Review Article

Obstet Gynecol Sci 2019;62(4):199-211
https://doi.org/10.5468/ogs.2019.62.4.199
pISSN 2287-8572 · eISSN 2287-8580

Obstetrics & Gynecology Science

Initiation of human parturition: signaling from senescent fetal tissues via extracellular vesicle mediated paracrine mechanism

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A better understanding of the underlying mechanisms by which signals from the fetus initiate human parturition is required. Our recent findings support the core hypothesis that oxidative stress (OS) and cellular senescence of the fetal membranes (amnion and chorion) trigger human parturition. Fetal membrane cell senescence at term is a natural physiological response to OS that occurs as a result of increased metabolic demands by the maturing fetus. Fetal membrane senescence is affected by the activation of the p38 mitogen activated kinase-mediated pathway. Similarly, various risk factors of preterm labor and premature rupture of the membranes also cause OS-induced senescence. Data suggest that fetal cell senescence causes inflammatory senescence-associated secretory phenotype (SASP) release. Besides SASP, high mobility group box 1 and cell-free fetal telomere fragments translocate from the nucleus to the cytosol in senescent cells, where they represent damage-associated molecular pattern markers (DAMPs). In fetal membranes, both SASPs and DAMPs augment fetal cell senescence and an associated 'sterile' inflammatory reaction. In senescent cells, DAMPs are encapsulated in extracellular vesicles, specifically exosomes, which are 30–150 nm particles, and propagated to distant sites. Exosomes traffic from the fetus to the maternal side and cause labor-associated inflammatory changes in maternal uterine tissues. Thus, fetal membrane senescence and the inflammation generated from this process functions as a paracrine signaling system during parturition. A better understanding of the premature activation of these signals can provide insights into the mechanisms by which fetal signals initiate preterm parturition.

Keywords: Amniochorion; Aging; Exosomes; Preterm birth; Fetal membranes

Introduction

Despite advances in medical care, the preterm birth (PTB) rate has been steady globally at up to 10.0% for the past several decades [1]. The most common phenotype (60%) of PTB occurs spontaneously with 30–40% being preceded by preterm premature rupture of the fetal membranes (pPROM) [1]. Current interventions to reduce the risk of preterm labor have been designed primarily based on our understanding of signaling at the maternal myometrium, specifically in terms of minimizing contractions to prolong gestation. A higher rate of spontaneous PTB globally warrants a better understanding of these signals and their mechanisms that initiate normal term pregnancies, which can provide insights into the pathological activation of signals associated with preterm parturition [2].

PTB and pPROM are associated with intra-amniotic inflammation [3-8]. Sterile inflammation, in the absence of infection, is increasingly being reported in PTB and pPROM and

Received: 2019.01.02. Revised: 2019.03.06. Accepted: 2019.03.20.
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is hypothesized to be a trigger for term birth as well [9,10]; however, etiologies contributing to sterile inflammation in adverse pregnancies are difficult to ascertain. This is partly because inflammatory pathways and biomarkers overlap, irrespective of the etiology [11]. Both infectious and non-infectious risk factors during pregnancy can cause oxidative stress (OS) and OS-mediated damage to cells and cellular organelles, which can lead to inflammation [12,13]. Similarly, in normal term pregnancies, OS-induced cellular damage and sterile inflammation can contribute to labor initiation pathways. Increased inflammation, irrespective of term or preterm status, is associated with decidual activation [14,15], transition of the quiescent myometrium to an active contractile state [16,17], and cervical ripening [2,18]. However, the mechanisms that generate sterile inflammatory mediators that can affect normal term parturition have still not been elucidated.

