Biochem 158/258
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Final Project

Genomic Imprinting: Relevance to human disease and theories of origin

Introduction

Genomic imprinting is an epigenetic phenomenon in which the expression of a gene or chromosomal region is modified depending on the sex of the transmitting parent. In case of single genes, this generally equates to partial or complete silencing of one of the parental alleles for a diploid locus. In other cases, an imprinted locus can include a variety of maternally expressed, paternally expressed and biallelically expressed transcripts. Some of these transcripts can produce different proteins through alternate splicing, or noncoding RNA transcripts. The exact number of imprinted loci remains unknown, but it is clear that these loci form only a small minority of the mammalian genome.

The unequal expression of some maternally and paternally derived genes reduces, or even eliminates, the benefits of diploidy. The most widely accepted explanation for the predominance of diploidy among complex multicellular organisms is that the possession of two functional copies of each gene masks the effects of deleterious recessive mutations. In this view, genomic imprinting is paradoxical, because it forgoes the diploid advantage. There has to be some type of selective advantage to genomic imprinting, to outweigh the loss of the diploid benefits. Several theories have been presented on the origin of genetic imprinting.

This project aims to discuss genetic imprinting from an evolutionary point of view, and review the main theories that have been suggested for the origin of genetic imprinting. A plausible theory should be able to explain the diversity of imprinted genes and their phenotypes, but at the same time give a reason for why most genes are not imprinted.

The outline of the project is as follows: Some general features of genetic imprinting in mammals are described first, followed by a brief review of diseases in humans due to genomic imprinting. Theories of the origin of genetic imprinting are then described, followed by discussion.

Some of the relevant MeSH terms for a PubMed search include "Genomic Imprinting"[MAJR], "Models, Genetic"[MAJR], "Genetic Predisposition to Disease"[MAJR] and "Evolution, Molecular"[MAJR].

The key references include the following review articles:

Jon F Wilkins & David Haig: What good is genomic imprinting: the function of parent-specific gene expression *Nature Reviews Genetics* **4**, 359-368 (May 2003)

Francisco Ubeda and Jon F Wilkins: Imprinted Genes and Human Disease: An Evolutionary Perspective. *Adv Exp Med Biol* **626**, 101-115 (2008)

A more complete list of references is included at the end of the paper.

Genomic Imprinting in Mammals

Imprinted genes in mammals are generally found in clusters referred to as "imprinted domains", and often oppositely imprinted genes occur within a single domain. These clusters vary from a few dozen up to thousands of kilobases in size. Each cluster can contain as few as two imprinted genes, or as many as several dozen imprinted genes. It is common that imprinted genes are interspersed with non-imprinted genes within a cluster. The clustered organization is thought to reflect coordinated regulation of genes in a chromosomal domain. Imprinted gene expression across the clusters is regulated by imprinting control regions (ICRs) which can be up to several kilobases in size.

