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United we stand not dividing: The syncytiotrophoblast and cell senescence

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ABSTRACT

The multinucleate syncytiotrophoblast of the human placenta is responsible for transport functions between maternal and fetal blood supplies and is a major site of protein synthesis and steroid production. It is formed by cell fusion of the underlying cytotrophoblast cells. The nuclei of the multinucleate syncytiotrophoblast are non-mitotic yet the mechanism of cell cycle arrest in the syncytiotrophoblast is not known. The recent publication by the group of Krizhanovsky (2013), demonstrates that cell fusion induces cell senescence. The work reported the exciting finding that term placenta syncytiotrophoblast displays markers associated with cellular senescence. Cellular senescence is perhaps best known as a component of aging, a response to stress and an important factor in preventing tumor cell growth. The aforementioned study suggests myriad avenues of investigation in placental biology with intriguing possibilities to furthering our understanding of placental development and aging, health of pregnancy and placental pathologies having their origin in placental stress.

1. Introduction

The outer layer of the chorionic villi of the human placenta, the syncytiotrophoblast, is unique in both structure and function. The multiple roles of this multinucleate structure, the site of essential protein synthesis and molecular transport between maternal and fetal blood, raises some perplexing questions. Among them are how cell cycle arrest is permanently maintained in a structure formed by constant fusion of the underlying cytotrophoblast progenitor cells and how protein synthesis is controlled in this continuous epithelium [1–5]. It was recently demonstrated that the syncytiotrophoblast expresses proteins associated with cell senescence [6]. Cell senescence is perhaps best known as a means to maintain permanent cell cycle arrest in damaged cells, as a response to certain types of stress, and as a major player in aging.

This finding of syncytiotrophoblast cell senescence may shed light on the role of permanent cell cycle arrest in the multinucleate syncytium, while its vital functions in pregnancy are maintained. It may also offer a link among diverse placental pathologies including those associated with stress or placental insufficiency, such as IUGR and preeclampsia. Syncytial senescence may also be a mechanism of the aging process in this organ, designed for a nine month life span, which must ideally continue full functioning until the moment of parturition. This current topic and opinion will focus on the new finding of cell senescence in the syncytiotrophoblast and the roles that cell senescence may play in normal placental development and aging, as well as its implications to placental health and pathology.

2. Syncytiotrophoblast development and function

The syncytiotrophoblast expands rapidly during pregnancy. Its surface area increases thirteen fold between twelve weeks and term: the surface area of the term placenta is almost 12 m^2, the size of a parking space [7]. The syncytiotrophoblast is a powerhouse of protein synthesis, yet almost paradoxically, transcription as well as splicing complex snRNA (small nuclear RNA) expression is reduced [1–5]. This transcriptional reduction is particularly seen in syncytial knots, structures of the aging syncytiotrophoblast [4]. Reduced transcription in many nuclei of the syncytiotrophoblast serves to balance the maintenance of the necessarily large surface area essential for the transport function between mother and fetus with the regulation of protein expression. As the syncytiotrophoblast is composed of nuclei of cytotrophoblast cells that fused at different times during pregnancy, it is not at all surprising that the appearance of chromatin in the syncytiotrophoblast varies for nuclei:

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recently fused nuclei have a euchromatic appearance while nuclei of the syncytial knots are mostly heterochromatic [8].

The process of progenitor cytotrophoblast fusion to form the syncytiotrophoblast continues throughout pregnancy, contributing to the growth of the placenta and damage repair of the chorionic villi. Some of the molecular players in the process have been revealed. The syncytin genes are key effectors and mediators of fusion in the placenta. Syncytin-1 is the envelope gene of an endogenous human defective retrovirus expressed in all trophoblast lineages. Its receptor, MFSD2A (Major Facilitator Superfamily Domain-Containing Protein 2A), is expressed in the syncytiotrophoblast [9], whereas syncytin-2 is expressed exclusively in cytotrophoblasts [10]. The nuclei of this terminally differentiated and continuous epithelium, which lacks lateral cell borders and covers the chorionic villi, are non-mitotic and at term are estimated to number almost sixty billion [7]. Until recently the mechanism governing exit from the cell cycle of the nuclei in this multinucleated syncytium was unknown. Cell senescence has been known for decades as a mechanism to arrest cell cycle progression [11]. Krizhanovsky and colleagues demonstrated that cell fusion induced cell senescence [6] and that the syncytiotrophoblast expressed proteins associated with cell senescence. One may speculate that cell fusion activated senescence may allow this multinucleate, terminally differentiated, post-mitotic syncytium to function in a united fashion in its essential roles to sustain pregnancy, while permanently maintaining cell cycle arrest.

