Placenta and Reproductive Medicine

PERSPECTIVE

Fetal membrane at the feto-maternal interface: An underappreciated and understudied intrauterine tissue

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INTRODUCTION

While most intrauterine tissues are thoroughly studied for their role in pregnancy maintenance and their contribution to labor initiation, the fetal membranes (*i.e.*, amniochorionic membranes) are primarily overlooked.[1,2] The fetal membrane lines the intrauterine cavity (Figure 1A) and provides critical mechanical, immune, and endocrine support to protect the fetus during gestation[1,3-12] and has been shown to provide vital labor initiating signaling at term and preterm.[2,5,13-20] The function of the fetal membrane is derived from its unique makeup of multiple collagen layers,[21-23] along with fetal-derived cells that line with maternal decidua, forming the feto-maternal interface. A summary of the structure and function of the fetal membranes and the challenges researchers face studying this tissue are described below.

FETAL MEMBRANE ANATOMY

The fetal membrane and the maternal decidua form one of the feto-maternal interfaces during gestation (Figure 1B). The fetal membrane comprises two epithelial membranes, the amnion, and chorion, that are connected by collagen-rich multiple layers of extracellular matrix.[2,24] The amnion membrane, which maintains most of the fetal membranes' tensile strength,[10,11,25-29] consists of an amnion epithelial layer connected to the fibrous-spongy layer of the extracellular matrix via a Type IV collagen-rich basement membrane.[22,23] These collagen layers contain various stromal cell types, including amnion mesenchymal cells, fibroblasts, immune cells, and chorion mesenchymal cells.[30-34] Stromal cells within the fetal membrane secrete Type I and III collagens to create a variety of extracellular matrix layers, forming a fibrous skeleton responsible for maintaining membrane integrity.[22,35] The chorion membrane plays a crucial role in immune tolerance.[36-38] It contains the reticular layer and connects to the chorion trophoblast cells through another Type IV collagen-rich basement membrane.[39,40] These fetal membrane layers are fused with the maternal decidua parietalis containing leukocytes to form the feto-maternal interface during pregnancy.[24,41-43]

REGIONS OF THE FETAL MEMBRANE

The fetal membranes are divided into different regions based on their proximity to maternal or fetal organs. They are generally divided into a region lining the placental bed (*i.e.*, the region lining the apical side of the placenta), or reflective membranes that line the intrauterine cavity.[44,45] Though they have similar architecture, the membrane lining of the placental bed contains a condensed extracellular matrix and chorion layer. It only includes a small portion of the overall surface area of the fetal membrane.[46] Furthermore, the reflective membranes can be classified as the peri-placental zone (*i.e.*, two–three inches from the placenta), mid-zone (*i.e.*, middle and largest region), and cervical zone (*i.e.*, overlaying the cervix) depending on their proximity to the placenta or the cervix.[44,45] Within the cervical zone is a region of the fetal membrane termed the zone of altered morphology (ZAM) which contains

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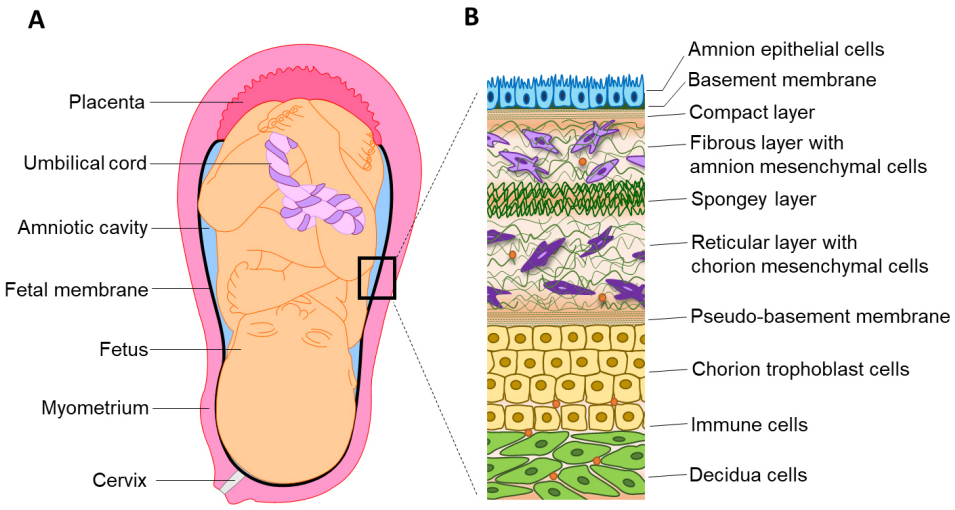