Although signals initiating parturition may arise from both fetal and maternal uterine tissues; a precise understanding of the true initiator is yet to emerge. It is unclear on who (mother vs. fetus) determines the timing of the inflammatory activation on maternal uterine tissues. One of the theories is based on fetal organ maturation and endocrine signaling [19-23]. Mature fetal organs release various biochemical mediators into the uterine environment [24]. These biochemicals are pro-inflammatory and can increase the overall inflammatory load in feto-maternal uterine tissues to induce labor. A classic example was provided by Mendelson et al. [25], who reported the role of surfactant protein-A and platelet-activating factor (PAF) expression, which increased in the developing fetal lung. These proteins can increase myometrial inflammation and labor. Endocrine signals are also well-reported time determinants of parturition [26-30]. Tan et al. [17] and Mesiano et al. [31] described the functional progesterone withdrawal theory based on the changes in progesterone receptor function in the myometrium. The quiescent state of the myometrium is maintained during pregnancy via progesterone-progesterone receptor (PR) B function. At term, this state is compromised and the active labor state is generated when PRA phosphorylation and progesterone binding contribute to a pro-inflammatory milieu [17,32]. Similarly, cervical remodeling and ripening is also impacted by changes in the endocrine and inflammatory mediators in response to fetal maturation signals [18]. In summary, parturition is a timed event where the fetus signals mature through various biochemical and endocrine mediators. These biochemical mediators include, but are not limited to, platelet activation factor [33], endothelins [34-36], transforming growth factor [37], and platelet-derived growth factor, all of which enhance inflammation in various feto-maternal tissues. Thus, inflammation disrupts homeostasis of various uterine functions, resulting in labor-associated changes.

The functional impact on maternal uterine tissues imposed by various biochemical signals and the signal-generated pathways leading to inflammation, which transition a quiescent state to an active labor state, has been well-reported [38-43]. However, very few studies have examined the contributions of fetal tissues, specifically fetal membranes (amniochorion), in this process [44-56]. Fetal membranes line the intrauterine cavity where they are enriched by the amniotic fluid composed of various biochemicals produced by the maturing fetal organs. Disruption of the functional and mechanical integrity of the fetal membrane, chorioamnionitis (infiltration of leukocytes), or mechanical derangement in response to various endogenous and/or exogenous factors are antecedent to both term and preterm parturition [48,57-60]. Since fetal membranes act as a barrier between the fetus and uterine tissues, they play a major role in maintaining pregnancy by protecting the fetus. Fetal membranes are hypothesized to promote parturition as they are exposed to various biochemical and physiological stressors at term. These stressors can disrupt fetal membrane homeostasis, leading to their dysfunction and/or rupture. A stressed and inflamed fetal membrane can signal term parturition. Our laboratory has recently elucidated the mechanisms by which OS inducers contribute to parturition by forcing fetal membranes to undergo senescence, a mechanism of aging [61]. The aging of a cell is a non-reversible process and is often associated with sterile inflammation, referred to as the senescence-associated secretory phenotype (SASP) [62]. The rest of this review will be dedicated to summarizing the recent developments in fetal membrane senescence research and how membrane senescence may signal term and preterm parturition.

Fetal membrane

1. Fetal membrane development

Fetal membranes consist of 2 major cell layers: a single cuboidal amnion epithelial layer and the chorion trophoblast

layer. Both of these layers are connected to a collagen-rich extracellular matrix via type IV collagen-rich basement membranes. Amnion and chorion mesenchymal cells can be seen dispersed in this extracellular matrix. The development of the amnion and chorion begins with embryogenesis, although they do not participate directly in the formation of the embryo or fetus. Like the fetus, early growth of the amnion and chorion layers is rapid and independent of each other. The formation of the amniochorion as a combined structural unit is completed between the 13th and 15th week of gestation. The growth and development of the amniochorion correlate with fetal growth, with a longevity period of 40 weeks (term gestation period).

2. Fetal membrane senescence

Fetal membrane cells have stem cell-like properties, as they are capable of growth, DNA replication, and transition at term, as well as exhibiting stem cell transcription factors [63]. Recent work using primary amnion epithelial cells showed that these cells can proliferate, migrate, express stem cell markers, and transition into other cell types [63]. These properties are essential for fetal membrane remodeling and to maintain membrane integrity, as membranes during pregnancy are constantly subjected to shear stress and stretching because of the fluid and fetus, respectively. During growth, membrane cells are constantly shed and gaps referred to as microfractures are often created [64]. Stem cell-like properties, proliferation, and cell transitions help to rebuild any structural compromises created by cell shedding [63]. This process also generates localized inflammation, which is required for membrane matrix remodeling. Uterine cavity OS levels change during gestation [65-67]; however, redox balance during pregnancy sustains this remodeling process as well as other reproductive functions [68]. Interestingly, the process is stalled as the membrane reaches the end of its longevity period at term and demonstrates structural, functional, and biomolecular changes that are characteristic of aging [61]. Two key function-based definitions proposed by Masoro [69] and Finch [70] may aid in understanding the biological aging process of fetal membranes: 1) Fetal membranes are expected to deteriorate during gestation once its maturation is completed around the 12th week of pregnancy, and will be vulnerable to subtle changes in the intrauterine environment, decreasing survival ability; 2) Senescence is a mechanism associated with the deterioration process of the membranes, which alters its function and decreases vitality [71].

