Revista Médica del
Hospital General de México

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EDITORIAL

Maternal-fetal communication

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The placenta is a temporary organ (40 weeks) and functions as the bridge of maternal-fetal communication. Placentation is a fundamental process that begins with the implantation of the blastocyst in the endometrium, around day 6-7 after fertilization. The trophectoderm of the blastocyst gives rise to cytotrophoblasts, which branch out into structures known as "placental villi," before 12 weeks of pregnancy, the trophoblast differs from the blastocyst in two layers: The syncytiotrophoblast and the cytotrophoblast, as implantation progresses, the syncytiotrophoblast creates vacuoles that form gaps filled with maternal blood, Necessary for communication between the mother and the developing fetus, the syncytiotrophoblast invades the spiral arteries, forming structures known as a column of cytotrophoblast cells that give rise to the trophoblastic plug, whose function is to temporarily block blood flow to create a hypoxic environment, thus promoting vascular remodeling and anchoring between the placenta and the decidua.

Extravillous trophoblasts, which differ from the column of cytotrophoblast cells, migrate to the decidua and superior myometrium (extravillous interstitial trophoblast) or temporarily block the maternal spiral arteries (endovascular extravillous trophoblast), preventing maternal blood flow to the intravillous space, until approximately 12 weeks of gestation, at which time these plugs are detached. Extra-villous trophoblasts and utero-resident immune cells, such as uterine Natural Killer (NK) cells and regulatory T cells (Treg), are actively involved in the remodeling of maternal spiral arteries. The radial arteries of the uterus divide into two or more branches, which end in the myometrium or decidua (basal arteries) or open in the intravellous space, after week 12, the trophoblastic invasion progresses, allowing the plugs to detach, which increases maternal blood flow to the placenta and favors fetal oxygenation. The spiral artery becomes a large-caliber, low-resistance blood vessel, facilitating adequate placental perfusion for fetal growth[1].

Extracellular vesicles are a heterogeneous group of vesicles formed by lipid bilayers, secreted from the cytoplasmic membrane both "*in vivo*" and "*in vitro*" by various cell types, extracellular vesicles according to their size are classified into three groups: (1) Vesicles of 30-100 nm called exosomes, which are derived from the endolysosomal pathway, formed in multivesicular compartments; (2) Vesicles of 0.1-1 μm called microvesicles, which have a greater variability in size and come directly from the cytoplasmic membrane; (3) Apoptotic bodies (1-4 μm), generated during late apoptosis. Extracellular vesicles include proteins, lipids, DNA, RNAs and miRNAs, reflecting the characteristics of the cells from which they originate, likewise molecules typical of the different types of extracellular vesicles have been described that are used as markers, using Alix, TSG101 and flotiline for exosomes, scramblase, cholesterol, flotiline and phosphatidylserine for microvesicles, while for apoptotic bodies annexin and phosphatidylserine are included. The mechanisms by which extracellular vesicles interact with the target cell and how their contents are transferred are not yet fully understood. However, three mechanisms have been proposed: (a) Binding to surface receptors with activation of signal transduction pathways; (b) Internalization, and (c) Membrane fusion[2].

The biological activity of extracellular vesicles is determined by their contents, which are transferred to the target

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Date of reception: 30-10-2025
Date of acceptance: 01-12-2025
DOI: 10.24875/HGMX.M25000062

Available online: 12-02-2026
Rev Med Hosp Gen Mex. 2026;89(1):1-2
www.hospitalgeneral.mx

cells when the vesicles are internalized by the cells or activate receptors on their surface. However, the role of vesicles in the implantation of the fertilized egg and placental development, as well as in pathological processes, is little studied. The syncytiotrophoblast is the main source of placental-derived vesicles and may constitute the main signaling mechanism between the product and the mother, modifying the physiological activity that allows its presence and satisfies the demands of the developing fetus.

Syncytiotrophoblast-derived vesicles do not express paternal human leukocyte antigen; however, they express minor paternal histocompatibility antigens, such as DDX3Y and HA-1 bound to syncytial nuclear aggregates, which constitute a specific antigen mechanism inducing regulatory T cells that confers maternal immunological tolerance, in the early lacunar stage (1-3 days post-implantation) intervillous blood flow begins. Where the oxygen tension is 1%, while in primary cultures of cytotrophoblast cells it has been shown that under this oxygen tension there is release of vesicles, which transport proteins that lead to proliferation and invasion of cells. Low oxygen tension triggers cytotrophoblast proliferation through mechanisms involving hypoxia-inducible transcription factor 1 alpha (HIF1α), which regulates the expression of genes such as erythropoietin, placental vascular angiogenic factor, and nitric oxide synthase, in the human placenta HIF1α expression is increased during the first trimester and decreases around week 9. When circulation and consequently oxygenation to the fetus increases, the persistence of elevated levels of HIF1α indicates placental stress and announces the development of pathology, such as preeclampsia, in fact, the placenta of women with preeclampsia overexpresses HIF1α and HIF2α, the molecular mechanisms that mediate the remodeling of the spiral arteries are still under debate. During normal placentation, cytotrophoblast differentiates from an epithelial phenotype to an endothelial one, a process called "pseudo-vasculogenesis" or "vascular mimicry," this transition does not take place in pre-eclampsia.

Cytotrophoblast that does not invade maternal spiral arterioles does not express endothelial adhesion markers, such as VE cadherins and $\alpha1\beta1$ and $\alpha V\beta3$ integrins that are expressed by normal invasive cytotrophoblast. Extracellular vesicles of the syncytiotrophoblast in maternal plasma are increased in pre-eclampsia and the increase in their level tends to reflect the severity of the disease[3-5].

Conclusion

– The placenta is a temporary organ that functions as a maternal-fetal communication bridge. Placentation is a process that begins with the implantation of the blastocyst after fertilization.
– The trophoblast differs from the blastocyst in two layers: the syncytiotrophoblast and the cytotrophoblast, the syncytiotrophoblast creates vacuoles that form gaps filled with maternal blood, for communication between mother and fetus, and invades the spiral arteries, forming a column of cytotrophoblast cells originating a trophoblastic plug, blocking blood flow creating hypoxia and promoting vascular remodeling, involving HIF1α, which regulates the expression of genes such as erythropoietin, placental vascular angiogenic factor, and nitric oxide synthase, as well as immune cells (NK and regulatory T).
– Extracellular vesicles of syncytiotrophoblast in maternal plasma are increased in pathologies such as preeclampsia, and the increase in their level tends to reflect the severity of the disease.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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