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Toward an integrated evolutionary understanding of the mammalian placenta

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Abstract

The placenta is fundamentally important for the success of pregnancy. Disruptions outside the normal range for placenta function can result in pregnancy failure and other complications. The anatomy of the placenta varies greatly across mammals, as do key parameters in pregnancy such as neonatal body mass, length of gestation and number of offspring per pregnancy. An accurate understanding of the evolution of the mammalian placenta will require at minimum the integration of anatomical, developmental, physiological, genetic, and epigenetic data. Currently available data suggest that the placenta is a dynamic organ that has evolved rapidly in a lineage specific manner. Examination of the placenta from the perspective of human evolution shows that many anatomical features of the human placenta are relatively conserved. Despite the anatomical conservation of the human placenta there are many recently evolved placenta specific genes (e.g. *CGB*, *LGALS13*, *GH2*) that are important in the development and function of the human placenta. Other mammalian genomes have also evolved specific suites of placenta-expressed genes. For example, rodents have undergone expansions of the cathepsin and prolactin families, and artiodactyls have expanded their suite of pregnancy-associated glycoproteins. In addition to lineage-specific birth-and-death of gene family members, the pattern of imprinted loci varies greatly among species. Taken together, these studies suggest that a strategy reliant upon the sampling of placenta expressed and imprinted genes from a phylogenetically diverse range of species is appropriate for unraveling the conserved and derived aspects of placenta biology.

Placenta Evolution

The placenta is a complex organ that promotes physiologic exchange between developing embryos/fetuses and their mothers [1]. The placenta is most well studied in extant eutherian mammals (i.e. placentals) [2–4], but it also exists in marsupials [5] and monotremes [6]. Moreover, other viviparous creatures including viviparous vertebrates such as some squamate reptiles [7,8] and fish [9] have developed placentas and placenta-like structures. Placenta-like structures have even been described in invertebrates such as the onychophoran velvet worms [10]. That each of these and other species have evolved placentas independently forces us to ask whether the same genetic elements have been co-opted for the parallel evolution of the placenta as has been proposed in the case of eye development [11]; or, alternatively, whether the origins of placentation are truly independent. In the current work, I will examine some of what is known about anatomical and genetic evolution in the placentas of the most famously studied animals, the placental mammals. The purpose

of this exercise is to take a small step toward the development of an integrated framework for deciphering the evolution of the placenta.

Several recent studies have examined the evolution of the placenta in the context of advances in understanding of the phylogenetics of mammals [12–14]. These studies agree in several aspects. Importantly, all studies agree that the last common ancestor of primates had an invasive, hemochorial placenta. Many studies have also inferred these character states were present at the time of the last common ancestor of placental mammals [12,13], but some studies with limited taxonomic sampling among xenarthrans, have inferred an endotheliochorial placenta interface at this time [14]. Xenarthrans (i.e. members of the clade Xenarthra), most of which have hemochorial placentas, include armadillos, anteaters and sloths. Xenarthra is one of the four major clades of extant placental mammals, the other three being, Afrotheria, Laurasiatheria, and Euarchontoglires (Fig. 1). The methods that have so far been developed for reconstructing the evolution of these features require that the ancestral state exist in extant taxa, and it is possible that the last common ancestor of placental mammals had a placenta that did not resemble any seen today. The inference that humans have a relatively conserved placenta anatomy makes sense because among mammals, primates are considered to be rather generalized mammals [15]. Despite this conserved anatomy in humans, the placenta evolves rapidly and there are transitions among the three major types of placenta interface (hemochorial, endotheliochorial, and epitheliochorial) in each of the four main clades. This rapid evolution means that the placenta is one of the most variable organs within mammals. Moreover, the fetus is an immunologically distinct organism from the mother, and immune tolerance is therefore necessary at the maternal fetal interface [16]. Unraveling the specific immunological reactions that take place at the maternal fetal interface is crucial in knowing why some pregnancies are successful while others fail [17]. Genes involved in immune processes evolve rapidly [18], as do genes involved in reproductive processes [19]; thus, it is not surprising that the organ that mediates both maternal-fetal immune tolerance and reproduction is also rapidly evolving. Moreover, it is well appreciated that there are many placenta-specific genes [20].

Genetics and adaptive evolution of protein coding genes

Several studies have demonstrated that genes involved in placentation have evolved adaptively during mammalian descent [21–25]. Adaptive evolution can be measured by comparing the per site rates of nonsynonymous (dN) to synonymous (dS) substitutions in protein coding sequences. The ratio of these substitution classes is called dN/dS or w . The values = 1, >1, and <1, are [20] interpreted as signifying neutral evolution, positive selection, and purifying selection, respectively [26]. dN/dS can be measured in a variety of ways [27], but most studies that measure dN/dS are designed to test for evidence of positive selection on particular evolutionary lineages.

Much work has focused on adaptive evolution of primates, and specifically, humans. During the evolution of the human species gene families including members that have placenta-specific gene expression show evidence of adaptive evolution. These families include those containing the beta subunit of chorionic gonadotropin [23], the growth hormone/chorionic somatomammotropin family [28], and the placenta specific galectin subfamily [29]. Additionally, cadherin genes involved in maternal fetal interactions show the signature of positive selection [30]. Genes involved in immunity at the maternal fetal interface including killer-cell immunoglobulin-like receptors (KIRs) have also been subject to intense selective pressures [31].