3. Mechanism of fetal membrane senescence

In normal pregnancies, the methodical progression of senescence is under physiological control and is an inevitable process [61]. Senescence in fetal membranes is a telomere-dependent process, where telomere (cap structures protecting chromosomal edges and biological markers of aging) lengths are progressively shortened as gestation progresses [71-73]. The "Hayflick Phenomenon" explains this process by demonstrating the halt in cell division after a certain number of divisions [74,75]. Telomere length reduction in fetal membranes inversely correlates with fetal growth and reduction peaks at term when the fetus is mature [76,77]. One of the key accelerators of telomere length reduction is OS, as the guanine-rich telomere region is highly susceptible to OS [78,79]. As mentioned previously, redox balance maintains the structural remodeling of the membranes during gestation. However, term pregnancy is characterized by increased intrauterine OS due to the following reasons: 1) increase in the metabolic demands of the fetus [80,81]; 2) no change in the supplies of the maternal substrate to meet fetal metabolic demands [82,83]; 3) no change in the antioxidant status in both the fetal and maternal uterine tissues at term [53,84]; and 4) increase in the reactive oxygen species levels in the amniotic fluid at term when compared to other periods of gestation [85-88]. OS increase accelerates an already progressing aging process in fetal membranes through the activation of the p38 mitogen-activated protein kinase (p38MAPK) pathway, a stress-associated signaling pathway. OS specifically causes damage to various cell components, and this damage in fetal membranes can result in the activation of p38MAPK to cause senescence [12,61,71,89-93]. This mechanism of fetal membrane aging was confirmed when the antioxidant, N-acetyl cysteine, and a p38MAPK inhibitor reversed OS-induced and p38MAPK-mediated senescence and the senescence-associated secretory phenotype (SASP) in our *in vitro* and *in situ* animal models [13,90,92-94].

4. Consequence of fetal membrane aging

Fetal membranes attain an irreversible senescent phenotype due to increased OS prior to the initiation of labor at term. OS-p38MAPK-mediated senescence also diminishes the proliferative and transitional capacities of fetal membrane cells, thereby losing their functional and mechanical properties

[13,55,63,93,95]. This deterioration in fetal membrane function at term is a natural and physiological indicator of fetal membrane longevity. As mentioned previously, the dysfunctional status of fetal membranes coincides with fetal organ maturation, thereby indicating fetal readiness for delivery. Senescence of the fetal membrane increases SASP, a unique inflammatory signature [61]. Therefore, senescence of fetal membranes can be detrimental to the existence of pregnancy as the inflammatory signals (SASP) from senescent fetal membranes are uterotonins and could potentially trigger parturition [61]. Besides SASP, senescence-associated cellular injury increases damage-associated molecular patterns (DAMPs; which consist of high mobility group box 1 [HMGB1], uric acid, S100 proteins [a family of 25 members], interleukin [IL]-33, heat-shock protein 70, and telomere fragments) in cell-free fetal DNA (cffDNA) from term membranes. DAMPs from senescent fetal membranes act as signals arising from the maturing fetus and generate inflammation in other intrauterine compartments, readying them for labor. We have also reported how DAMPs may exaggerate an ongoing inflammatory onslaught on fetal membrane and other tissues. A description of their functional contributions in terms of increasing overall inflammation is provided below.

