Endogenous Retroviruses and Placental Diversity

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In mammals, although size differences exist, most of organs consists of the same cells and exhibits the same structures. However, placentas are quite diverse in cell components, structures and the association between fetal membranes and maternal uteri. These differences have not been well characterized. Recently, endogenous retroviruses (ERVs) have been thought to have caused such diversity, which require both PEG type genes and syncytins.

placenta structural diversity endogenous retroviruses (ERVs) mammals

1. Introduction

Placentas are most diverse organs across mammalian species. Although the mammals obtained several new genes specific to pregnancy recognition and/or maintenance, which are often species' specific, gene expressions for placental development and/or their structural diversity have not been well characterized. It has long been thought that viral/transposon components exist in organism' genomes. In 2000, Mi et al. found that endogenous retrovirus (*ERV*, *Syncytin-1*) exists in the human placenta [1]. Since then, *syncytin*-type *ERV* structures and their functions have been reported in many animal species [2][3][4], but none of them contain the same nucleotide structures, strongly suggesting that these *ERV*s are independently captured and integrated into mammalian genomes [5].

2. Placental Diversity in Mammals

Mammalian placentas are extraordinarily diverse in terms of cell types, structure and their association with maternal blood, although placentas play the same roles such as physical and immunological protection against the maternal immune system, nutrient and gas exchanges, and endocrinological regulation [6]. During the last several decades, scientists in developmental biology and/or virologists have occasionally proposed retrovirus's role in placental evolution. For example, Haig (2012) proposed that the placenta became a mammalian tissue in which retroviral genes were domesticated to serve an adaptive function in the host [7]. Such an interplay may have contributed to evolutionally mechanisms associated with genomic imprinting of numerous genes.

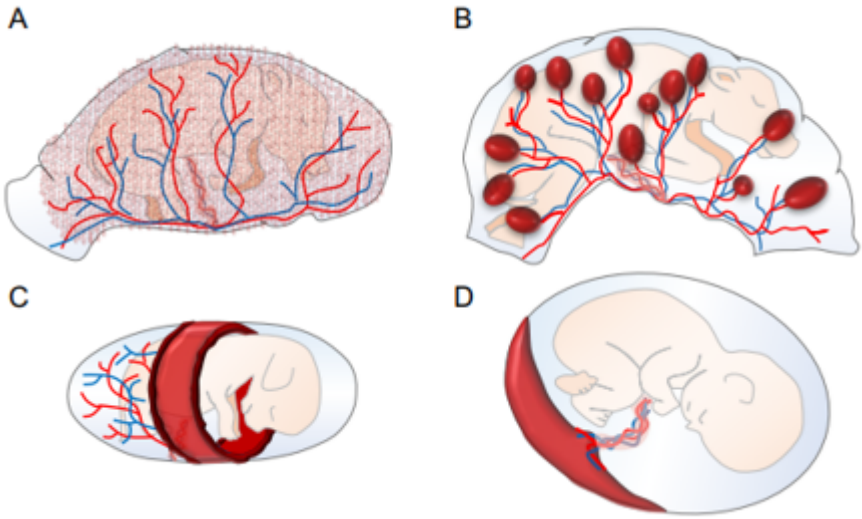

Figure legend: Mammalian placentas as classified by the distribution of chorionic villi. **A**: Diffuse placentas to which pigs and horses belong. **B**: Cotyledonary placentas, commonly found in ruminant ungulates. **C**: Zonary placentas to which dogs and cats belong. **D**: Discoid placentas, seen in murine and primate species including humans.

