotypic effects of the uniparental disomy (9). Thirteen subchromosomal regions were eventually defined by these experiments and these regions harbor most imprinted genes of the mouse. Cloning experiments performed in the 1980s noted that both the maternal and the paternal genomes were needed to construct a viable embryo (38, 55). Attempts at the construction of gynogenetic and androgenetic mouse embryos failed; although both types of embryos were diploid, neither could successfully develop a viable embryo. The appreciation that the maternal and paternal DNA contributions to the developing embryo contained information specific to their parental origins was immediately fascinating to biologists and led to efforts in numerous groups around the world to identify imprinted genes and to study the mechanisms underlying the phenomenon.

The first imprinted genes, found in 1991, were *Igf2* (14) and *Igf2r* (5), a receptor for Igf2. Soon after, a noncoding RNA, H19, was found within 100 kb of the *Igf2* gene (6). H19 is expressed from the maternal allele, whereas Igf2 is expressed from the paternal allele. As more genes were found, mechanistic studies began to reveal that differentially methylated regions (DMRs) characterized imprinted loci. The differential methylation occurs because different patterns of methylation are placed on genes during gametogenesis in the male versus the female germline. There are also DMRs that are not based directly on marks placed during gametogenesis but rather are placed during early embryonic development in response to other marks that did derive from the respective parental germlines. Most, but not all, orthologs that are imprinted in humans are also imprinted in mice (39).

Imprinting mechanisms are a potential target for therapies to ameliorate pathophysiology. An interesting recent example that shows the potential for an epigenetic-based therapy is the discovery, via chemical screening, that topoisomerase inhibitors can improve neural function by unsilencing the dormant allele of the *Ube3a* gene, a gene within the Prader-Willi/Angelman syndrome region (33). For further discussion of molecular mechanisms underlying imprinting, involving DNA methylation and other epigenetic marks, see a review by Abramowitz & Bartolomei (1).

X INACTIVATION

For X-inactivated genes, there is coordination across the X chromosome of monoallelic expression. Early events in setting up this monoallelic expression include interactions between a number of *cis*-regulatory elements and noncoding RNAs in a region called the X-inactivation center. The Xist noncoding RNA ultimately becomes fixed in its transcription at only one of the two X chromosomes and coats most of this chromosome in *cis*, which results in transcriptional silencing of most genes on that chromosome (12). Among other epigenetic marks associated with the inactive X are late replication, DNA methylation at CpG islands, and hypoacetylation of histones as well as unusual histone subunit deposition. In 2007, Asaf Hellman discovered that there is allele-specific DNA methylation on the active X in areas outside of CpG islands and somewhat focused on gene bodies (29). This was the first demonstration of gene body methylation in mammals. The initial random choice between the two X chromosomes is followed by a stable mitotic transmission of monoallelic expression. In the case of X inactivation, a random choice is made in individual cells early in female development (37). There are genes that escape X inactivation in humans, and the extent of escape can vary among individuals (8).

Although X inactivation is random, there is sometimes skewing of X inactivation, either because of sequence polymorphism, which leads to primary skewing, or mutation on one or another gene on the X, which leads to secondary skewing due to differential growth/survival of cells. The extent to which skewing of X inactivation plays a role in brain phenotypes is difficult to assess, but undoubtedly the potential for such a role is there. Rett syndrome, a neurodevelopmental disorder, is caused by mutations in the X-linked *MeCP2* gene and is a disease in which skewed X inactivation has been considered (3).

AUTOSOMAL RANDOM MONOALLELIC EXPRESSION

The first autosomal genes discovered to be subject to RMAE were the genes encoding antigen receptors on B and T lymphocytes: immunoglobulins and T-cell receptors, respectively. Allelic exclusion was discovered for immunoglobulins in the 1960s by Pernis and colleagues (45), prior to the isolation of the immunoglobulin genes. Allelic exclusion was subsequently shown to be due to DNA rearrangement, first for immunoglobulin genes (32) (for which Susumu Tonegawa won the Nobel Prize) and later for T-cell receptor genes. The immunoglobulin and T-cell receptor genes remain the only known mammalian genes subject to somatic DNA rearrangement.

Until the mid-1990s, it was thought that the immunoglobulin and T-cell receptor genes were special cases, and allelic exclusion of other genes was not entertained as a mechanism. In 1994, a report of RMAE of odorant receptor genes, a family with more than 1,000 members (in the mouse genome), led to the idea that autosomal RMAE may affect additional autosomal genes (11). Over the ensuing decade or so, the class of autosomal randomly monoallelically expressed genes was expanded with the addition of a handful of examples that are generally involved in chemosensory or immune system functions. Genes found to be subject to RMAE included

pheromone receptor genes (which are similar to odorant receptor genes), interleukin genes, and genes encoding receptors on natural killer (NK) cells (7, 28, 30, 47–49).