HMGB1 exists predominantly as a nuclear 25 kDa, non-histone chromatin-associated protein that binds double-stranded DNA and stabilizes nucleosomes during DNA repair and recombination [96,97]. However, the acetylation of lysine residues translocates HMGB1 to the cytoplasm, where it functions as a pro-inflammatory cytokine [98,99]. HMGB1 is known to be expressed in the human endometrium [100], placenta [101,102], decidua [101,103], cervix [104], fetal membrane cells [105,106], and immune cells, and has been reported in chorioamnionitis cases [105,107,108]. Higher HMGB1 concentrations in the amniotic fluid of laboring (term and preterm) vs. non-laboring women suggest that it has a role in parturition [9]. An increase in HMGB1 indicates cellular damage, suggesting that it can be a critical mediator in both infectious and sterile inflammatory processes, as seen in both preterm and term labors. Buhimschi's lab showed the impact of HMGB1 in animal inflammation models and documented that RAGE-dependent HMGB1 induced the activation of fetal inflammation [109]. In our own studies using fetal membrane cells, we were able to demonstrate that HMGB1 secretion was higher in OS-induced fetal membrane cells [110]. HMGB1 utilizes a positive feedback loop to enhance fetal cell senescence, tissue injury, and inflammatory cytokine production, which are capable of functioning as pro-parturition molecules. The enhancement of senescence by HMGB1 in these cells is mediated via Toll-like receptors (TLRs) and by increasing p38MAPK activation [110]. Interestingly, antioxidant, N-acetyl cysteine, and p38MAPK inhibitor, SB203580, treatments reduced the pro-senescent and pro-inflammatory effect of HMGB1 on fetal membrane cells [110]. This mechanism is similar to the OS effect seen on fetal membranes, suggesting that HMGB1 released from an OS-damaged cell can enhance senescence and inflammation in a feed-forward loop [92].

Dr. Mark Phillippe's group [111,112] has suggested that cffDNA in maternal circulation may activate human parturition. In his report, Dr. Phillippe [111]mentioned that an increase in cffDNA, which is released during apoptosis in the placenta and fetal membranes at term, has the ability to stimulate TLR9, leading to the increased release of cytokines and chemokines. One important component of cffDNA is fragmented telomeres. Telomere length in the fetal membranes decreases progressively throughout gestation with the shortest telomeres seen at term, which is consistent with *in utero* aging [72]. We also found a significant labor-associated increase in the abundance of cell-free fetal telomere fragments (cffTFs) in the amniotic fluid [73,113]. Additionally, cffTFs are also reported to have similar functional effects as HMGB1. To determine the functional consequences of increased cffTFs, *in vitro* and *in situ* animal model studies were conducted. Similar to the HMGB1 reports, cffTFs produced a positive feedback loop to enhance fetal cell senescence, tissue injury, and inflammatory cytokine production. Senescence induced by cffTFs were also associated with p38MAPK activation. To further determine the impact of cffTFs in parturition, we injected cffTFs into mouse models of pregnancy, thereby resulting in mouse fetal membrane p38MAPK activation, senescence, and inflammatory cytokine production [94,113].

Although our studies were restricted to HMGB1 and cffTFs, other reports showed an association between other DAMPs like uric acid [102,114], S100 proteins [109,115], IL-33 [116], and HSP70 [117] during pregnancy complications [118]. In summary, parturition signaling can be viewed from the fetal membrane perspective, where a novel paracrine signaling mechanism mediated by fetal tissue stress (i.e., physiological or pathophysiological senescence and/or OS) generates

sterile inflammation within the maternal-fetal interface (fetal membranes, decidua, and myometrium). Term labor can be triggered by factors collectively referred to as DAMPs, which are produced from senescent fetal membrane cells.

Can the mechanism of senescence explain the pathobiology of preterm birth and preterm premature rupture of the fetal membranes?

The ultimate goal of all of these studies is to identify the initiators and mechanistic effectors of PTB and pPROM. Having determined that fetal membrane senescence may be one of the mechanisms triggering parturition at term, we examined similar pathways in PTB and pPROM. For this, fetal membranes and amniotic fluid samples were collected from women with PTB and pPROM. Molecular, biochemical, and histological markers were used to document differences in OS and antioxidant enzyme status, DNA damage, secondary signaling, MAPK activation, and senescence activation between the membranes in both groups. OS was higher and antioxidant enzymes were lower in pPROM when compared to PTB. PTB membranes had minimal OS and DNA damage, no p38MAPK activation, and minimal signs of senescence [119]. Conversely, pPROM had higher numbers of cells with OS, DNA damage, p38MAPK activation, and signs of senescence [119]. Telomere lengths were also substantially shorter in pPROM membranes than in PTB membranes and fetal cord blood samples supported the hypothesis that pPROM may have a pathology due to premature aging of membranes [72]. Histologically and biochemically, pPROM membranes resembled normal term-delivered membranes, whereas PTB membranes were distinctly different. Both pPROM and normal term birth are associated with fetal membrane senescence, inflammation, and dysfunction. Hence, pPROM is a disease of the fetal membrane where the premature activation of senescence predisposes them to rupture [120]. We concluded that PTB and pPROM arose from distinct pathophysiological pathways. OS and OS-induced cellular damage are likely determinants of signaling pathways and phenotypic outcomes. This conclusion does not rule out OS in PTB, as a subset of women with exposure to OS may still develop this pathway, ultimately leading to labor; however, it is more dominant in pPROM. We also postulate that pPROM is a disease of the fetal membrane and senescence, with senescence leading to dysfunctions that act as the primary mediators of this mechanism [120].

