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## Review

# Evolutionary perspectives into placental biology and disease<sup>☆</sup>

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## ABSTRACT

In all mammals including humans, development takes place within the protective environment of the maternal womb. Throughout gestation, nutrients and waste products are continuously exchanged between mother and fetus through the placenta. Despite the clear importance of the placenta to successful pregnancy and the health of both mother and offspring, relatively little is understood about the biology of the placenta and its role in pregnancy-related diseases. Given that pre- and peri-natal diseases involving the placenta affect millions of women and their newborns worldwide, there is an urgent need to understand placenta biology and development. Here, we suggest that the placenta is an organ under unique selective pressures that have driven its rapid diversification throughout mammalian evolution. The high divergence of the placenta complicates the use of non-human animal models and necessitates an evolutionary perspective when studying its biology and role in disease. We suggest that diversifying evolution of the placenta is primarily driven by intraspecies evolutionary conflict between mother and fetus, and that many pregnancy diseases are a consequence of this evolutionary force. Understanding how maternal–fetal conflict shapes both basic placental and reproductive biology – in all species – will provide key insights into diseases of pregnancy.

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## 1. Introduction: Pregnancy Diseases Vary Among Mammals

Live birth is a hallmark characteristic of eutherian mammals. This specialized reproductive strategy maximizes protection of offspring during fetal development, which is clearly effective as mammals are

thriving – humans are now seven billion and counting. However, such a strategy comes with devastating tradeoffs in the form of diseases that profoundly affect mothers and their babies during pregnancy, including morning sickness, miscarriage, hemorrhage, growth restriction, gestational diabetes, premature labor, and preeclampsia. Diseases of pregnancy occur in all mammalian species, but notably, pregnancy diseases display substantial variability between species (Johnston et al., 2001; Noakes et al., 2001). In the horse, for example, neonatal/fetal death is often caused by sepsis, hypoxic–ischemic brain injury, twinning, and placental abnormalities (Acland, 1993; Hong et al., 1993; Smith et al., 2003). These diseases are much less common in multiparous species such as the cat or the dog (Acland, 1993; Jonker,

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2004; Kirkbride, 1992; Lopez-Gatius et al., 2002; Verstegen et al., 2008). Conversely, sheep, goats, and cattle have high rates of ketosis as a complication during the last month of pregnancy, and hypocalcemia (milk fever) is common in dogs and cattle (Fthenakis et al., 2012; Johnston et al., 2001). However, such metabolic conditions are not common in horse or in humans. These interspecific variations are further illustrated by the high incidence of preeclampsia in the human population, which has no clear equivalent in any other species outside the great apes. Indeed, even the closely related new world monkeys do not appear to be affected by this disease (Carter and Pijnenborg, 2011; Crosley et al., 2013; Pijnenborg et al., 2011a,b).

As the incidence and the type of pregnancy-related disease vary significantly between mammals, this suggests that pregnancy disease is the consequence of differing environmental, nutritional and – importantly – physiological adaptations related to pregnancy. Significantly, the unexpected variation of pregnancy disease across mammalian taxa may also be a result of divergent evolution of the placenta and consequent placental diseases and disorders. Placental anatomy and function vary vastly across species and may be the result of biological adaptations unique to each lineage. We suggest that the diversifying evolution of the placenta is primarily driven by intraspecies evolutionary conflict between mother and fetus, and that many pregnancy diseases are a consequence of this evolutionary force. Understanding how maternal–fetal conflict shapes both basic placental and reproductive biology will provide key insights into diseases of pregnancy.