In addition to candidate gene based studies such as those described above, genome-wide scans for adaptive evolution have identified genes that have undergone positive selection in primate evolution. Uddin et al. [22] determined that of 1240 human genes that show evidence of adaptive evolution in primates 70 are highly expressed in placenta. Similarly, Hou et al. [21] identified 94 human genes that are highly expressed in placenta and have evolved adaptively during human evolution since the time of the last common ancestor of eutherian mammals. These genes include those that are known to be associated with pregnancy complications as well as those that when disrupted in mice result in aberrant placenta phenotypes.

The pattern of adaptive evolution in human genes that function in placenta can be extended to other lineages. Mice show a rapid rate of evolution of many placenta specific and placenta predominant expressed genes, especially placental cathepsins, prolactins, and placental carcinoembryonic antigens [24]. The pregnancy-associated glycoproteins have evolved adaptively in cattle [32]. Genes encoding prolactin-related proteins also show evidence for positive selection in the cattle lineage [33]. Adaptive evolution of genes has been studied in the afrotherian African elephant [34], but it is unclear which of these adaptively evolving genes are expressed in the elephant placenta.

Birth and death of placenta-specific gene families

Recent work has demonstrated that gene families often evolve under a “birth-and-death” model in which new genes are created by duplication after which some copies survive while others are inactivated or deleted [35]. Most of the placenta-specific gene families described in the above section on adaptive evolution are members of gene families that have evolved under the birth-and-death model. Fig. 2 shows three of the anthropoid primate gene families that contain genes with placenta-specific expression. *LGALS13*, is a gene that encodes a galectin also known as PP13. Maternal serum levels of this protein show promise as a biomarker for predicting the onset of preeclampsia [36]. *LGALS13* belongs to a cluster of at least five genes found on human chromosome 19 [29]. These genes evolved via duplication, and the cluster is found only in anthropoid primates. In addition to active genes there are several pseudogenes in this cluster as is the case with the growth hormone cluster also found only in anthropoid primates. Growth hormone genes have been proposed to be involved in fetal resource acquisition during pregnancy [37], and the family has more greatly expanded in New World monkeys than in catarrhines (Old World monkeys and apes) [38], a finding that suggests these primates may have elaborated their ability to obtain resources. Lineage- and placenta-specific genes and gene families are also found in non-primates [20].

Evolution of imprinting

Genomic imprinting, also known as allele-specific expression is found in marsupials and eutherians but not in monotremes [5]. To date, over 1300 imprinted loci have been identified in mouse, and approximately 50 in humans [39]. Imprinting has been advanced as a mechanism through which maternal-fetal exchange can be mediated, especially in terms of parental resource allocation to the fetus. Maternal-fetal conflict theory suggests that in imprinted genes, paternally expressed alleles are advantageous to the fetus while maternally expressed alleles are advantageous to the mother [40]. Moreover, there is evidence that some genes are imprinted in a placenta-specific manner [39,41]. As with adaptive evolution and birth-and-death of gene families, genomic imprinting appears to be highly lineage specific. Interestingly, a subset of known imprinted genes do not show significant duplication or adaptive evolution in mammals, suggesting some sort of phylogenetic constraint may be acting on these genes [42]. Unfortunately, there have been no studies describing imprinting

in atlantogenatan (i.e. afrotherians and xenarthrans) mammals. These data will be necessary to infer the phylogenetically conserved signals of imprinting in placental mammals.

Summary

There is no doubt that the placenta shows a pattern of evolutionary dynamism in its anatomy and in the genes it expresses. Unraveling how genetic and anatomical diversity in the placenta go together is a major challenge, but this challenge is worthy of pursuit because understanding can lead to effective management of pregnancy in humans and other animals. Much work remains to be done in identifying the conserved and derived aspects of placenta biology in mammals.

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Fig. 1. Phylogenetic relationships among mammals

This figure depicts the current view of the phylogenetic relationships among major superordinal mammalian clades [43–45]. The Eutheria includes all extant placental mammals and is made up of four extantsuperordinal clades: Euarchontoglires (e.g. Primates, Rodentia), Laurasiatheria (e.g. Carnivora, Perrisodactyla), Xenarthra (e.g. Pilosa, Cingulata), and Afrotheria (e.g. Proboscidea, Sirenia). Euarchontoglires joins Laurasiatheria to form Boreoeutheria, and Xenarthra joins Afrotheria to form Atlantogenata. Metatheria refers to the marsupial mammals, and Prototheria includes the egg-laying monotremes.

The figure depicts the orientation, exon/intron structure, and location of three gene clusters that have genes with placenta-specific expression in anthropoid primates [23,28,29]. These gene families expanded via duplication during primate evolution. A) A cluster of galectins located on human chromosome 19. *LGALS14* is expressed only in the placenta, and has been shown to have two splice variants as depicted in the figure. Other genes in this cluster with predominant placenta expression include *LGALS13* and *LGALS16*. B) The chorionic gonadatropin cluster is located on human chromosome 19. Microarray studies [su] demonstrate that the gene encoding the beta peptide of human chorionic gonadotropin (*CGB*) is highly expressed in the placenta as are *CGB5*, *CGB7*, and *CGB8*. The gene encoding luteinizing hormone, *LHB*, is found in non-anthropoids. C) The gene cluster containing the human growth hormones/placental lactogens is found on human chromosome 17. Many of these genes have multiple splice variants. All genes are expressed in the placenta with the exception of *GHI*, in which expression is restricted to the pituitary. A pituitary expressed GH gene is found in non-anthropoids.