How does fetal membrane senescence signal parturition?

As detailed previously, *in vitro* and *in situ* animal models demonstrated the consequences of fetal membrane senescence. Senescence and sterile inflammation mediated by SASPs and DAMPs are uterotonins, which are capable of inducing labor. However, the question remains whether this inflammation and cellular damage is restricted to the membranes or if membrane-derived inflammatory mediators are propagated to other feto-maternal uterine tissues to trigger inflammatory changes. Although the diffusion of these mediators is possible, it is unlikely that molecules like HMGB1 can traverse through the feto-maternal tissue layers and still be functionally viable at distant sites [121]. Our group has hypothesized that signal propagation between feto-maternal tissues can be effectively achieved via extracellular vesicles, specifically exosomes, which are bioactive, spherical, cell-derived vesicles (30–150 nm in size) that are secreted during the process of exocytosis. Exosomes contain molecular constituents of their cell of origin, including proteins and RNA that reflect the physiological state of the cell source [122-125]. In addition to common membrane and cytosolic molecules, exosomes harbor unique cell-specific subsets of proteins. Exosomes are released from the cell when multi-vesicular bodies fuse with the plasma membrane. They contain high concentrations of cholesterol and detergent-resistant lipid membranes, which make them extremely stable and efficient carriers of molecules across tissue layers [126-128]. Exosomes mostly act as transporters of paracrine signals between tissues, but can regulate intracellular pathways by sequestering signaling molecules from the cytoplasm, thereby reducing their bioavailability [127,128].

Amniochorion cell-derived exosomes carry inflammatory mediators

To test whether fetal membrane cells produced exosomes, we isolated and characterized primary amnion cell-derived

exosomes. We also treated amnion cells with OS-inducing agents to mimic the conditions experienced at term. Amnion cells were previously shown to produce exosomes that exhibited classic characteristics; however, OS treatment changed their cargo contents [129]. Inflammation was also witnessed in exosomes derived from cells grown under normal conditions and in cells exposed to OS [129]. The nature of inflammatory mediators differed between normal and OS-treated exosomes. Bioinformatic analysis of the proteomic contents in exosomes derived from cells grown under normal cell culture conditions exhibited nuclear factor (NF)-κB signaling pathways, whereas transforming growth factor β (TGFβ)-related signaling was dominant in OS-exposed cell-derived exosomes. Although both represent inflammation, the underlying cellular physiology contributing to the distinct inflammatory mediators in the exosomes reflects the specific exposure and the OS-associated state of cells [129]. TGFβ has been previously reported to increase with term labor and is an activator of p38MAPK, a senescent inducer in fetal membranes [95]. Besides these inflammatory pathways, senescent amnion cell-derived exosomes (from amnion cells grown under OS conditions) contain HMGB1 and cffTFs. These exosomes also carry both genomic and mitochondrial DNA [130]. Although our published reports focus on amnion cell-derived exosomes, ongoing work in our laboratory demonstrates that amnion mesenchymal cells and chorion mesenchymal and trophoblast cells also generate exosomes with distinct cargo contents in response to various stimulants.

Trafficking of exosomes carrying fetal signals between feto-maternal compartments

Propagation of senescent fetal cell-derived signals via exosomes and the trafficking of exosomes from fetal to maternal compartments was previously determined using animal models [131]. In this study, pregnant CD-1 mice were intra-amniotically injected on gestational days 16 and 17 with exosomes isolated from primary human amnion epithelial cells fluorescently labeled with the lipophilic dye, 1,1-dioctadecyl-3,3,3,3-tetramethylindotricarbocyanine iodide (DiR). *In vivo* imaging of the mice showed fluorescence in the uterus on the exosome-injected side, whereas the uterine tissues on the non-injected side and in saline and dye alone-injected animals remained negative. Histological analysis of the placenta showed exosome migration from the fetal to the maternal side of the placenta. Fluorescence released from the exosomes was seen in maternal blood samples and in the maternal uterus and kidneys, demonstrating that exosomal cargo can be carried via the systemic route from the fetus to the maternal side of the uterine tissues during pregnancy. This supports our hypothesis that fetal signals can be delivered via exosomes to the maternal side. A similar form of exosomal trafficking was also reported by other study groups [132].

