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Human fetal membranes at term: Dead tissue or signalers of parturition?

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ABSTRACT

Various endocrine, immune, and mechanical factors produced by feto-maternal compartments at term increase intrauterine inflammatory loads to induce labor. The role of fetal (placental) membranes (amniochorion) as providers of parturition signals has not been well investigated. Fetal membranes line the intrauterine cavity and grow with and protect the fetus. Fetal membranes exist as an entity between the mother and fetus and perform unique functions during pregnancy. Membranes undergo a telomere-dependent p38 MAPK-induced senescence and demonstrate a decline in functional and mechanical abilities at term, showing signs of aging. Fetal membrane senescence is also allied with completion of fetal maturation at term as the fetus readies for delivery, which may also indicate the end of independent life and longevity of fetal membranes as their functional role concludes. Fetal membrane senescence is accelerated at term because of oxidative stress and increased stretching. Senescent fetal membranes cells produce senescence-associated secretory phenotype (SASP-inflammation) and also release proinflammatory damage-associated molecular patterns (DAMPs), namely HMGB1 and cell-free fetal telomere fragments. In a feedback loop, SASP and DAMPs increase senescence and enhance the inflammatory load to promote labor. Membranes increase the inflammatory load to disrupt homeostatic balance to transition quiescent uterine tissues toward a labor phenotype. Therefore, along with other well-described labor-promoting signals, senescent fetal membranes may also contribute to human term parturition.

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Normal term human parturition is initiated when fetal organ systems are matured around 37–40 weeks' gestation. Conventional theories of parturition initiation signaling are primarily linked to feto-maternal endocrine and immune changes in the intrauterine cavity, correlating with fetal growth and development [1–3]. Homeostatic imbalances produced by these changes lead to an inflammatory overload that disrupts the maintenance of pregnancy, resulting in labor-related changes [4,5]. Nonetheless, the signature of these signals and their precise mechanism in initiating

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parturition are still unclear. Interventional strategies to reduce the risk of preterm labor have been designed primarily based on our understanding of signaling effects by maternal compartments. However, higher rates of spontaneous preterm births (PTB) warrant further investigation of these signals and their mechanisms in normal term pregnancies; additional studies can provide insight into pathologic activation of signals associated with preterm parturition. Fetal endocrine signals as well as signals generated as a result of fetal organ maturation have been well reported in the literature as signalers of parturition [4]. A new type of fetal-derived signaling that occurs at term through senescent fetal (placental) membranes (amniochorion) and placental cells has been reported [6,7]. Senescence of the membranes generates "sterile inflammation" that can potentially increase the inflammatory load required to trigger parturition [7–9]. Since the concepts of fetal membrane senescence-associated aging, aging-induced sterile inflammation, and their roles in parturition are novel and being developed, this review summarizes the development of fetal membrane senescence and how senescent fetal cells may function as signalers of human parturition.

1. Fetal membrane structure and function

Human fetal membranes, the innermost tissue layers that form the intrauterine cavity, are fetal in origin and serve as a barricade between the feto-placental and maternal compartments. Fetal membranes comprise the amnion (innermost layer of the intra-amniotic cavity) and the chorion (fetal tissue connected to maternal decidua) and are connected by the collagen-rich extracellular matrix (ECM) [10]. ECM, which is made up of fibrous proteins embedded in a polysaccharide gel and various types of collagen, provides the architectural and structural framework of fetal membranes [11]. The amnion is constantly bathed in amniotic fluid, signifying its importance as a primary responder to changes in the amniotic cavity. The chorion is in close proximity to maternal decidua and maintains the immune tolerance at the maternal-fetal interface [12–14].