A defining feature of these autosomal genes is that they (like X-inactivated genes) are monoallelically expressed in a random manner. For some of these genes, half the cells express the maternal allele and half the cells express the paternal allele. Other genes also falling into the randomly monoallelically expressed class have some cells with biallelic expression (BAE) in addition to the cells with monoallelic expression. Here, for the most part, I am focusing on an all-or-none pattern such that the nonexpressed alleles appear to be completely, or almost completely, silent in those cells in which they are not expressed. Notably, autosomal RMAE can significantly impact biological function because it leads to three distinct expression states for each gene: expression of both alleles in some cells and expression of either the maternal allele or the paternal allele in other cells. Thus, RMAE can lead to unique cell identity for individual cells.

Improvements in technology have led to an appreciation of the widespread nature of RMAE across the genome—beyond chemosensory and immune system genes. Around the turn of the century, the initial sequencing of the human genome was complete. The ensuing extensive characterization of common human polymorphisms, along with the development of arrays capable of determining the genotype at hundreds of thousands of loci in a single experiment set the stage for genome-scale analyses of RMAE. In 2007, a genome-wide survey that analyzed clonal human cell lines (as well as freshly isolated tissues) revealed a surprisingly large extent of random autosomal monoallelic expression: upward of 5% beyond the few percent of the genome encoding odorant receptors (24).

Although the earlier-known autosomal genes subject to RMAE were for the most part involved in the immune system or chemosensory systems, the genes uncovered in the genomic survey are widely distributed across functionalities. Also, most gene ontology (GO) categories are represented, indicating that these genes have wide-ranging functions. In addition to variation in the types of proteins they encode, they also vary in their respective expression patterns. Unsurprisingly, tumor suppressor genes are not randomly monoallelically expressed. Some randomly monoallelically expressed genes are abundantly expressed, whereas others are expressed at low levels.

Even though the functions of genes subject to RMAE are widely varied, there is an excess of genes encoding cell surface markers. This excess suggests a role for RMAE in the specification of unique cellular identity. Examining the GO category "transmembrane receptor" using GOstat, one would expect the number of monoallelically expressed genes in the gene list from the article by Gimelbrant et al. (24) to be ~3%; however, the observed value was much higher: 8.8%. The overrepresentation of cell surface molecules suggests the possibility that RMAE is involved in generating unique cellular identity for individual cells. Such cells might otherwise have been indistinguishable based on their sharing respective developmental histories, locations, and gene expression programs.

Studies in mice have also shown the presence of RMAE genes. Zwemer et al. (58) showed that the frequency of monoallelic expression was ~10%, slightly higher than what was observed in human cells. When comparing mouse and human, the number of autosomal orthologs demonstrating RMAE in both species was greater than would be expected by chance. RMAE in the mouse is broadly similar to that in human cells: It is widespread throughout the genome, lacks chromosome-wide coordination, and varies between cell types. However, for some mouse genes, there appears to be skewing, in some ways resembling skewed X inactivation, wherein one allele is more frequently active. RMAE in mouse has also been found in embryonic stem cells (20) as well as in neural progenitor cell lines (20, 23).

An exciting development in the field of RMAE was the finding of a chromatin signature for RMAE genes by Gimelbrant and colleagues (42, 43). The chromatin signature consists of

H3K36me3, a chromatin mark associated with active transcription, and H3K27me3, a chromatin mark associated with silencing, both present in the gene body. The explanation of the chromatin signature is that the transcribed allele has the H3K36me3 mark and the silent allele carries the H3K27me3 mark. A database of RMAE genes (dbMAE) has also been created (51).

Another fascinating mechanistic line of work has come from Matthew Thayer and colleagues, who have been characterizing a locus on mouse chromosome 6 that has many properties similar to Xist, the noncoding RNA involved in X inactivation (19, 54). The ASAR6 noncoding RNA is monoallelically expressed on the opposite chromosome, as are other nearby RMAE genes, and undergoes asynchronous replication. Recently, the Thayer group has made further discoveries on chromosome 15 (18). Note that earlier studies of asynchronous replication showed coordination across autosomes in both mouse (52) and human (21). Curiously, although the asynchronous replication of RMAE genes is coordinated, their expression is not necessarily coordinated (24, 58), leading to the idea that late or early replication serves to distinguish the two alleles but perhaps does not dictate which allele is expressed.