Figure 1. Intrauterine and fetal membrane anatomy. (A) Within the intrauterine cavity, there are a variety of maternal (*i.e.*, myometrium and cervix) and fetal (*i.e.*, placenta, umbilical cord, and an amniotic cavity containing amniotic fluid, and the fetal membranes) derived organs that surround the fetus and contribute to pregnancy maintenance. The fetal membranes (black) line the cavity and are derived from multiple fetal cellular and collagen layers to form the feto-maternal interface. (B) The amnion epithelial cells (blue) are connected to the basement membrane (dark green) and compact layer (green dashes) of the extracellular matrix (ECM) forming an amniotic fluid-tight barrier. Within the first layer of the ECM (*i.e.*, the fibrous layer), amnion mesenchymal cells (light purple) migrate and interact with the collagen environment. Separating the fibrous and reticular layers of the ECM is the spongy layer that separates the amnion (blue) and chorion (yellow) portions of the fetal membranes. The reticular layer of the ECM contains chorion mesenchymal cells (dark purple) that is connected to the pseudo-basement membrane of the chorion. The multi-layer of chorion trophoblast cells (yellow) forms the second epithelial layer of the fetal membranes and is critical for immune homeostasis. The fetal chorion layer is directly connected to the maternal decidua layer (green) forming the feto-maternal interface of the membranes. Resident immune cells predominantly live in the decidua layer but can migrate into the chorion and amnion layers if stimulated.

loose collagen structures that may contribute to the rupture of the membranes at term.[21,47,48] A better understanding of the region from which membranes are sampled and its histology is essential when studying fetal membrane structure and its cellularity and function.

FETAL MEMBRANE FUNCTION DURING GESTATION AND PARTURITION

The fetal membrane is not an inert tissue that lines the maternal decidua or the inner uterine cavity, instead, it is a complex multicellular organ that plays a distinct and vital role in maintaining pregnancy and the onset of labor signaling.[49] Throughout gestation, the amnion component of the fetal membrane plays a critical role in sustaining membrane integrity by undergoing cellular remodeling.[4,50-53] This process upholds the amnion tensile strength providing a watertight barrier and structure to the intrauterine cavity. The chorion component of the fetal membrane plays a distinct role from the amnion, as it is responsible for creating immune homeostasis in various ways. Chorion trophoblast cells modulate the immune environment by producing anti-inflammatory hormones[9,36,54,55] and cytokines,[12] and by buffering maternal (decidual) immune cell invasion[47,56] and immune intolerance by abundant expression of human leukocyte antigen G (HLA-G).[3] These endocrine and paracrine signalers help to maintain immune cell homeostasis at the choriodecidual interface.[12,57]

At term, close to 40 weeks gestation, both fetal and maternal tissue contribute to an increased inflammatory load and immune cell activation that promotes myometrial contractions and cervical ripening leading to delivery of the baby.[1,2,20,58] The fetal membrane has been recently shown to play a substantial role in initiating this labor cascade.[2,17,20] Traditionally, it is known that fetal membranes produce cyclooxygenase-2 and prostaglandins that contribute to membrane weakening and rupture at term.[59-64] Recent studies suggest that fetal membranes from both humans and mice undergo a reactive oxygen species induced (due to intrauterine oxidative stress at term), telomere-dependent, activation of p38 mitogen-activated protein kinase (p38MAPK).[24,31,65-68] p38MAPK is a stress signaler that can contribute to various cell fates.[66,69,70] Increased p38MAPK activation at term causes fetal membrane senescence, or a mechanism of tissue aging, and secretion of senescence-associated secretory phenotypes (SASP) comprised of pro-inflammatory cytokines, chemokines, growth factors, cell-free fetal DNA, and matrix metalloproteinases.[24,29,34,54,71,72] SASP represents sterile inflammation in fetal tissues that propagates to the maternal side and transitions the quiescent myometrium and cervix into a contractile (active/labor) phenotype. This induction of stress-activated p38MAPK also causes fetal membrane epithelial cells (*i.e.*, amnion and chorion) to undergo cellular transitions (*i.e.*, epithelial-to-mesenchymal transition or EMT).[5,50,52,53,73] EMT increases the number of mesenchymal cells, promotes collagen degradation, and changes the inflammatory status at the feto-maternal interface.[50,73] These mesenchymal cells promote collagen degradation by increasing matrix metalloproteinases nine that can contribute to the development of microfractures (*i.e.*, biologic fissures) within the extracellular matrix of

the membranes.[17,40,53] It is postulated that these pro-labor inflammatory signals described above could propagate in two different ways: diffusion through microfractures or exosomes (30–160 nm size extracellular vesicles) released from fetal membrane cells. Microfractures are higher in number and morphometrically (width and length) at term.[17,40,53] Experimentally, we have recapitulated that in vitro conditions mimicking labor also increases appearance of microfractures with larger and deeper features.[17,40,53] This suggests their relevance in the propagation of parturition signals. Exosomes are capable of carrying contents from the cell of their origin. It is reported that exosome cargo from oxidatively stressed fetal membrane cells contains active forms of p38MAPK and SASPs capable of promoting labor signaling.[14,16,74-76]