The amnion and chorion, fetal tissues in origin, function as a single unit and can potentially be conceptualized as an organism that maintains its own homoeostatic balance. This organism plays a major role in maintaining pregnancy by providing multilevel protection to the growing fetus. Fetal membranes accommodate constant challenges (immune, structural, mechanical, and endocrine) during pregnancy, continue to grow, and mechanistically and biochemically maintain elasticity to the stretches experienced during fetal growth. Despite the fact that membranes overlying the placenta and cervix face distinctly different environments and insults during pregnancy, they still maintain the homeostatic balance necessary to sustain fetal growth without interruption. This companionship between the fetus and membranes continues until term, when the fetus reaches maturity and the membranes reach longevity. As fetal membrane cells multiply and grow during pregnancy, they undergo a telomere-dependent cellular senescence, resulting in an aging phenotype indicative of its life expectancy. Histologic and biochemical changes associated with senescence and senescence-associated secretory phenotype (SASP), a unique inflammatory signature, have been documented in term fetal membranes at delivery [6,15]. This review describes the function of fetal membranes and proposes a novel mechanistic model, wherein aging but viable and inflamed fetal membrane cells at term may act to signal fetal maturity and their own dysfunctional status and, in turn, prompt parturition.

The composition of the membrane and its ability to produce a broad spectrum of biomarkers at different gestational stages illustrate the fetal membrane's contribution to the growing fetus, as well as its potential role in adverse pregnancy outcomes [16]. Fetal membrane biomarker responses are difficult to determine until after placental delivery, and therefore their contribution to normal or abnormal parturition is always subject to the 'cause or effect' quandary. Growth of fetal membrane cells during pregnancy plateaus at term, retaining the capacity for DNA replication [17]. The presence of stem cells further depicts the contribution of fetal membranes during in utero fetal life. Delivery of fetal membranes along with the fetus ends their organismal life.

2. Fetal membranes in adverse pregnancy outcomes

A hostile intrauterine environment can force a homoeostatic imbalance on various fetal membranes' physiologies, leading to their dysfunction and contributing to adverse outcomes. Fetal membranes are often discussed in association with preterm premature rupture of the membranes (pPROM) with imminent preterm birth (PTB) or in normal term pregnancies experiencing spontaneous rupture or requiring artificial rupture of the membranes prior to delivery. Histologic chorioamnionitis (neutrophil infiltration of the membranes) is a pathologic state of the membranes often associated with adverse pregnancy outcomes and is used to assess the status of the preterm neonate [18]. Fetal membrane disturbances [19] at various levels, including epigenetic [20,21], immunologic [22–29], endocrine [30–33], and mechanical [34–37], have been associated with spontaneous preterm labor and delivery and pPROM in response to various risk exposures during pregnancy. Disturbances to multitudes of interacting factors that maintain the fetal membrane's functional integrity during pregnancy can lead to heightened inflammation and oxidative stress, both of which are detrimental to maintain normal pregnancy. Biochemical and mechanical responses from fetal membranes are also decisive in delineating the pathways of spontaneous onset of labor with intact membranes or a subset of women with pPROM [34,38–40]. This author has characterized ***"pPROM as a disease of the fetal membranes"*** based on multiple pieces of evidence that are unique to fetal membranes from pPROM when compared to gestational age-matched membranes from PTB with intact membranes [15,41]. Thus, membranes play a major role in determining adverse pregnancy outcomes, at least in a major subset of PTB.

3. Physiologic aging of fetal membranes in normal term deliveries, and pathophysiologic activation of premature aging in early pPROM

A systematic review recently published by Polettini et al. [42] on aging of intrauterine tissues and adverse pregnancy outcomes identified 2 major knowledge gaps: 1) although aging of uterine tissues is mentioned in several studies as a factor associated with adverse pregnancy outcomes, no studies have reported any biomarkers or clinical indicators of premature aging as pathologies of PTB and pPROM; and 2) no studies have provided evidence of mechanistic pathways contributing to physiologic aging of uterine tissues or how risk factors can contribute to premature activation of aging and aging-associated pathologies. The review also highlighted the need for more studies to understand the mechanisms of uterine tissue aging. Our report is an extension of our prior systematic review and provides a summary of ongoing work. Several biomarker studies provide evidence for the proinflammatory/oxidative stress status of fetal membranes [43–45]. These studies are normally conducted using normal term fetal membranes, either from not in labor (collected from cesarean sections) or from term labor (vaginal deliveries) as a control group to assess various changes associated with PTB and pPROM. However, several lines of evidence now imply similarities between fetal membranes from