We have recently shown that the *FOXP2* gene, which is involved in developmental verbal dyspraxia, is subject to RMAE (2). Also, studying an individual with developmental verbal dyspraxia, we identified a deletion 3 Mb away from the *FOXP2* gene, which impacts *FOXP2* expression in *cis*. Together, these data suggest the intriguing possibility that RMAE impacts the haploinsufficiency phenotypes observed for *FOXP2* mutations. In general, RMAE can lead to a nonclassical model of haploinsufficiency wherein instead of each cell having a phenotype due to half the amount of expression, some cells have normal levels and others have no expression. Evidence that, as a class, RMAE genes impact neurodevelopment disorders has been presented (34).

NETWORKS OF IMPRINTED GENES

In this section, I consider recent work pointing to gene networks involving imprinted genes. Such networks could impact the physiology seen in extant species as well as reveal aspects of the evolution of imprinting. The evolutionary drivers underlying imprinting have been the subject of numerous reviews and are not discussed at length here. One proposed evolutionary driver of imprinting is that it affords a mechanism to prevent parthenogenesis. Another potential evolutionary driver of imprinting was proposed by David Haig and is known as the Haig hypothesis, which stipulates that imprinting arose from gender-based evolutionary conflict over maternal resources (40). Meanwhile, a number of further theories have been proposed that do not involve conflict between the sexes. For a good place to explore the evolution of imprinting, I suggest the review of nonconflict theories by Spencer & Clark (53) as well as a review by Holman & Kokko (31).

Studies of gene interactions suggest interesting networks of genes that include both imprinted and nonimprinted genes. A recent study in mice concluded that a strikingly large fraction of quantitative traits show parent-of-origin effects on heritability (93%, 91/97 tested) (41). These parent-of-origin effects are confounded by family structure. Interestingly, knockouts of two nonimprinted genes impacted the regulation of many imprinted and nonimprinted genes. The authors propose that network interactions can allow a nonimprinted gene to generate parent-of-origin effects by interactions with imprinted loci. This study raises more questions than it answers, which will certainly stimulate more studies and lead to new insights, and it will be interesting to see how future work in this area advances.

Another recent study (4) extended earlier work showing that 15 imprinted genes interacted (56), thus extending the network to include all imprinted genes and showing that this imprinted gene network also includes nonimprinted genes. Genes in this network are enriched for extracellular matrix genes as well as cell cycle exit and differentiation genes. The authors also suggest (4) that

the network they have identified could explain some of the parent-of-origin effects seen in the study by Mott et al. (41). This will be an interesting avenue of research to follow in the coming years.

HOW TO MEASURE ALLELE-SPECIFIC EXPRESSION

The advent of next-generation sequencing allowed for experiments searching for imprinted genes and RMAE genes in mRNA-seq data and for consideration of caveats to this type of approach (15, 57). One question emerging from considering all of these studies is what level of skewing toward one parental allele should be considered substantial enough to study further. The early reports of imprinting suggested that those early-found genes were absolute in their imprinting. Regarding RMAE genes, for immunoglobulin genes and for olfactory receptor genes, expression can be shown most of the time to be entirely from one allele with no expression of the other, i.e., 100% allele 1 and 0% allele 2. How should one think about genes with more subtle skewing? With enough data, even slight bias toward one of the two alleles, for example 52% versus 48%, can be statistically significant, but it becomes more difficult to build biologically plausible impacts of differential expression as the difference between the two alleles approaches zero. Sure, it is possible for subtle effects to impact biology in a meaningful way. However, the numerous technical artifacts that can arise in sequencing experiments also need to be carefully considered in all experiments but especially if focusing attention on subtle effects.

Note that there were two widely discussed reports from Catherine Dulac and colleagues in 2010 that used RNA-seq and claimed that there are more than 1,300 imprinted genes in the mouse brain (25, 26). However, technical and analytic mistakes (which led to the overexuberant tallying of imprinted genes) were explicitly pointed out by DeVeale et al. (17) in work that reanalyzed the primary data from the earlier reports from the Dulac group (25, 26) and also analyzed independently obtained data sets. DeVeale et al. (17) estimated the number of imprinted genes to be around 175. An earlier manuscript (57) examined neonatal mouse brain and found three novel imprinted genes, all of which were near known imprinted genes. Unfortunately, in more recent studies from Dulac and colleagues in which they analyze a different brain region and essentially find no new imprinted genes (44), they still refer to the conclusions of the Gregg et al. (25, 26) reports without discussing whether they now agree with the conclusions of DeVeale et al. (17) that the vast majority of the novel reported imprinted genes in the Gregg et al. reports were artifacts.