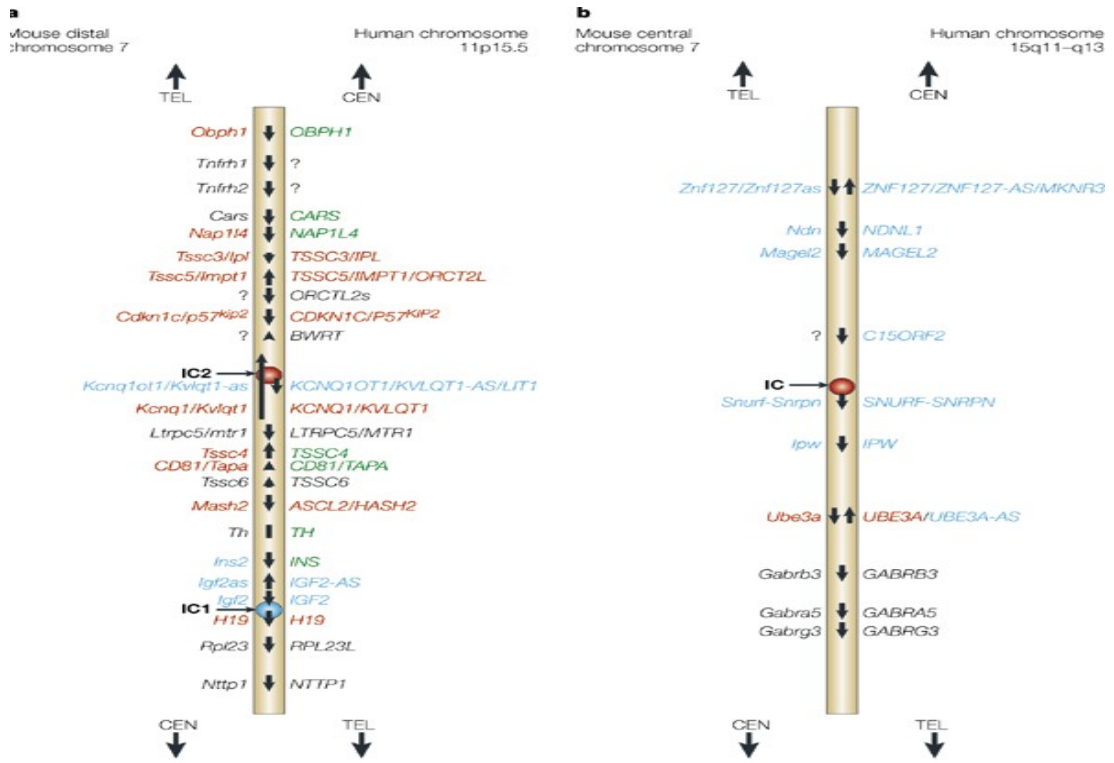

Figure 1: Examples of imprinting clusters in human and mouse, including human chromosomes 11p15.5 and 15q11-q13 as well as the orthologous clusters on mouse chromosome distal 7 and central 7. (Source: Reik & Walter, Genomic imprinting: parental influence on the genome, Nature Reviews

Genetics 2, 21-32 (2001)).

Currently, there are approximately 150 known imprinted genes identified in mice (Mammalian Genetics Unit Hartwell http://www.mousebook.org/catalog.php?catalog=imprinting). In the mouse, many chromosomal regions associated with imprinting show phenotypic effects of growth, viability, behavior, or some combination of the three. Many of the genes imprinted in mice are imprinted in humans as well (Catalogue of Parent of Origin Effects, http://igc.otago.ac.nz/home.html). It is estimated that there may be as many as several hundred imprinted genes in the mammalian genome and more imprinted genes are expected to be found.

DNA methylation is a key molecular mechanism of imprinting; methylation marks the imprinted genes differently in egg and sperm cells, and inheritance of these epigenetic marks leads to differential gene expression. Imprinted genes are unusually rich in CpG islands compared to the rest of the genome. Also, clustered, direct repeats are common within or in the vicinity of CpG islands. However, neither the repeats nor the CpG islands are unique to imprinted genes, so these features can't be used in a systematic search for new imprinted genes.

Epigenetic modifications within imprinted domains include differential methylation of DNA, differential acetylation of histones, and differential methylation of histones. In genomic imprinting, modifications appear on specific loci during gametogenesis. These epigenetic marks are called "imprints". Molecular studies have determined that imprinting is controlled by cytosine methylation at ICRs. DNA methylation imprints are maintained throughout embryonic development and postnatal life. The imprints control parental-allele specific expression to nearby genes in the developing embryo. However, methylation at ICRs is erased in the primordial germ cells of the developing embryo, and new imprints are re-established at later stages. The sequential events of establishment, maintenance and erasure constitute the developmental cycle of imprinting.

