ISSN: 2837-4614

DOI: 10.33552/ARM.2024.01.000516

Archives of Reproductive & Medicine

Iris Publishers

Mini Review Article

Endogenous Retroviruses, Master Regulators for Embryonic and Placental Developments

Kazuhiko Imakawa* Ph.D.

[1]*Laboratory of Molecular Reproduction, Research Institute of Agriculture, Tokai University, Japan*

Corresponding author: Kazuhiko Imakawa Ph.D., Laboratory of Molecular Reproduction, Research Institute of Agriculture, Tokai University, Kumamoto 862-8652, Japan

Received Date: February 06, 2024

Published Date: February 19, 2024

Introduction

In most mammals, life begins with fertilization of the egg and sperm, followed by mitotic cell divisions during which fertilized oocytes/gametes undergo zygotic genome activation (ZGA) and/or the establishment of the first two cell lineages, the pluripotent inner cell mass (ICM) and the surrounding outer trophectoderm (TE). The ICM is characterized with the expression of the octamer-binding 4 (OCT4) and the sex-determining region Y box 2 (SOX2), the foundation of pluripotency in early embryo [1] while the TE expresses caudal type homeobox 2 (CDX2) [2].

During the last several decades, virologists often proposed the role of retroviruses in placental evolution. In 2000, the expression of a captive retroviral envelope protein, syncytin, was found in the human placenta [3]. It was found that the expression of murine endogenous retrovirus with leucine transfer RNA primer binding site (*MERVL*) is activated at the two-cell stage [4] concomitant with ZGA [5]. High levels of *MERVL* are found in mouse embryonic stem cells (ESC), a rare transient cell population, and induced pluripotent stem cell cultures, of which expression was independent of two-cell specific genes such as *Oct4*, *Sox2* or *Nanog* [6].

ERVs as master regulators

It was proposed that numerous retroviral genes become domesticated, endogenous retroviruses (ERVs) in the placenta, which serves an adaptive function in the host [7]. These observations opened a totally new field of research in which ERVs play crucial roles in embryonic as well as placental developments. Although expression of *MARVL* is shown, its role has not been characterized until recently. Using knockdown and CRISPRi-based repression of *MARVL* [8] demonstrated that full-length *MARVL* transcripts, but not encoded retroviral proteins, are required for simultaneous and successive regulation of transcriptional activity and their chromatin structures of the host during preimplantation development. Quite recently [9] demonstrated using cutting-edge genetic and biochemical techniques in mice that a retroviral protein, MARVL-gag, was found as a crucial moderator of pluripotent factors OCT4 and SOX2 during lineage specification. MARVL-gag tightly works with the unconventional prefoldin RPB5 interactor (URI), required for pluripotency in mouse blastomeres, though the function of the URI prefoldin-like complex remains largely unknown. These observations suggest that endogenization of retroviruses causes coevolution of the host genome for the generation of transcriptome and/or proteasomal systems for early embryonic development.

It is generally accepted that endogenization of LTR retrotransposons, including ERVs, has occurred throughout mammalian evolution. It was hypothesized that earlier integration of *PEG10* caused the formation of primitive placenta in eutherians [10] while the acquisition of *PEG11/RTL1* and *LDOC1/SIRH7/RTL7* resulted in the establishment of basic structures and functions of the chorioallantoic placenta [11,12]. These events were followed by structural diversity facilitation throughout mammalian evolution in each lineage of eutherians by endogenization of *syncytins* [13]. As seen in humans, *syncytin-2* (*ERVFRDE1*) integrates into the lineage, followed by *syncytin-1* (*ERVWE1*). Similarly, *syncytin-Rum1* entered the Bovidae, followed by *BERV-K1* (*Fematrin-1*) integration. It appears that exaptation of one ERV is neither a rare nor singular event during evolution. There may be successive cycles in which the lineage integrates one ERV, that is later followed by another ERV

which subsumes its role with likely increased efficacy in placental development. These ongoing ERV acquisitions are called "a baton pass hypothesis", in which a new ERV replaced the preexisting ERV gene and acquired the role that the gene had played [14]. Diversification of the mammalian placenta has not been fully explored, but it could be explained through the successive co-option of unrelated ERVs in different mammalian species. It has become apparent that the insertion of ERVs and its own LTR is sufficient to transcribe its own gene segments, which serves as the cis-acting element, resulting in the activation of a host gene. It can make use of transcription factors used by the pre-existing gene, as per the baton-pass hypothesis. It is also possible that the ERV is co-opted along with its promoter/enhancer in the integrated genome.

Future Direction

For the last twenty years, new methods such as RNA-seq, iTRAQ, ChiP-seq, and even one cell analysis have become available to analyze whole transcripts, proteins and their up-stream events to regulate such expression. These advancements and more would allow dissection of molecular events regulating pluripotency specification, preimplantation embryo developments and placental diversity. Undoubtedly, more and more functions of ERVs on the regulation and/or co-function of host's functional genes would become available. Such elucidation will allow the reconstruction of molecular events of embryonic as well as placental developments.

Acknowledgments

This reserach was supported in part by Japan racing and livestock promotion foundation and Grant-in-Aid For JSPS KAKENHI 23HO2356 (Co-investigator). The authors would like to thank Robert Moriarty for the English editing.

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