3. Fusion induces cell senescence

Cellular senescence is perhaps best known as a response to stress or DNA damage, and as a phenomenon of aging cells. Cell senescence is recognized as a method to curb tumorigenesis [11]. Krizhanovsky and colleagues arrived at their finding of syncytiotrophoblast senescence from first studying cell fusion and activation of cell senescence in several in vitro systems [6]. The authors used IMR-90 (diploid fibroblasts), MCF-10A (immortalized epithelial) and A549 (alveolar adenocarcinoma) cells to demonstrate that cell fusion induces cellular senescence. They induced cell fusion by two different methods, using ERVWE1 (syncytin-1) and infection by measles virus. They showed that senescence was induced in both these cell fusion model systems. Using immunohistochemistry they demonstrated that the syncytiotrophoblast expressed proteins known to be activated by cell senescence including senescence-associated beta-galactosidease (SAβ-Gal), CDK (Cyclin Dependent Kinsase) inhibitors p21 and p16, and tumor suppressor p53 and the hypophosphorylated pRB (retinoblastoma protein).

4. Developmental vs. classical cell senescence

Most recently, a role for cellular senescence in normal development and embryogenesis has been elucidated [12–15]. These publications discuss a role for cell senescence in embryogenesis of the inner ear, the developing kidney, and in limb formation of the apical ectodermal ridge, as well as several other tissues. The developmental pathway of senescence has been shown to differ in several ways from classical cell senescence. In placental senescence for example, p21 is activated and the p53 pathway of senescence appears functional. But in developmental senescence, p21 is activated in a p53 independent pathway [6,12–15]. In senescent cells P16 maintains pRb in its active hypophosphorylated state, preventing cell cycle progression by inhibiting transcription factor E2F [11] but unlike the syncytiotrophoblast, developmental senescent cells do not express p16.

Furthermore, while these studies describe embryonic cell senescence in the mouse, they make no mention of the placenta [12–15]. Although both human and mouse placentas are hemochorial, their structures differ in several ways. The mouse placenta has two syncytial layers, ST-l and ST-ll, whose formation is controlled by endogenous retroviral genes syncytin A–B [16]. In addition, although genome endoreplication is a prominent feature of the hormone producing, non-dividing trophoblast giant cells in the mouse placenta, endoreplication is not a mechanism found in the syncytiotrophoblast of the human placenta. However, there are several reports showing that the polyploid nuclei of the large polygonal cell type of extravillous trophoblast result from genome endoreduplication [17,18]. Despite such differences, as the syncytium of the mouse placenta is formed by cell fusion, the mouse may indeed afford a model system to study senescence in the human syncytiotrophoblast [10]. Interestingly, loss of Rb was shown to result in embryonic lethality from placental defects [19]. Krizhanovsky and colleagues have demonstrated that syncytiotrophoblast senescence more resembles that of cell aging than it does the newly described embryonic pathway of cell senescence. This suggests that senescence in the syncytiotrophoblast may perhaps be related to placental aging.

5. Cell senescence, placental aging, and pathologies

As the placenta is an organ with a limited lifespan of nine months, the senescence markers that the authors found in term placenta may indeed reflect placental aging in analogy to other aging tissues. Perhaps as the placenta reaches the end of its lifespan the senescence program is activated. However, since only term placenta was investigated we do not yet know whether syncytial senescence is a function of cytotrophoblast cell fusion or a finding of the near end of life of this organ, or perhaps both. Most likely, cytotrophoblast cell fusion itself would invoke senescence programming, rather than aging of the placenta per se. Investigation of senescence marker expression in chorionic villi throughout the trimesters of pregnancy should in part resolve this question.

Following these lines of thought, it would be interesting to investigate if the accelerated aging/maturation, termed the Tenney-Parker change, found in the placenta of preeclampsia [20] is related to aberrant or premature senescence. Tenney-Parker changes, especially arrested release of syncytial knots, have been observed in pathologies of both preeclampsia and IUGR [21]. As the placenta of preeclampsia is thought to suffer from oxidative stress and senescence can be induced by this stress factor, it is tempting to speculate on an association between oxidative stress of preeclampsia, senescence and accelerated placental aging. Fogerty and colleagues [4] recently used immunohistochemistry for 8-oxo-deoxyguanisine to demonstrate that the mostly heterochromatic nuclei of the syncytial knots showed signs of oxidative damage [4]. This may suggest another possible association between aging and senescence in the placenta. In addition, shortening of telomere length is a known trigger of cell senescence. Placentas of IUGR (intrauterine growth restriction) and perhaps the degenerating placenta associated with stillbirth, may provide a link to accelerated placental aging, senescence and major obstetric complications [22–25]. These pathologies may include the placenta of trisomy 21, where defects in cell fusion and differentiation of the syncytiotrophoblast, mediated by the oxidative status of the trophoblast, have been described [26].

We do not yet know if there is an association with telomere length of DNA of syncytial nuclei, senescence and normal placental aging. Krizhanovsky and colleagues do show that the syncytiotrophoblast is positive for the senescent marker γH2AX, a nuclear marker for the DNA damage response (DDR) that is triggered by telomere shortening. Interestingly, the senescent marker DCR2 (decoy death receptor) that prevents apoptosis is also expressed in