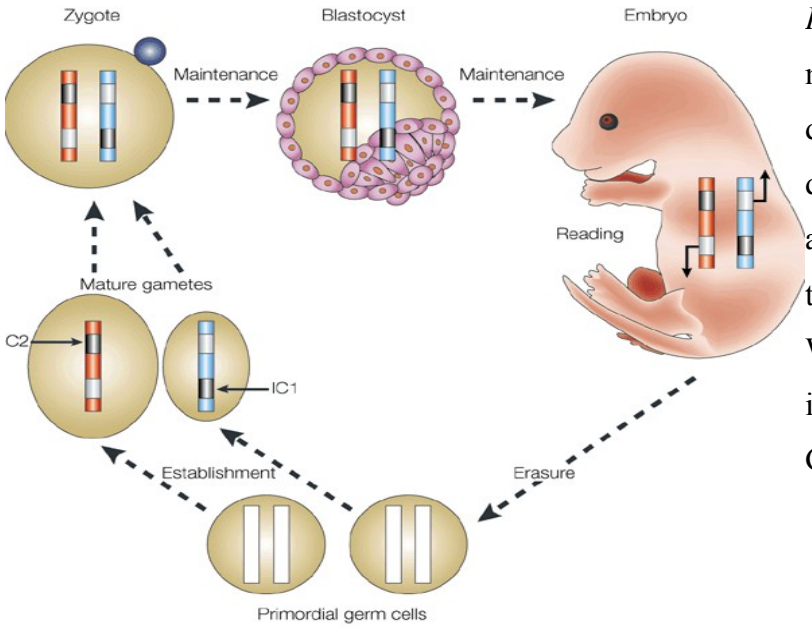

Figure 2: Erasure, establishment and maintenance of methylation imprints during germ cell and embryonic development. Grey indicates modification and white indicates no modification in at the corresponding alleles. (Source: Reik & Walter, Genomic imprinting: parental influence on the genome, Nature Reviews Genetics 2, 21-32 (2001))

DNA methylation in mammals is regulated by members of the DNA methyltransferase (DNMT) family, and DNMTs play an important role in the establishment and maintenance of methylation imprints. Mammalian genetic imprinting appears to have evolved in the common ancestor of marsupials and eutherian (placental) mammals, coinciding with the origination of viviparity (retention and growth of the fertilized egg within the maternal body until the offspring is capable of independent existence). Many of the genes that are imprinted in mammals have homologs in lower organisms. However, these homologs are not imprinted like their mammalian counterparts. Genetic imprinting also appears to have evolved independently in some other phylogenetic clades. For instance, genetic imprinting is observed in angiosperms (flowering plants) as well as insects.

It has been found that monoallelic expression of imprinted genes is not always absolute. In some cases, basal levels of expression from the "silent" allele have been observed. Imprinted genes are involved in various biological processes, and perturbation of their expression can cause embryonic or postnatal lethality, aberrant growth and abnormal behavior.

Some examples of genomic imprinting can be seen in animal breeding. In the crossing of two species that are able to interbreed, such as horse and donkey, or lion and tiger, the offspring exhibits different phenotypes depending on how the two species were crossed.

Figure 3: Examples of genomic imprinting in the horse/donkey breeding, resulting in mule/hinny offspring and the lion/tiger breeding resulting in liger/tigon offspring. In both cases, the size and appearance of the offspring is highly dependent on which way the parents were crossed. (Images from http://atlasgeneticsoncology.org/Deep/GenomImprintID20032.html and http://www.furrybones.com/ligers-tiglons-tigons-information.html)

Diseases in Humans due to Genomic Imprinting

Dysregulation of genomic imprinting can cause a variety of human diseases. There are two main reasons why an imprinted gene might be more likely to express a disease phenotype, or be more susceptible to mutations. First, imprinted genes are functionally haploid, and recessive mutations are exposed on the active genes. Deleterious recessive mutations which would have no consequences when heterozygous at an unimprinted locus may have severe effects at an imprinted one. Second, the expression of imprinted genes is conditioned by epigenetic factors, and the genes are therefore susceptible to epimutations. These epigenetic modifications include DNA methylation on cytosines in CpG nucleotides and histone modifications including methylation and acetylation. The epigenetic mechanisms may result in phenotypes that bear resemblance to genetic disorders but are not associated with mutations in the DNA sequence.