## 2. Placental variation at the heart of pregnancy disease

Placental pathology and failure are at the heart of diseases of pregnancy. While defects in placentation may not be the root cause of all pregnancy disease, the placenta is essentially the primary physiological interface between mother and fetus, and, as such, is central to all categories of pregnancy disease in all species. As the placenta, in essence, holds reproductive physiology together, its biological differences across species are likely to provide important clues as to why pregnancy diseases also differ across species. Interestingly, although the placenta performs the same basic physiological and respiratory functions in all eutherian species, it is widely considered the most morphologically variable organ. Unlike other organ systems – which generally exhibit conserved shape, structure and/or organization across taxa – the placenta has rapidly evolved completely different shapes, structures and even cell types between closely related species (and even strains) (Ford, 1997; Grosser, 1909; Kaufmann, 1983; Konno et al., 2011; Mossman, 1937, 1987). Nearly every feature of placentation exhibits variation across mammals. For example, placental morphology is classified into four distinct categories (Mossman, 1987). Primates and rodents have single, disk-shaped, or discoid, placentas. Zonary placentas, consisting of a complete or incomplete band of tissue that wraps around the fetus, are found in carnivores such as cats and dogs, and also in elephants. Diffuse placentas, where the placenta spreads widely across the entire uterine surface, are found in horses and pigs. Finally, ruminants such as sheep have cotyledonary placentas where the placenta consists of multiple, discrete areas of attachment between mother and fetus. Other major variable features include the structural organization of the barrier between fetal and maternal vasculature and the mode of blastocyst implantation (Cha et al., 2012). Intriguingly, none of these different features of placentation correlate well with species phylogeny. The overall diversity and paraphyletic distribution of placental traits indicate that the placenta has undergone continuous and rapid evolution across all major mammalian taxa, and any similarities of placentation between distantly related species are the result of convergent evolution.

The mystery remains, however, why the placenta has undergone such extensive diversifying evolution with many disastrous

complications – particularly in humans where maternal and fetal mortality continues to be high. Considering that placental function is fundamental to pregnancy, any environmental or ecological pressure that affects reproductive strategy – e.g. gestation length or litter size or even brain size – would impose direct evolutionary pressures on the placenta (Brown et al., 2013; Haig, 1993). Therefore, the wide variation in mammalian reproductive strategies (and resulting disease) is likely to be reflected by variation in placental form and function. Further, these changes in form may also lead to various compromises in different species. For example – in the human, the highly invasive placental cells make a stronger connection between mother and fetus, allowing more direct nutrient and oxygen transport (Enders and Carter, 2004; Kliman, 2000; Mossman, 1987; Ramsey et al., 1976; Robillard et al., 2002). Many have hypothesized that this highly nutritious environment allowed for larger brain development (Cunnane and Crawford, 2003; Cunnane et al., 1993; Martin, 1983, 2007; Rosenberg and Trevathan, 2002). Yet while this invasive adaptation might have led to a very successful strategy for the species at large, it created a situation where the fetus requires massive resources from the mother. Systematic failure of invasion is correlated with prevalent diseases of human pregnancy including spontaneous premature labor and preeclampsia – demonstrating that the invasive adaptation in humans, while having positive consequences for the species, may have horrific consequences for individuals (Fisher, 2004; Myatt, 2002; Norwitz, 2006). Further, animals such as cows and elephants with prolonged gestation times must contend with the immunological complication of hosting the fetus as a foreign tissue for long periods. These animals tend to have a less invasive placenta in comparison to smaller species, such as rodents, which only gestate for much shorter periods (Enders and Carter, 2004; Mossman, 1987). One could surmise that, in these animals, inappropriate invasion may cause early embryonic rejection, although this is not yet been documented. Overall, complex environmental and ecological factors interact to determine the optimal reproductive strategy for a species and these are unlikely to be static for a single species over time. Thus, it may be expected that the evolution of the placenta would reflect the immense variation in environments and exposures facing different mammals, including stresses from predation, nutrition, and exposure to toxins and – in turn – these adaptations led to susceptibility to different diseases.

## 3. The placenta as the battlefield between parent and offspring

In addition to external ecological factors, strong intrinsic reproductive pressures are predicted to emerge from within a species. Because parent and offspring are genetically distinct, there exists inevitable evolutionary conflict over the optimal allocation of parental investment (Haig, 1993). Parent–offspring conflict may be intrinsic to all sexually reproducing species, but the mammalian placenta importantly enabled offspring to directly influence parental investment during pregnancy. The placenta is thus predicted to be a “battlefield” of the maternal–fetal evolutionary arms race. As an organ, the placenta is unique in that it is actually a conglomerate of vascularized tissue derived from two genetically distinct individuals, mother and offspring. The fetal portion is composed of vascularized trophoblast structures that invade and become tightly interdigitated with the maternal decidua, which is composed of vascularized epithelial tissue that forms at the site of blastocyst implantation in the uterus (Cha et al., 2012). Histologically, the maternal–fetal interface is crowded with cellular debris and maternal immune cells, harkening to the battlefield metaphor in which the fetal placenta releases an armament of proteases and hormones to establish a hold in the uterus (Redman and Sargent, 2000).

