Molecular Aspects of Medicine xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Molecular Aspects of Medicine

journal homepage: www.elsevier.com/locate/mam

Review

The role of imprinted genes in humans

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ARTICLE INFO

Article history:
Available online xxxx

Keywords:
Epigenetics
Genomic imprinting
Fetal growth
Imprinting disorders
Methylation
Placenta

ABSTRACT

Genomic imprinting, a process of epigenetic modification which allows the gene to be expressed in a parent-of-origin specific manner, has an essential role in normal growth and development. Imprinting is found predominantly in placental mammals, and has potentially evolved as a mechanism to balance parental resource allocation to the offspring. Therefore, genetic and epigenetic disruptions which alter the specific dosage of imprinted genes can lead to various developmental abnormalities often associated with fetal growth and neurological behaviour. Over the past 20 years since the first imprinted gene was discovered, many different mechanisms have been implicated in this special regulatory mode of gene expression. This review includes a brief summary of the current understanding of the key molecular events taking place during imprint establishment and maintenance in early embryos, and their relationship to epigenetic disruptions seen in imprinting disorders. Genetic and epigenetic causes of eight recognised imprinting disorders including Silver–Russell syndrome (SRS) and Beckwith–Wiedemann syndrome (BWS), and also their association with Assisted reproductive technology (ART) will be discussed. Finally, the role of imprinted genes in fetal growth will be explored by investigating their relationship to a common growth disorder, intrauterine growth restriction (IUGR) and also their potential role in regulating normal growth variation.

Contents

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http://dx.doi.org/10.1016/j.mam.2012.06.009

Please cite this article in press as: Ishida, M., Moore, G.E. The role of imprinted genes in humans. Molecular Aspects of Medicine (2012), http://dx.doi.org/10.1016/j.mam.2012.06.009

1. Introduction

In diploid mammalian cells, most autosomal genes are expressed equally from the paternal and maternal alleles, resulting in biallelic expression. There is, however, a small subset of genes that show monoallelic or highly biased expression, according to the parental origin of the allele. This phenomenon is termed genomic imprinting, controlled by epigenetic marks set differently in the parental germline, without changing the DNA sequence.

Although early evidence of parent-of-origin effects was noted almost 40 years ago through studies of insects, plants and mammals, definitive evidence of genomic imprinting in mammals was provided by a set of seminal mouse experiments involving pronuclear transplantation in the early 1980s (McGrath and Solter, 1984; Surani et al., 1984). In these studies, diploid mouse embryos were created with either two female pronuclei (gynogenotes) or two male pronuclei (androgenotes). As neither conceptuses were viable post implantation, these experiments demonstrated that both maternal and paternal genomes are essential for normal embryonic development and that they are not functionally equivalent.

Subsequent observations in mice which were uniparental disomy (UPD) for specific chromosomes or sub-chromosomal regions, created by interbreeding mice heterozygous for known Robertsonian and reciprocal translocations, revealed that the parental origin effect was not prevalent throughout the genomes, but localised to specific chromosomal regions (Cattanach and Kirk, 1985; Searle and Beechey, 1990). Further studies in mice narrowed down the regions containing parent-of-origin effects to clusters of genes, and in some cases to single genes, with the first mouse imprinted gene insulin-like growth factor 2 receptor (*Igf2r*) identified in 1991 (Barlow et al., 1991).

At present, over 100 genes have been confirmed to be imprinted in mice and approximately 50 of these maintain their imprinted status in humans. Although recent transcriptome sequencing studies have reported more than 1000 potential imprinted genes in the mouse brain (Gregg et al., 2010a, b), the vast majority of these findings were not verified by another independent study (Deveale et al., 2012). In addition, other studies using similar approaches identified only 3–6 new putative imprinted genes (Babak et al., 2008; Wang et al., 2008). Thus, the evidence so far suggests that the total number of imprinted genes is likely to be around the initial estimate of a few hundred genes (Barlow, 1995). A regularly updated list of mammalian imprinted genes can be obtained from University of Otago's Catalogue of Parent of Origin Effects (http://igc.otago.ac.nz/) and at the Harwell mouse database (http://www.har.mrc.ac.uk/).

The diploid state confers on organisms increased protection against the effects of any exposure to deleterious mutations and/or epimutations occurring on one allele. Selection for monoallelic expression of imprinted genes, therefore, seems paradoxical and its evolutionary benefits must outbalance the vulnerability associated with functional haploidy. Remarkably, the phenomenon of genomic imprinting is observed predominantly in eutherian mammals (mammals with long-lived placenta), but not in prototherians (egg-laying mammals), birds or reptiles (Hore et al., 2007). Imprinting has also evolved independently in flowering plants where the endosperm has a placenta-like function (Scott and Spielman, 2006). The close association between the acquisition of imprinting and placenta during the course of evolution has led to several hypotheses to explain the reason for the emergence of genomic imprinting. The kinship theory, also commonly referred to as the parental conflict theory (Moore and Haig, 1991), is considered the most widely accepted theory. It predicts that paternally expressed genes are driven to promote fetal growth by extracting maximal resources from the mother, especially in a polygamous population. In contrast, the maternal genome discourages offspring growth by limiting its share of her resources, and ensures her survival and the equal allocation of nutrients among her offspring, both to the common aim of producing the maximum number of viable offspring carrying their genes. Consistently, imprinting is observed to occur predominantly in genes influencing fetal growth, particularly through placental growth, suckling and nutrient metabolism (reviewed in Frost and Moore, 2010; Piedrahita, 2011).

The conflict theory is supported by the example of the prototypical mouse imprinted gene *Igf2* and its receptor *Igf2r*. *Igf2* is a paternally expressed potent growth enhancer, whereas maternally expressed *Igf2r* products suppress growth by mediating the degradation of IGF-II proteins (Scott and Weiss, 2000). Mouse knockouts of these genes exhibited opposite growth phenotypes; *Igf2*-null mice are growth deficient whilst *Igf2r*-null mice show overgrowth phenotypes (Lau et al., 1994). Additionally, consistent with the conflict theory, mice lacking paternally expressed *Peg3* (paternally expressed gene 3) and *Mest* (mesoderm specific transcript) genes result in IUGR (Lefebvre et al., 1998; Li et al., 1999), whereas mice being null for maternally expressed genes *H19* and *Grb10* exhibit fetal overgrowth (Charalambous et al., 2003; Leighton et al., 1995). It is now argued that paternally expressed genes tend to promote fetal growth whereas maternally expressed genes restrict fetal growth.

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