Imprinted genes have been associated with a wide range of diseases. Many of the diseases associated with imprinting involve some type of a growth or feeding disorder. As many imprinted genes are involved in fetal growth and embryonic development, proper regulation of genomic imprinting is essential for mammalian embryos to develop normally.

Some diseases associated with genetic imprinting are highlighted below:

Prader Willi and Angelman syndromes

Prader-Willi syndrome (PWS) and Angelman syndrome (AS) were the first reported imprinting disorders in humans. The so-called PWS/AS chromosomal region 15q11-q13 comprises a large cluster of imprinted genes which are causally involved in these syndromes. PWS is a result of the absence of expression of paternally derived genes in the cluster, while AS is caused by loss-of-expression of maternally expressed genes in the same cluster.

AS is associated with enhanced activity, prolonged but poorly coordinated suckling, inappropriate laughter and developmental disorders including speech impairment, movement and balance disorders. PWS is associated with reduced activity, decreased muscle tone, poor suckling, sleepiness and decreased mental capacity. After weaning, a child affected by PWS develops an insatiable appetite which can lead to life-threatening obesity. PWS is also characterized by hypogonadism, short stature and small hands and feet.

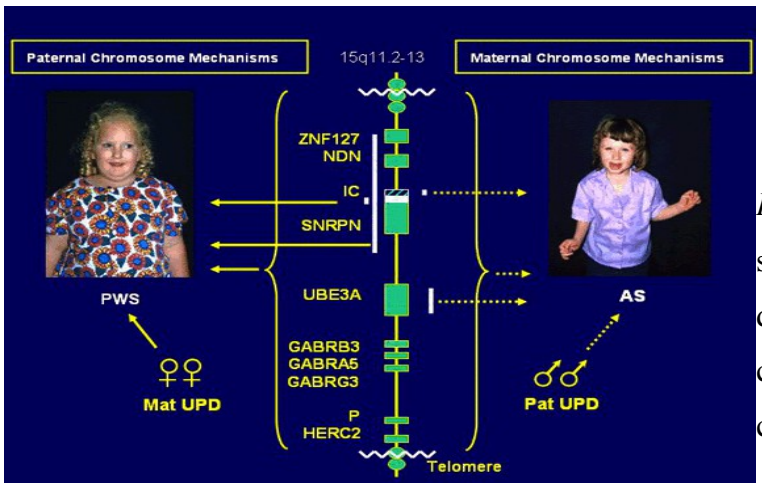

Figure 4: Angelman and Prader-Willi syndromes are caused by imprinting defects, parental disomy and large chromosome deletions in the 15q11-q13 chromosomal region. (Source: http://www.peds.ufl.edu/divisions/genetics/teaching/syndrome_gene_maps.htm)

Silver-Russell and Beckwith-Wiedemann syndromes

The fetal growth disorders SRS (Silver-Russell syndrome) and BWS (Beckwith-Wiedemann syndrome) map to chromosome 11p15. The two disorders have opposite phenotypes. While SRS is a type of dwarfism, BWS is an overgrowth disorder. SRS and BWS are most frequently caused by epimutations at the ICRs that control the gene cluster, while 11p15 duplications and other genetic changes are also possible.

Uniparental Disomies

Genomic imprinting can also induce hereditary defects called uniparental disomies (UPDs), in which a person receives two copies of a chromosome, or a part of a chromosome, from one parent and no copies from the other parent. Many UPDs are associated with growth abnormalities. UPDs affecting entire chromosomes or portions of chromosomes are involved in certain sub-types of PWS and AS as well as in the Beckwith-Wiedemann syndrome.

“Metabolic Syndrome”

An example of an environmentally driven epimutation with trans-generational consequences is the so-called “metabolic syndrome” resulting from poor nutrition during pregnancy, in which the descendants often suffer from glucose and insulin metabolism disorders, weight problems, hypertension, diabetes and cardiovascular diseases persisting in future generations.

Other diseases associated with dysregulation of imprinting include transient neonatal diabetes, pseudohypoparathyroidism, as well as different types of cancer.