GENOME-SCALE ANALYSES POINTING TOWARD AN IMPACT OF RANDOM MONOALLELIC EXPRESSION ON GENETIC DIVERSITY

A recent study by the laboratories of Alexander Gimelbrant & Shamil Sunyaev (50) suggests the exciting possibility that genes showing a RMAE signature have more genetic diversity than BAE genes, thus increasing the potential for cellular diversity within tissues of each individual.

To set the stage for describing the studies of diversity, I briefly discuss an idea I suggested in a prior review (10), which is that RMAE can increase evolvability (by facilitating positive Darwinian selection on heterozygous individuals) while simultaneously allowing a relaxation of purifying selection (negative selection) on heterozygous individuals. Although I considered more general examples in the prior review, here I focus on one hypothetical example from the olfactory system. RMAE is absolute in the murine olfactory system (11). Assume for this example that at some time in evolution a mouse species has one of the more than 1,000 olfactory receptors well adapted to smelling a unique food source, say strawberries. I apologize to the field studying the diet of mice if mice do not eat strawberries; in this hypothetical example, they do. The olfactory

system has a large number of neurons (typically greater than 1,000) expressing each olfactory receptor gene. Only one of the more than 1,000 olfactory receptor genes is expressed in a given neuron and as mentioned above RMAE is absolute. Now consider what would happen if a single mouse had a de novo single nucleotide substitution rendering the strawberry-detecting olfactory receptor now a raspberry-detecting olfactory receptor (while simultaneously losing its ability to detect strawberries). This mouse would now, because of RMAE, have half the normal number of strawberry-detecting neurons, but based on what is known about the olfactory system there would be no diminution in the ability of the animal to detect strawberries. Moreover, the new ability to detect raspberries would be an advantage. Thus, one can easily see that there would be heterozygote advantage, or overdominance.

Gimelbrant, Sunyaev, and colleagues performed an extensive genome-scale assessment of genetic variation in human RMAE genes (50). With good reason, they left out nonmitotically stable RMAE as well as imprinted genes. Taking advantage of the prior discovery of an epigenetic signature of RMAE genes from the Gimelbrant laboratory (42, 43), they assembled a large set of RMAE genes to compare with the rest of the genes in the genome. They also took advantage of recently emerging data sets describing genetic variation across the human genome in a variety of human populations.

A substantial portion of the genes in the human genome were analyzable based on the various filters they put into place to give confidence that the chromatin signature–based approach was doing a good job separating RMAE genes from BAE genes. Of 10,233 assessable genes, 4,227, or 41%, were classified as RMAE, whereas 6,006 were classified as BAE; the remaining genes in the genome were left out of the analyses. A key finding was that nucleotide diversity (π) determined from the 1000 Genomes Project data was higher for coding regions of RMAE genes than for BAE genes. The mean for RMAE genes was 5.0×10^{-4} (95% confidence interval $\pm$ 2.0×10^{-5}) and the mean for BAE genes was 3.3×10^{-4} (95% confidence interval $\pm$ 9.3×10^{-6}). The difference in diversity was independent of whether or not a given base is in a fourfold degenerate site, and the difference in diversity was found in various different populations and was not driven by particular GO categories.

One possible explanation for increased nucleotide diversity is the relaxation of purifying selection, but this was argued against with a variety of further analyses. The RMAE genes were not less highly represented in the Online Mendelian Inheritance in Man (OMIM) database; indeed, they were slightly more highly represented. Further analyses indicating similar purifying selection included examining the so-called d_N/d_S ratio (the ratio of the number of nonsynonymous substitutions per nonsynonymous site divided by the number of synonymous substitutions per synonymous site); the d_N/d_S ratio was 0.21 ± 0.01 for both the RMAE and BAE gene sets. A number of other analyses supported the conclusion that purifying selection is similar in the two gene sets.

Other possible contributors to increased diversity include recombination rate and CpG content, and these were shown to explain less than half the difference in nucleotide diversity. A greater impact appears to be caused by balancing selection. Genetic variation is older in RMAE genes, with human-chimpanzee *trans*-species polymorphisms (TSPs) enriched within the RMAE gene set (odds ratio of 1.89, $P = 6.3 \times 10^{-6}$).

In summary, the patterns of increased nucleotide diversity in RMAE genes are consistent with the idea of heterozygote advantage for RMAE genes because of the increased cellular diversity afforded by the combination of heterozygosity and RMAE. Thus, RMAE may provide a mechanism underlying heterozygote advantage. This is in contrast to the imprinted MAE genes, where parent-of-origin dictates expression and where the selective advantage is still a topic of intense discussion.

DISCLOSURE STATEMENT

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Errata

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