Signatures of evolutionary conflict are clearly evident in the process of placentation. For example, the pig placenta is unique in that it only superficially attaches to the uterus (Enders and Carter, 2004; Mossman, 1987). However, if the blastocyst is implanted *ex vivo* in another maternal tissue

such as the lung, the trophoblast successfully invades (Samuel and Perry, 1972). This demonstrates that the fetal “interest” is to attempt invasion but this process is maternally repressed at the site of implantation, which suggests that the level of placental invasion in pigs represents a co-evolutionary standstill between maternal and fetal demands rather than a stable optimal resolution. Intriguingly, the pig has seemed to compensate for the lack of placental invasion by dramatically increasing the surface area of its placental interface. Between days 10 and 15 of development, the pig blastocyst rapidly expands from a 10 mm sphere to a 1000 mm long conceptus, and the placenta eventually grows to be a full meter long and covers the entire surface of the uterus (Bazer et al., 2012). Conversely, the human placenta is considered to be the most invasive of the eutherian placentas, penetrating deeply into maternal tissues (Cha et al., 2012; Enders and Carter, 2004; Kliman, 2000; Mossman, 1987; Ramsey et al., 1976; Robillard et al., 2002). Evidence of maternal repression also exists in this context, as invasive placental cells can inappropriately extend as far as the mother's bladder after the uterus has been compromised by scarring (Washecka and Behling, 2002). This inappropriate invasion leads to the pregnancy disease percreta, which was rare 20 years ago, but due to extensive C-sections performed in the United States its incidence is on the rise (Rosen, 2008; Sinha and Mishra, 2012). Again, this suggests that there is a maternal repressive signal present in the uterus used to “block” fetal cell invasion. Defects in this signaling may affect reproduction profoundly, albeit differently, in both pig and human. Clearly, in the pig scenario, the mother is better at limiting fetal invasion, while the human signal is far more permissive – and if scarred potentially deadly.

#### 4. Molecular drivers of placental variation

How does parent–offspring conflict relate to the diversification of placental forms? As stated in (Crespi and Semeniuk, 2004), “outcomes of conflict vary among taxa, depending on differences in physiological and morphological starting points, sequences of mutational events, strengths of selection on the interacting parties, and the presence and form.” In other words, adaptations arising from parent–offspring conflict would be unique to each lineage, resulting in the diverse array of species-specific placental adaptations observed today. Given that parent–offspring conflict is a consequence of inherent genetic differences between mother and offspring, conflict-driven evolution should also be detectable at the genetic level. Though the placenta is much less understood at the molecular level than the embryo, our current knowledge has already revealed many clear signs of genetic conflict. Below we highlight the molecular conflicts that are supported by molecular evidence, including parent of origin bias (imprinting), gene evolution, and endogenous retroviral activity. We highlight these molecular forces as we see these areas as being central toward elucidating a more complete mechanistic knowledge of both reproduction and resulting pregnancy disease.

##### 4.1. Imprinted genes

All diploid organisms inherit both a maternal and paternal copy of the genome, and genes are generally expressed equally from both their maternally and paternally derived alleles. In therian mammals (marsupials and eutherians, but not monotremes) however, hundreds of genes break this rule through a process known as genomic imprinting (Renfree et al., 2009). Through various epigenetic processes that can include differential status of DNA methylation, post-translational histone modifications, and non-coding RNAs, certain genes are only expressed from the maternal allele, and others only from the paternal allele (Lee and Bartolomei, 2013). Genomic imprinting is restricted to specific tissues and stages of development, but the most prominent and well-studied site of imprinting is the placenta (Frost and Moore, 2010). Furthermore, because imprinting is restricted to therian mammals, the

initial evolution of imprinting was likely intimately tied with placental function (Renfree et al., 2009).

Why would the placenta exhibit genomic imprinting? The most widely accepted hypothesis is that imprinting has been maintained throughout evolution due to parent–offspring conflict (Renfree et al., 2009). Consistent with the conflict hypothesis, paternally expressed genes (representing “fetal interests”) are predominantly growth-promoting factors, such as *Igf2*, whereas maternally expressed genes (representing “maternal interests”) tend to be growth-repressing genes, such as *Igf2r*. The final product of paternal and maternal imprinted gene expression presumably balances to produce normal sized offspring. However, when the balance of imprinting is artificially disrupted – as in parthenogenic embryos – embryonic development fails and placenta is either abnormally large (two paternal genomes) or abnormally small (two maternal genomes) (Barton et al., 1984).