CHALLENGES STUDYING FETAL MEMBRANES

Researchers studying fetal membranes must overcome many obstacles to rationalize the importance of studying their tissue of interest to journal editors and funding agencies. The first hurdle they must overcome is the definition of the fetal membrane and the second is to convince reviewers that the fetal membranes are separate from the placenta. Heterogeneity in the nomenclature of the membranes (*i.e.*, amniotic sac, amniochorionic membrane, fetal membrane, placental membrane, feto-maternal interface) and which cell layers should be included in this terminology creates ambiguity.

The Fetal Membrane Society (FMS) is formed to educate reproductive biologists and perinatal biologists and scientists on the relevance and significance of the membranes. FMS is also involved in creating awareness of the importance of fetal membrane research among the public. As a major contributor to pregnancy maintenance and a determining factor in the timing of birth at term and preterm. As a contributor to fetal signals of parturition, regulating its pathological functions is critical to reducing the incidences of preterm birth. This topic was one of great interest at this year's FMS meeting held during the 2022 Society of Reproductive Investigation International meeting. The FMS concluded that a white paper should be published to define "fetal membranes" and standardize the nomenclature in the literature. The hope is that a set nomenclature will improve reproducibility and provide clarity when documenting the important role, the fetal membranes play during gestation and parturition. Additionally, the fetal membranes are classically misidentified as an extension of the placenta. As it is well known now, the fetal membranes are not a mere extension of the placenta but play very important mechanical, immune, endocrine, and communication roles between the mother and fetus.[1] These functions regulate membrane growth and maturation which contributes to pregnancy homeostasis. Misclassification of the membranes and not identifying them as a distinct tissue from the placenta has slowed fetal membrane-specific research and funding. This and the lack of an advocacy group or international organization that focuses on this topic have restricted scientific awareness of this fascinating tissue. The FMS has been trying to address some of these issues and developing strategies to generate awareness and fill knowledge gaps in fetal membrane biology and function.

Unlike other intrauterine tissues such as the myometrium or placenta, that have established in vitro methodology such as commercially available cell lines, ex vivo systems (*i.e.*, myograph and placenta perfusion),[77-80] organoids,[81,82] organ-on-chip devices,[83-88] and validated animal models, the fetal membranes lack a majority of these resources. Currently, there are no commercially available and validated iPS or cell lines for the amnion, chorion, or the decidua of the fetal membrane feto-maternal interface. Due to this, researchers are forced to use either contaminated (*i.e.*, amnion wish cells – HeLa) or improper cell types (*i.e.*, placenta choriocarcinoma – BeWo to mimic the chorion trophoblasts; decidualized endometrium to mimic the decidua parietalis) to conduct cellular studies. This limits research undertaken in the field and reduces new discoveries. Furthermore, unlike the other organs described above, very few organ-on-chip models of the fetal membranes exist,[46,52,89-91] and fetal membrane organoids are yet to be developed. These are both critical platforms needed in this field to truly understand cell-cell cell-collagen interactions responsible for pregnancy maintenance and pathology onset.

SUMMARY

The fetal membranes form a unique barrier that surrounds the neonate and promotes its survival during gestation. This membrane is comprised of two components, the amnion and chorion layers, that function as distinctly unique epithelial compartments promoting homeostasis during development. At term initiated by physiological signals, or preterm induced by pathology, these layers promote signaling cascades that contribute to labor onset. Advanced in vivo and in vitro methodology to study the fetal membrane, along with the formation of advocacy groups, are needed to truly understand and promote this unique tissue.

CONCLUSIONS

If studied adequately, the fetal membranes, as one of the feto-maternal interfaces, could answer many questions regarding labor induction, inflammation, infection, and pathologies that lead to preterm birth. A better understanding of all aspects of fetal membrane origin, as well as cellular characteristics, needs to be taken into account to tease out the mechanism behind the labor cascade and how to target said pathways therapeutically.

A global understanding of the role of fetal membranes in parturition highlights the critical function of the membranes during pregnancy and in the prevention of adverse pregnancy outcomes.

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Conflict of Interest

Ramkumar Menon is an Editorial Board Member of the journal. The article was subject to the journal's standard procedures, with peer review handled independently of this member and her research group.

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