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Advances Perspectives in Syncytin-1 From Biology to Clinical Practices

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1. Abstract

Syncytin-1 serves as an enveloped membrane glycoprotein encoded from env gene and expressed in placenta specifically as HERV-W member product of human genome playing an essential role in cell fusion process of from trophoblast to syncytiotrophoblast during each individual pregnancy. It is widely maintained that unusual expressive levels of syncytin-1 have close relationships to obstetrical syndromes such as pre-eclampsia as a typical gestational hypertension symptom. In this review, correlations between syncytin-1 and related diseases are in detailed discussions.

Human Endogenous Reversal Transcription Viruses (HERVs) take an estimated 8% loci of human genome address length being composed of including Group-Specific Antigen (gag), polymerase (pol), envelop (env) genes and non-coding Long Terminal Repeated Sequences (LTRs) of both 5' and 3' terminals as well [1]. Most of HERV genes have yet lost abilities of encoding via a historic long-term evolution, mutation, deletion, trans-location and recombination while a tiny group of HERV members survive to reversal transcription and expression onto viral particles by their intact open reading frames [47]. In recent years, HERV genes uncommonly stop muting to help lead to many illnesses and syndromes, which has been solidly verified further more.

2. Concepts of Syncytin-1

The gag and pol genes of HERV-W family have lost their coding abilities owing to some genetic interruptions such as code-shifter insertion resulted in frequent translation terminal codes while neither does the env gene for its intact open reading frame. The env locates on 7q21.2 which encodes syncytin-1, a 80kD enveloped glycoprotein with 38aa residues translocating to the placenta trophoblastic cell membrane to help fusion during pregnancy [2,3]. Two subunits SU and TM of syncytin-1 function to binding ASCT2 receptor as well as mediate virus-cell or cell-cell interactions respectively [4], based on which fusion of human sperm and egg and in furtherance of from trophoblast to syncytiotrophoblast and else [6], fusion of multinucleic osteoclasts [5], can easily occur. Also, syncytin-1 correlates with non-fusion activities as proliferation, immunoregulation and anti-apoptosis suchlike etc [7,8,9].

3. Embryonic Development and Pre-eclampsia

Syncytin-1 helps prompt to cell fusion process of from trophoblast to syncytiotrophoblast to keep placenta in well clinical conditions by interaction with ASCT2 receptor. Chen et al reported the expressive level of syncytin-1 curves in parabola with the maximum value around about 37w chronologically in consensus with the variation curve of trophoblastic develop biological level [10]. The expression of syncytin-1 is silenced by the CpG island methylated promoter in normal somatic cells but trophoblast, in the latter cytosine demethylations appear in large scale leading to a high-level syncytin-1 expression [11]. Gimenez et al reported that the methylation of U3 region in 5'-LTR is basically rare during early pregnancy rather than up to 33.3% during terminal pregnant stage [12]. Pre-Eclampsia (PE) is considered as a starring hypertension-typed obstetric compliant clinically resulting in many abnormalities including deficiency of trophoblastic invasion, differentiation and chorioplacental precocity especially in HELLP syndrome and Intrauterine Growth Restriction (IUGR) etc. [13]. sufferers, the placenta of which have a relative low-level expression of syncytin-1 and with dysfunction of trophoblastic fusions [14,15]. Syncytin-1 has been down-regulated expressed in PE sufferers by GCM1 and TGF-β via both SMAD-dependent

SMAD2/7 and SMAD-independent, i.e. the PAARD6/SMURF1 pathway [16]. Up-regulated expression of B-Cell Lymphadenoma 6 (BCL6) in PE sufferers leads to expressive silence of HCG and syncytin-1 as failure of trophoblastic fusion [40]. Down-regulated expression of GCMa and high-level methylation of syncytin-1 promoter as well as over-expression of BCL6 altogether contribute to trophoblastic differentiation, fusion and the pre-eclampsia [15,17,40]. Down-regulated syncytin-1 also mediates in increased trophoblastic apoptosis and cellular period hindrances leading to cell fusion failures and placenta increta deficiencies. Qiao et al reported that a significant morphological abnormality such as asymmetric distributive patterns or absences of blood capillary occurs in the placenta or fetus of mice with syncytin-A (homologous to human syncytin-1, a putative factor mediated in fetus mice angiogenesis and pre-eclampsia) knocked-out mutants [18].