Further evidence for the role of imprinting in parental conflict can be observed in hybrids between sister species that exhibit opposing reproductive strategies. For example, the deer mouse *Peromyscus maniculatus* is polyandrous, and its sister species *Peromyscus polionotus* is monogamous (Birdsall and Nash, 1973; Foltz, 1981). Parent–offspring conflict is predicted to be more severe in polyandrous species where siblings are less related to each other on average (Long, 2005; Parker and MacNair, 1979). Consistent with this prediction, a monogamous female *P. polionotus* mated to a male *P. maniculatus* produces significantly overgrown offspring, whereas a polyandrous female *P. maniculatus* mated to a male *P. polionotus* produces significantly underdeveloped offspring (Rogers and Dawson, 1970). This observation is thought to result from disrupted imprinting (Vrana et al., 1998, 2000). The monogamous female does not “expect” imprinted overexpression of paternally expressed growth factors, and did not coevolve mechanisms to repress these genes. Conversely, the polyandrous female *P. maniculatus* has coevolved with selfish offspring and the maternal genome appropriately expresses repressive factors, even within *P. polionotus* hybrids, which results in smaller offspring. This phenomenon is not restricted to rodents. Hybrids of female tigers and male lions (“ligers”) are much larger than either parental species, whereas hybrids of female lions and male lions (“tigons”) are not (McKinnell and Wessel, 2012). As in the case of deer mice, this may result from the promiscuous nature of lions relative to tigers, which are much more solitary by comparison.

Altogether, the discovery of imprinted genes in the placenta is convincing evidence for parent–offspring conflict driving placental evolution at the molecular level. Notably, flowering plants also exhibit genomic imprinting in the endosperm (Feil and Berger, 2007), which is a nourishing tissue in the seed analogous to the mammalian placenta, and contains both maternal and paternal genomes. The convergent evolution of genomic imprinting in flowering plants and mammals is a strong indication that imprinting is directly tied to parent–offspring conflict.

##### 4.2. Genes in conflict

Most functionally important proteins are expected to exhibit conservation across species. However, comparative genomic analyses across many animal taxa have revealed that certain classes of proteins tend to evolve more rapidly than expected (Bustamante et al., 2005; Clark et al., 2003). In animals ranging from flies to humans, proteins involved in the immune response or sexual reproduction often show an excess of nonsynonymous mutations that cause amino acid substitutions compared to “silent” synonymous mutations (Swanson, 2003). When the rate of nonsynonymous mutations exceeds the rate of synonymous mutations for a gene, this pattern is considered a signature of positive selection, which is a characteristic of genes involved in conflict—such as those involved in host pathogen interactions, immunology, or reproduction (Crespi, 2010; Moffett and Loke, 2006; Swanson and Vacquier, 2002; Wildman, 2011). Interestingly, in mammals, placentally secreted

hormones exhibit clear patterns of positive selection – this has been shown in rodents, primates, and cows (Chuong et al., 2010; Hou et al., 2009; Liu et al., 2001; Maston and Ruvolo, 2002; Rawl and Cross, 2008). Furthermore, comparison between sister species within each taxa reveals additional variation between gene families at the copy number and amino acid levels (Rawl and Cross, 2008). Altogether, molecular characterization of placental hormones from different taxa has revealed that the placenta is rapidly evolving at the physiological level in a manner strongly suggestive of parent–offspring conflict (Crespi, 2010; Hou et al., 2009; Moffett and Loke, 2006; Wildman, 2011).

#### 4.3. Endogenous retroviruses in the placenta

One of the most unexpected observations of the placental transcriptome is that in addition to the host of secreted hormones, proteases, and other genes discussed above, the placenta is a major site of retroviral expression (Haig, 2012; Rowe and Trono, 2011). Viral particles have been observed in placentas across all mammalian taxa for decades, but the functional role of these viruses remains unknown (Harris, 1998; Johnson et al., 1990; Kalter et al., 1973, 1975; Simpson et al., 1996). Importantly, these viral particles are not the result of exogenous viral infections, but rather they are transcribed directly from the fetal genome (Rowe and Trono, 2011). When retroviruses infect germline cells, they become integrated into the host genome as heritable mutations known as endogenous retroviruses (ERVs). Once integrated, ERVs are highly mobile and often continue to expand within the genome. Due to this continued activity, ERVs make up 5–10% of mammalian genomes—a much greater portion than even native protein-coding genes, which comprise 1.5% of the genome (Gifford and Tristem, 2003). Unchecked, ERV activity promotes chromosomal instability and tumorigenesis, and is generally detrimental to host fitness (Feschotte and Gilbert, 2012). Therefore, all organisms have evolved multiple epigenetic mechanisms to repress the activity of ERVs and other transposable elements (TEs). In mammals, shortly after blastocyst implantation, a global wave of *de novo* DNA methylation proceeds in the inner cell mass (Koukoura et al., 2012). This process acts to stably restrict the gene expression program for cell differentiation and also to silence ERVs and TEs. Importantly, the wave of DNA methylation does not occur in the trophoblast lineage and its derivatives, which results in a relatively hypomethylated placenta that is epigenetically permissive to ERV activity (Chuong et al., 2013; Feschotte and Gilbert, 2012; Koukoura et al., 2012).