Theories of Origin of Genomic Imprinting

It is not well established how genomic imprinting has become quite prevalent in mammals. Several different theories have been proposed to explain what the selective advantages are. Some of the most plausible theories are discussed below.

Host Defense Theory

The host defense theory proposes that genomic imprinting is part of the host defense system against foreign viruses and retrotransposons. According to the theory, the epigenetic mechanisms of DNA methylation and histone modification are recruited to silence foreign DNA elements integrated into the genome. The insertion and rapid expansion of foreign DNA elements within the cell attracts DNA methylation and histone modifications. This hypothesis is supported by the finding that the same enzyme required for genomic imprinting, de novo methyltransferase 3L, also plays a major role in the methylation and silencing of retrotransposons in the male germline.

One limitation of the host-defense model is that it fails to explain why imprinting is limited to placental mammals and a small number of other clades. (Renfree 2009)

Evolvability Models

It has been suggested that imprinting has evolved because functional haploidity results in increased evolvability on a population. Genomic imprinting blends the haploid and diploid states so that individuals may be functionally haploid but the population explores the advantages of nearly all alleles in the diploid genome over a few generations. The models propose that the silent alleles can accumulate numerous mutations, since they are masked from natural selection, potentially for several consecutive generations. This may increase the rate of of adaptive evolution because it increases the probability of adaptive changes that require interaction between multiple mutations that would individually be deleterious. The masking of the silent allele may also shield temporarily deleterious alleles from selective elimination in changing environments. In the evolvability models individuals are subject to selection, but the benefit accrues to the group or population through greater phenotypic variability.

However, there is significant criticism of evolvability models. As with single mutations, the effects of most double, triple and quadruple mutations are deleterious, and multiple individually deleterious mutations are unlikely to result in beneficial synergisms. Also, for most silent alleles, the number of generations since the allele was last active is small, and the chance of multiple mutations during the

period is also small. The potential benefit of enhanced adaptability is to the group rather than to individuals, but the evolvability model does not address how imprinting becomes establishes in the group, and how the group benefit is maintained in competition with individual benefits if reverting to biallelic expression.

Evolvability models also fail to explain why most loci are not imprinted, and what determines which loci are imprinted. The proposed selective advantage should be equally valid for any diploid organism, but the frequency of genomic imprinting is not the same across different diploid organisms. Finally, the models have no prediction on whether the silenced allele is the maternal or paternal one. (Beaudet & Jiang 2002, McGowan & Martin 1997)

Ovarian Time Bomb Hypothesis (OTB)

It is possible for an unfertilized egg cell to spontaneously initiate development, resulting in ovarian teratomas. Teratomas are relatively benign, and they do not differentiate into trophoblasts. A potential explanation for this is that paternally derived genes are required for normal development of trophoblasts. It has been proposed that the function of genetic imprinting is to inactivate genes responsible for trophoblast development in the oocytes to prevent ovarian trophoblastic disease. The active copies of these genes are required for successful implantation and growth, and are provided by the sperm genome after fertilization.

Criticisms of this theory include the fact that it does not explain imprinting of genes that are not involved in trophoblast development, and it offers no explanation for why genes in paternal germlines can also be silenced. It has been suggested that some genes may be “innocent bystanders”, and become inadvertently imprinted. (Weisstein et. al. 2002)

Parental Conflict Hypothesis (tug-of-war hypothesis, kinship theory)

The parental conflict hypothesis is perhaps the most widely accepted of the different models and theories. This hypothesis was first described as a “parental tug-of-war” by Moore and Haig (1991) and is based on the premise that paternal and maternal evolutionary interests may be in conflict with one another, and imprinted genes are a consequence of this conflict between maternally inherited and paternally inherited alleles at a locus. The parental conflict/ tug-of-war hypothesis is also called Kinship Theory, and as the evolvability models, it relies on the notion of inclusive fitness of an allele, including not only the fitness of the individual carrying the allele, but also the fitness of other individuals who may have inherited the same allele.