Senescent fetal membrane-derived exosomes cause functional changes in maternal uterine cells

After documenting fetal exosome traffic to the maternal side, we tested the hypothesis that fetal exosomes could produce inflammatory changes in maternal uterine cells. The pro-inflammatory effect of fetal exosomes on maternal cells will be considered as a signaling mechanism by the fetal membranes to initiate the labor process by enhancing the inflammatory load. To test this theory, primary amnion epithelial cells were grown in normal cell cultures or exposed to OS, and myometrial and decidual cells were treated with various doses of exosomes derived from amnion cells. Treatment resulted in the increased production of inflammatory mediators (IL-6, IL-8, and PGE2) and activation of NF-κB. This is suggestive of fetal membrane cell-derived exosomes contributing to labor-associated inflammatory changes in maternal uterine cells [133]. Similar to our data, Holder et al. [134] showed that macrophage-derived exosomes caused the release of pro-inflammatory cytokines from the placenta. Another study suggested the ability of the placenta to respond to maternal inflammatory signals mediated by the interaction of maternal immune cell exosomes [134].

Recently, we tested the hypothesis that exosomes, as paracrine signaling molecules, can cause parturition. For this, maternal plasma exosomes from CD-1 mice were isolated and characterized throughout gestation and the biological pathways associated with differentially-expressed cargo proteins were determined. The results indicated that the shape and size of the exosomes remained constant throughout the gestational period; however, a progressive increase in the

quantity of the exosomes carrying inflammatory mediators was observed from embryonic day 5 (E5) to E19. Moreover, intraperitoneal injection of E18 exosomes (enriched in inflammatory mediators) into E15 mice caused them to undergo PTB when compared to mice that were injected with E9 exosomes (minimal levels of inflammatory mediators) or normal saline. The injection of E18 exosomes produced inflammation in the cervix and uterus on the penultimate day of delivery. Thus, these results support the functional role of exosomes as paracrine signaling molecules in causing parturition. Notably, this study used total exosomes rather than fetal exosomes; therefore, it is not a true *in situ* replication of the reported *in vitro* data.

Studies have also reported about the role of exosomes in implantation [135,136], placental immunomodulation [137], and their biomarker potential in various pregnancy complications [135,138-143]. Abnormal quantity and cargo contents of exosomes may serve as biomarkers of various adverse pregnancy events. Thus, ongoing studies, both in our laboratory and many other laboratories, are examining the biomarker potential of exosomes in predicting PTB [134].

Summary and conclusions

PTB pathways, biomarkers, and intervention strategies remain an enigma in the obstetric world [144]. Although multiple initiator and effector signals from both the fetus and mother have been proposed, the rate of PTB continues to rise. Thus, this suggests that our current knowledge is inadequate to reduce PTB risk. A better understanding of normal term birth and its pathways is needed to re-examine the premature activation of such pathways as triggers during preterm labor conditions. This manuscript provides an overview of a novel mechanism of parturition initiation signal based on well-reported data. The data summarize the progressive senescence of fetal membrane cells as term approaches. Senescent fetal cells generate inflammatory cargo-laden exosomes that move from the fetus to maternal uterine tissues in order to cause parturition by promoting inflammation. This can be considered a signal from the fetus, or specifically the fetal membrane, which indicates its longevity and dysfunctional status. The loss of fetal membrane integrity due to senescence and generation of inflammation (SASPs and DAMPs) can be considered to be one of the signals required to initiate parturition. The premature activation of membrane senescence in response to various pregnancy-associated risk factors can be attributed to a major subset of PTBs and pPROM. A better understanding of senescence activators and exosomal signaling may help us to sub-classify PTBs with such pathologies. Exosomes may also serve as biomarkers indicative of risk status.

Acknowledgements

This work was supported by the National Institutes of Health/National Institute of Child Health and Human Development (grant number 1R21AI140249-01A1 (NIH/NIAID) awarded to Menon R.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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