Why would the placenta allow retroviral activity? Several theories, which are generally not mutually exclusive, attempt to explain their potential function (Haig, 2012). The most basic explanation is that the placenta is transient and, therefore, the potential tumorigenic potential of ERVs is irrelevant. Alternatively, retroviruses able to integrate into the placenta gain a direct transmission route to both the mother and current and future offspring, which may explain placental ERV expression as a byproduct of this infection bias with no functional benefit to the host. A functional hypothesis is that ERVs may play a defensive role in blocking exogenous retroviral infection. This has been observed in sheep, where endogenous betaretroviruses enJSRV is highly expressed during pregnancy and directly blocks the infection cycle of sheep exogenous viruses ENTV and JSRV (Black et al., 2010), thereby protecting the developing fetus by “fighting fire with fire.” More intriguingly, an emerging pattern is that ERVs frequently donate functional placental genes to their host. Though ERV cooption has been documented in embryonic tissues, it is far more prevalent in the placenta, where intrinsic placental ERV activity may facilitate cooption (Feschotte and Gilbert, 2012; Haig, 2012). Genome-wide screens for functional ERV proteins have revealed several putative functional proteins under purifying selection, most of which are specifically and highly expressed in the placenta. In humans, a pair of genes – named syncytinA and syncytinB – was derived from a human ERV family and has been shown to mediate cell fusion between

trophoblast cells (Mi et al., 2000). These findings indicate that humans have recruited the retroviral Env protein that is normally used by the virus to penetrate the host cell, and have repurposed the protein to facilitate trophoblast cell fusion to form a multinucleate barrier between fetal and maternal bloodstreams. Similar placentally expressed syncytin-like genes have been identified in diverse mammalian taxa including mouse, pigs, rabbits, and most notably, all are independently derived from unrelated ERV families (Dupressoir et al., 2012; Feschotte and Gilbert, 2012). As ERVs are among the most rapidly evolving class of genomic mutations, this has led to speculation that recurrent cooption of placental ERVs may be a major factor underlying the rapid evolutionary diversification of the placenta (Chuong, 2013; Chuong et al., 2013; Malik, 2012).

#### 5. Evolutionary perspectives will provide insight into placental biology and disease

Understanding the reproductive differences – and the underlying evolutionary changes such as imprinting, rapid gene evolution, or ERV co-option – between species will provide a fertile ground of which to identify causes of pregnancy disease. Genomic data can be used to target specific processes at the heart of maternal–fetal conflict. For example, aberrations in imprinting status of placental genes are strongly associated with placental diseases and many imprinted loci in the placenta are widely thought to have evolved in response to maternal–fetal conflict (Frost and Moore, 2010). Notably, though many genes exhibit conserved imprinting status across mammals, there are clear instances where the imprinting status of specific loci differs across species. For example, the placental transcription factor *Ascl2* is imprinted in mouse, but not in human (Frost and Moore, 2010). However, there has been a lack of comprehensive genome-wide catalogs of placentally imprinted genes, and as a result there has been no accurate estimate of how many placental genes show conserved or species-specific imprinting status. Recently, RNA-Seq based assays of reciprocal hybrids in rodents and equids have generated unbiased genome-wide lists of placenta-specific imprinted genes (Finn et al., submitted for publication; Okae et al., 2012; Wang et al., 2011, 2013). Such data is not yet available for humans, but as data from sequencing family trios becomes available, a comprehensive list of human imprinted genes should soon be available. Ultimately, such studies will likely reveal that many genes show species-specific imprinting status. While well-studied conserved imprinted genes such as the *IGF2/IGF2R* locus are clearly implicated in some placental disease, their imprint status may represent “stable” coevolutionary outcomes under the context of maternal–fetal conflict (Frost and Moore, 2010). Conversely, genes that are imprinted only in human have likely only recently evolved imprinted status, and may affect human-specific aspects of placentation. As such, we suggest that aberrations in the imprinted state of genes may indicate that these are high value candidates for some species-specific placental diseases.

