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Review

Epigenetic and non-epigenetic regulation of syncytin-1 expression in human placenta and cancer tissues

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ABSTRACT

Syncytin-1 is a human endogenous retroviral envelope gene (HERVW1) product specifically expressed in placental trophoblasts. By mediating the formation of syncytiotrophoblasts through cell–cell fusion, syncytin-1 plays a critical role for the placental barrier, endocrine and exchange functions. During pregnancy, syncytin-1 expression is dynamically regulated by various pathophysiological factors and pathways. This review summarizes and examines published data on epigenetic and non-epigenetic regulation of syncytin-1 gene expression, with a focus on the changes of syncytin-1 DNA methylation and expression in placental trophoblasts under preeclamptic and hypoxic conditions. The functions of syncytiotrophoblasts, the fusogenic and non-fusogenic activities of syncytin-1, and aberrant activation of syncytin-1 expression in cancer cells are also discussed. New findings on the epigenetic regulation of syncytin-1 in placentas from monozygotic/dichorionic discordant twins are analyzed. The close correlation among changes of DNMTs expression, syncytin-1 gene methylation, and syncytin-1 mRNA levels, in placentas associated with discordant fetal growth indicated a dynamic nature of syncytin-1 regulation.

Contents

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1. Introduction

1.1. The significance of syncytiotrophoblasts for placental function and the maintenance of normal pregnancy

The essential role of placenta for fetal development is largely determined by its anatomical location between the mother and the fetus. Serving as an interface separating, yet at the same time connecting, the maternal and fetal circulations, placenta carries out multiple functions including those for physiological barrier, endocrine, and passive exchange or active transport of oxygen and other gases, electrolytes, glucose and other nutrients, vitamins, and metabolism wastes[1]. Placenta produces large amounts of estrogen, progesterone, human chorionic gonadotropin (hCG), human chorionic somatomammotropic (hCS), placental growth hormone (PGH), placental protein 13 and gonadotropin-releasing hormone, which are required for the maintenance of pregnancy, fetal development, and maternal adaptation changes [1,2]. It is noteworthy that most of these functions are carried out by syncytium, the continuous layer of intravillous syncytiotrophoblasts formed by the terminal differentiation of trophoblastic linage [3,4]. Placental syncytium also constitutes a barrier that insulates the fetal circulation from the maternal one to avoid immune attack from maternal system [5]. As frequently observed in clinical practice, under the conditions of genetic disorders, IUGR, preeclampsia, as well as therapeutic interventions, any disruption or interference of the above functions could lead to increased fetal as well as maternal morbidity and mortality [6].

1.2. Trophoblast differentiation

Placental trophoblastic linage arises from the trophectoderm in the blastocyst stage, and the separation of trophectoderm from inner cell mass, which will develop into the fetal organs, represents the first linage specification in embryo development [7]. Trophoblast linage develops into two major groups of cells migrating to different directions. The extravillous trophoblasts will invade into the uterine decidua basalis, reaching the inner third of myometrium. These cells functions to remodel the endometrium and maternal vasculature to ensure the sufficient blood supply for the fetus. Although some extravillous trophoblasts will undergo limited (in comparison to intravillous trophoblast fusion) cell–cell fusion to form extravillous syncytiotrophoblasts and the multinucleated trophoblastic giant cells, the role of syncytin-1 in these cells has not been systematically characterized. The current review will focus on the better studied syncytin-1 expression and functions in the second group of cells, the villous/intravillous trophoblasts. For convenience, the usage of trophoblast or syncytiotrophoblast throughout this review refers to the intravillous group of trophoblasts.

1.3. Formation of syncytiotrophoblasts; Syncytin-1 fusogenic and non-fusogenic activities

It is well established that single nucleated cytotrophoblast (or simply trophoblast) cells undergo extensive cell–cell interaction and fusion action to form multinucleated syncytiotrophoblasts, or syncytium in a histological term [8]. As illustrated in Fig. 1, cell fusion is considered a hallmark for terminal trophoblast differentiation and function. Syncytin-1, a retroviral envelope gene (HERVWE1, human endogenous retrovirus-WE1) product located on cell membrane, is the key molecule for the fusion of cytotrophoblasts [9–11]. Placenta-specific expression of syncytin-1 is subject to a dynamic regulation by epigenetic as well as non-epigenetic pathways along the progression of pregnancy or under various pathological conditions [12–16]. It was observed that syncytin-1 expression continues to increase from the first to the third

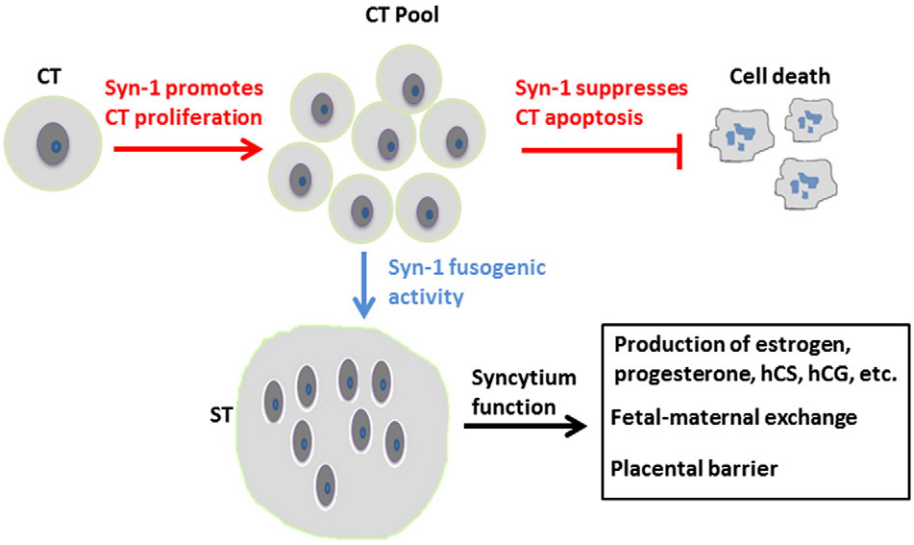

Fig. 1. The fusogenic and non-fusogenic activities of syncytin-1 and their implications for preeclampsia. Sufficient levels of syncytin-1 are required for cytotrophoblasts (CT) proliferation and the prevention of cell apoptosis. These non-fusogenic activities (indicated by red arrows) are important for the homeostasis of trophoblast "pool" which provides the material for the formation of syncytium composed of syncytiotrophoblasts through cell fusion mediated by syncytin-1 fusogenic activity (blue arrow). A healthy syncytium serves as placental barrier, produces estrogen, progesterone, hCS and hCG, and carries out fetal–maternal exchange function. The co-regulation of the three activities by a single factor may help to maintain the balance between the input (proliferation) and "output" (fusion) of cytotrophoblasts and a normal placental function. Under pathologic conditions, decreased syncytin-1 will directly affect cell fusion. In addition, the decreased cell proliferation and/or increased cell apoptosis could also cause syncytium deficiency by depletion of the cytotrophoblast "pool" through the two non-fusogenic activities.