4. Autoimmune Diseases

Many recent studies disclose the correlation of between HERV and autoimmune diseases since HERV serves as an relative-constant expressive autoantigen which would have an immunological tolerance during the embryonic development. The study on correlation of between HERV-W and Multiple Sclerosis (MS) starts with the bioinformatic similarity and identity of between reversal transcription virus separated from MS suffers and HERV(or syncytin-1 directly [2]. Syncytin-1 is highly expressed oligodendroglial cells in brain tissues and pericyclic monocytes in blood, the former taken as a putative pathological mechanism to MS [21-25]. Cytokines as during CD14 responses are stimulated to additional expression in relapsing-remitting MS. HERV-W env production also Triggered Toll-Like Receptor 4 (TLR4) to induce cascade of IL-1, IL-6 and TNF-α overexpression, Th-1 lymphocyte polarization, TLR4 activation and up-regulation of nitric oxide synthase, and nitration of tyrosine [26-28]. HERVs are also considered as reasons for autoimmune diseases since its similarity with exogenous virus which recruits immunological responses. About 70% and 57% probabilities of HERV-W-env protein and its upstream RNA messenger could be detected in serum and peripheral monocyte of T1D autoimmune disease sufferers respectively [19]. Syncytin-1 is expressed in 75% pancreatic acinar cells to suppress the secretion of insulin in human Langerhans' cells. HERV-W-env products demonstrate a significant relationship to macrophage infiltration by wide immunohistochemical analysis of pancreatic exocrine. Hyperglycemia, low insulin level and pancreatic immunological cellular infiltration are obviously shown in transgenetic mice with gain-of-function HERV-W-env expression. Based on the fact above, GBbAC1 and IgG4 monoclone antibodies have already been developed aiming to neutralize HERV-W-env expression by specific target in vitro and vivo. Providing the safety and efficiency of GNbAC1 performances to T1D sufferers during its clinical experiments, it would be an opening door to novel methodologies of clinical therapy to T1D disease [20,32]. Besides MS and T1D disease, syncytin-1 expression has been verified in many other autoimmune diseases as Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Systematic Lupus Erythematosis (SLE), Schizophrenia (SZ) and many other autoimmunological dermatosis, the mechanisms of which above of HERV-W-env are still remained poorly understood [33-36]. It is so well widely accepted that HERVs stimulates body's immunological response by its bioinformatic similarity of exogenous virus envelope to induce further autoimmune. HERV expressed physiologically in somatic cells can be identified by innate immunological pattern recognition receptor (PRR) as Pathon-Associated Molecular Pattern (PAMP), a super antigen which triggers inflammation, T helper lymphocyte differentiation and cytotoxicity, and biosynthesis of autoimmune antibodies and cytokines induced to release as well [19,20].

5. Tumour

Many studies of HERV-W and its product syncytin-1 seems to put more emphases on multiple oncogene as breast, colorectal, lung, leukemia and endometrial cancer. Fei et al reported that syncytin-1 is highly expressed in CRC tissue and correlates with CRC tumor's differentiation and metastasis. Syncytin-1, CD9 and CD47 are significantly up-regulated to express in HCT116 and LoVo cell lines as well as c-Jun but PKA RIa and JNK1 to the contrary, which demonstrates syncytin-1, CD9 and CD47 may probably contribute to the oncogenesis of Polyploid Giant Cancer Cell (PGCC) together with its mediated cell fusion process regulated by cAMP/PKA and JNK signaling pathways [37]. Syncytin-1 is expressed in different up-regulated levels in EC tissues according to different assessments and survival ratios. Overexpression of syncytin-1 may probably lead to lymphocyte proliferation, shortened cellular cycle and cellular migration and invasion while vice versa. Also, syncytin-1 increase expressive levels of genetic products of EMT-related genes such as vimentine, E-cadherin, SLU and ZEB1 and significantly decrease the epithelial biomarker N-cadherin. Hence the correlation of between syncytin-1 and EMT signaling pathway has been solidly proofed since above mentioned [38]. Roberto et al reported that syncytin-1 homologous protein SyHP has been verified to help form the cytoplasmic bridge of T47D breast cancer cell lines and among the survival cells perform as an enhanced resistance to their previous under radioactive therapies [39]. Syncytin-1's unusual expressions have been already detected in nearly two third of leukemia blood samples. Sun et al argues an enhanced syncytin-1 level among Acute Myeloid Leukemia (AML) and Acute Lymphocytic Leukemia (ALL) cell lines, especially, much higher in the former. Rather than else AML leukemia, M5/M5a/M5b AML demonstrate the highest syncytin-1 expressive level. Given a much higher CD8+ T lymphocyte ratio in AML sufferers than in ALL counterparts, syncytin-1 expressive level may probably relate positively to the CD8+ T lymphocytes ratios [41,42]. The syncytin-1 expression in placenta is regulated by the methylated level of ERVWE1 promoter CpG island. Benesova et al re-

ported that lower methylated level of ERVWE1 promoter appears together with higher syncytin-1 expression in seminoma-related cell lines, which may deliver that the demethylation of ERVWE1 promoter open the door to expression of syncytin-1's expression to function [43]. Cell fusion has been widely accepted to serve as the driving force of carcinoma invasion and metastasis. Yan et al reported that TNF-α promotes up-regulated expression of syncytin-1 and ASCT-2 in OSCC and HUVEC respectively and enhances the fusion between the above two lines by activating Wnt /β-catenin signaling pathway [44]. Immuno histochemical studies illustrate us that syncytin-1 are mainly located in NSCLC cell membranes with higher level rather than para-carcinoma tissues. And higher syncytin-1 level may lead to a lower viability according to survival analysis [45]. High level expression of syncytin-1 in UCCB is always accompanied with its proliferation and activation and the combination of c-Myb and 3'-LTR is accelerated by mutations in 3'-LTR and activate syncytin-1 expression in furtherance [49].

In summary, the pathological mechanisms of syncytin-1 to its related illnesses are still not enough clarified based on current genetic and biochemical studies. Further studies and discussions are required for novel and rational therapy, management and prevention of these above diseases.

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