In addition to imprinted genes, the placenta is a major site of expression for species-specific, rapidly evolving proteins. For example, under maternal–fetal conflict, fetal hormones that influence the allocation of maternal nutrients may be subject to positive selection. By applying functional genomics to identify the genes and regulatory elements active during placentation, and comparative genomics to further highlight loci under positive selection, we may pinpoint genes that are likely involved in maternal–fetal conflict and are thus good candidates for further study. Indeed, several studies have turned to using gene evolution to inform genomic data. For example, examining genes under strong selection, and potentially functioning, during reproductive processes may provide candidates involved in birth timing and preeclampsia (Brown et al., 2013; Plunkett et al., 2011). In rodents, molecular studies have revealed the placentally expressed Prolactin, Pregnancy-Specific Glycoprotein, and Cathepsin gene families have undergone massive recent gene duplications and show signatures of positive selection (Chuong et al., 2010; Knox and Baker, 2008). Furthermore, some genes, such as *tpbpa*, show

elevated polymorphism even across *mus* subspecies, strongly suggesting that they have undergone very recent adaptive evolution (Chuong et al., 2010; Knox and Baker, 2008). The human genome contains Galectins, as well as the Placental Lactogen and Chorionic Gonadotropin gene families, which are primate-specific placental genes derived from an ancestral Growth Hormone and show some evidence of adaptive evolution (Papper et al., 2009; Than et al., 2008). If these genes with human-specific placental expression have been under recent positive selection, such loci may exhibit genetic polymorphism within the human population, and as such may serve as excellent predictive markers of disease.

Another way in which an evolutionary perspective is vital to understanding placental disease is the apparent elevated rate of ERV co-option in the placenta. ERVs are highly polymorphic genomic elements, yet mammals have repeatedly co-opted these elements for placental function, very possibly under the context of maternal–fetal conflict (Chuong, 2013; Chuong et al., 2013; Haig, 2012; Malik, 2012). Therefore, while ERV and other repetitive elements are often ignored, they should be paid particular attention when examining the placenta. ERV biology is particularly relevant given that external stimuli during pregnancy may alter the epigenetic landscape of placental cells (Gheorghie et al., 2010; Novakovic and Saffery, 2012), which may aberrantly silence or activate ERVs with potentially dramatic consequences for placentation (Ruebner et al., 2013). Such considerations may provide clues as to why some women with very similar genotypes may experience distinct pregnancy outcomes.

## 6. Placental biology across species

One of the primary outstanding challenges to understanding human placental disease is the absence of good animal models. Indeed, rodent and ruminant placentas have been well studied, yet they are clearly different from the human placenta both at the morphological and molecular levels. Under the context of maternal–fetal conflict, such species-specific variation is to be expected. However, we suggest that these species differences do not completely remove the utility of studying other animal models, but rather require more nuanced interpretation in order to apply these findings to human disease. In particular, the evolution of the placenta in different taxa has resulted in striking examples of convergent evolution. The “syncytin” genes are a prime example, where retroviral envelope genes have been independently co-opted for nearly identical purposes – facilitating multinucleate syncytiotrophoblast formation – in at least five taxa (Dupressoir et al., 2012; Feschotte and Gilbert, 2012). Further, the rapidly evolving hormones secreted by the placentas of each major taxa are different, but there appear to be common trends in their biology. Primates, rodents, and ruminants all express taxa-specific families of Growth Hormones and Glycoproteins that likely perform similar functions despite having separate evolutionary origins (Rawn and Cross, 2008). Thus, understanding fully how conflict shapes evolution in model species will undoubtedly shed light on how the human placenta has evolved, and help us form hypotheses regarding the function of human-specific placental genes. Perhaps most importantly, investigating placenta biology in multiple species, including human, will reveal those aspects of placentation that are rapidly-evolving, and therefore most likely relevant to pregnancy disease.

The placenta is exquisitely and uniquely placed to rapidly evolve – responding to defensive signals from the mother and other external stimuli using multiple genetic mechanisms – and delivering hormones in a species specific manner to change maternal physiology. With disease so prevalent across all species, it seems that the complex physiology of this organ should no longer be ignored. We argue that human pregnancy – and indeed the prevalent diseases that it causes – will be greatly informed by a far more complete examination of the placenta and its unique pathologies in other mammalian species.

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