In the context of fetal growth, the differential expression of maternally and paternally derived alleles is

well understood. A gene that promotes fetal growth places a resource demand on the mother, reducing the availability of resources for her and her other offspring. An excessive demand could reduce the allele's inclusive fitness, even while increasing the fitness of the individual offspring. Therefore, the maternally inherited alleles tend to inhibit growth. Because the mother's other offspring may have a different father, the paternally inherited alleles in the fetus “care” less about the consequences of increased resource demand, and have a tendency to promote growth. Paternally expressed genes are evolutionally selected to promote the transfer of nutrients from the mother to the fetus, while the mother may limit the growth of each individual progeny during pregnancy by silencing the expression of growth-promoting genes. Conflicts over allocation of maternally allocated resources appear to have played an important role in the evolution of imprinting. There is a clear relationship between prenatal growth effects and imprinting. However, the same applies also to other traits where changes in gene expression affect the fitness of matrilinear an patrilinear kin differently. Many imprinted genes have behavioral effects including maternal care, reactivity to novel environments and social behaviors. After birth, mammals continue to rely heavily on maternal resources, and the conflict between maternal and paternal alleles shifts to the behavioral arena. Some of the postnatal behavioral effects of imprinted genes are a natural extension of the prenatal conflict over maternal resources, such as those affecting suckling and weaning behaviors. It is typical for maternally inherited alleles to favor weaning at an earlier age compared to the paternally inherited alleles. This reasoning has been used to explain at least some symptoms of the paternally inherited Prader-Willi syndrome and maternally inherited Angelman syndrome. The increase in the duration of suckling in AS is thought to be a result of the loss of maternally inherited alleles that would otherwise reduce the demand for maternal resources. On the other hand, PWS is associated with poor suckling, which may result from the loss of of paternally inherited alleles that would normally increase the demand for maternal resources. Similar reasoning also applies to the SRS/BWS syndromes.

The parental conflict hypothesis is consistent with many observations of imprinted genes. Although it can explain the functions of many imprinted genes, it is unable to account for the functions of some others. Also, the molecular mechanisms behind genomic imprinting show that it is the maternal genome that controls much of the imprinting of both its own and the paternally derived genes in the zygote, which makes it difficult to explain why the maternal genes would willingly give up their dominance to that of the paternally-derived genes.

Coadaptation theory

The coadaptation hypothesis is based on the idea that evolution may favor coadaptation of

complimentary maternal and offspring traits that positively affect offspring development and fitness. According to this theory, genomic imprinting evolved as a coadaptation between mammalian embryonic development and reproductive behavior. It is offered as an alternative to the parental conflict hypothesis, and it suggests that specific maternal-offspring interactions may reflect adaptive integration of coadapted maternal and offspring traits rather than conflict. In species where the mother is the primary caregiver of offspring, the coadaptation theory only addresses the expression of maternal alleles. However, it may offer an explanation to the fact that there is an abundance of maternally expressed genes at certain loci, such as the loci affecting traits that are vital for the development of the placenta. (Wolf & Hager, 2006)

Conclusion

Genomic imprinting is an epigenetic regulation in which one copy of a gene is active and the other one is either fully or partially silenced in a diploid cell in a parental origin dependent manner. All of the genetic imprinting theories discussed above can explain some aspects of the imprinting phenomena, but none of them can account for all of it. It is plausible that genomic imprinting has evolved due to different selective pressures at different loci, and each mechanism accounts for a portion of the imprinting phenomena. There may also be other, yet undiscovered mechanisms behind genomic imprinting. While several theories have been proposed, genomic imprinting remains somewhat of an evolutionary puzzle.

Abnormal expression of imprinted genes leads to a variety of human diseases. Future efforts aimed at understanding both normal and abnormal patterns of genomic imprinting will advance our knowledge in this interesting epigenetic phenomenon, and may also lead to potential therapeutic applications.

One general insight provided by evolutionary perspective to genomic imprinting is that natural selection does not necessarily act to optimize the fitness or health of an individual organism, as the optimization may occur at the group or population level instead. The selection to increase inclusive fitness can even work to the detriment of the individual. Additionally, imprinted genes are prone to generate conditions in which mutations (or epimutations) are particularly deleterious.

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