3. Involvement of *PEG10/PEG11/RTL1* in the Initial PlacentaFormation, *Syncytin*-type Genes in Their Structural Diversity, and Gene Usage/Regulation in Placental Environments

Imprinting genes such as those of paternally expressed genes, *PEG10* [8] and *PEG11/RTL1* [9], have been extensively studied for their contribution to the evolutional development of mammalian species. Through gene ablation studies, these genes are found necessary for the formation of placental structures [10][11]. Because PEG10 is acquired more than 146 million years ago, *PEG10* gene could explain the initial formation of placentas in mammals. However, structural diversity of placentas cannot be explained through the integration and function of *PEG10* and *PEG11/RTL1* genes. The phylogenetic record shows multiple independent instances of *syncytin*-type *ERV* genes' entry into disparate clades over the last 50 million years [5], strongly suggesting that *syncytin*-type genes as prime candidates for the emergence of structural diversification of mammalian placentas. Recently, more and more data have been accumulated, demonstrating that *syncytin*-type ERVs control gene expression of both functional genes as well as *ERV* themselves [12][13]. It is often observed that *ERV* integrations into mammalian genomes proceed successively: one *ERV* exaptation is followed by successive invasions of new *ERV*s. The new interloper retroviral genes may subsume the role previous *ERV*s played. These ongoing and successive *ERV* acquisitions for the establishment of more advantageous systems are explained by "a baton pass hypothesis" [14].

In general, the placentas have lower DNA methylation levels than embryos, allowing freer expression of *ERV*s and transposons during gestation, thereby facilitating selection of advantageous genes from a wider market. Such extraembryonic circumstances might have allowed for not only domestication of *ERV*s to establish novel

endogenous genes via multiple of selections but also the dissemination of *ERV*s and transposons throughout genomes as transcriptional regulators. Similarly, various degrees of maternal-fetal cell interactions in the uterine compartment may have led to change in kinds and degree of gene usage [7], possibly resulting in cellular and morphological changes in placentas. It is interesting to speculate that the placentas themselves might have served as an evolutionary laboratory to promote mammalian evolution [15].

4. New Models Explaining Placental Diversity

The outer most cell layer at the fetal side of placentas is called “trophectoderm”. Across mammalian species, the trophectodermal cells exhibit a great deal of fusogenic activity, notwithstanding the huge diversity in placental structures and type of placentation such as invasive (humans and murine) or non-invasive (pigs and ruminants) to the maternal endometrium. Based on actual experimentation and typical amino acid sequences, *ERV*s’ functions are generally limited to fusogenic activity and immunotolerance, which on their own are not sufficient to fully explain the structural diversity of placentas.

Dunn-Fletcher and colleagues (2018) have demonstrated that retroviral *THE1B* sequence serves as a cis-element for the regulation of corticotropin-releasing hormone (*CRH*) gene expression [16]. Recently, progress has been made on research into *ERV* sequences serving as transcriptional and translational regulators [12][13]. These sequences could be co-opted for newly integrated retroviral gene regulation.

Nevertheless, solid confirmation of a retrovirus integration into sperm or egg has not been obtained, and the mechanism of integration remains unclear. The rarity of such events owes in no small part to the narrow windows of possibility for infection, but conversion to active *ERV*s is also contingent on the perfect confluence of criteria as follows:

a) The insertion of *ERV*s can make functional genes of the host placenta-specific.

i.e., *Fematirn-1* integration into the intron 18 of pregnancy specific *FAT2* gene.

b) Its own LTR is sufficient to transcribe its gene segments, which serves as the cis-acting element(s), resulting in the activation of a host gene.

i.e., *IFNG*, *THE1B on CRH.*

c) It can make use of transcription factors utilized by the pre-existing gene, as per the baton-pass hypothesis.

i.e., A transcription factor GCM1 for *syncytin-1* and *syncytin-2*.

d) The *ERV* is co-opted along with its promoter/enhancer in the integrated genome.

i.e., Syncytin post-transcriptional regulatory element (SPRE).

e) There is cooperation with miRNAs and/or lncRNAs, yet not definitely characterized under placental/trophectodermal conditions, either alone or together with *ERV*

5. Conclusion

It is now clear that the emergence of mammalian placentas was made possible with the acquisition of therian *PEG10* and eutherian *PEG11/RTL1* genes, followed by independent, yet successive integrations of *syncytin*-type *ERV* genes. Structural variations in mammalian placentas could have been obtained through *ERV*s'own functions as well as the regulation of functional genes and/or *ERV*s themselves. A question still arises as to whether the placental structures that we know now are the ultimate forms or are still evolving. If the latter is the case, placental structures may still be diversifying and new variations could be awaiting discovery.

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