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Review

The endocrine and paracrine role of placental cytokines, growth factors and peptides

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Abstract

The human placenta plays a major role in pregnancy as it is the main organ of communication between the mother and the fetus. One of its actions is the secretion of a variety of substances. Cytokines, growth factors and peptides are secreted by the placenta during pregnancy and may act via endocrine, autocrine and paracrine pathways. Cytokines promote trophoblast implantation as well as fetal growth and regulate both nutrient transportation and the immune response of the placenta. Placental growth factors contribute to the growth and differentiation of the trophoblast: they promote cell proliferation, angiogenesis and lymphangiogenesis and induce prostaglandin and oxytocin synthesis. Placental peptides enhance CRH production and relaxation of the placental vascular tone. Additionally, clinically speaking they aid in screening tests for early prenatal diagnosis of fetal chromosomal abnormalities. The purpose of this review study was to investigate the actions of these substances in correlation with their potential involvement in pathophysiological pathways during pregnancy.

Key words: placenta; cytokines; growth factors; peptides

The human placenta is a unique organ with a major role during pregnancy and whose life ends with labor. It is considered to be the only organ of the human body with known duration of life. It is wholly associated with pregnancy, ensuring the supply of the developing fetus with oxygen, valuable nutritients and blood, and representing life's vital link between the mother and the fetus. Based on the abovementioned functions, the term 'fetal - maternal - placental unit' has been established in order to underline the harmonious synergy of the two organisms (mother and fetus) in the mechanism of hormones and macromolecules production, which otherwise would be imposible.

The placenta originates from the two main cellular structures of the blastocyst, the internal and the external. Among placental functions, that of its role as a temporary endocrine gland formed during pregnancy, which involves the production of over 30 hormones (peptides, polypeptides, proteins, glyco-

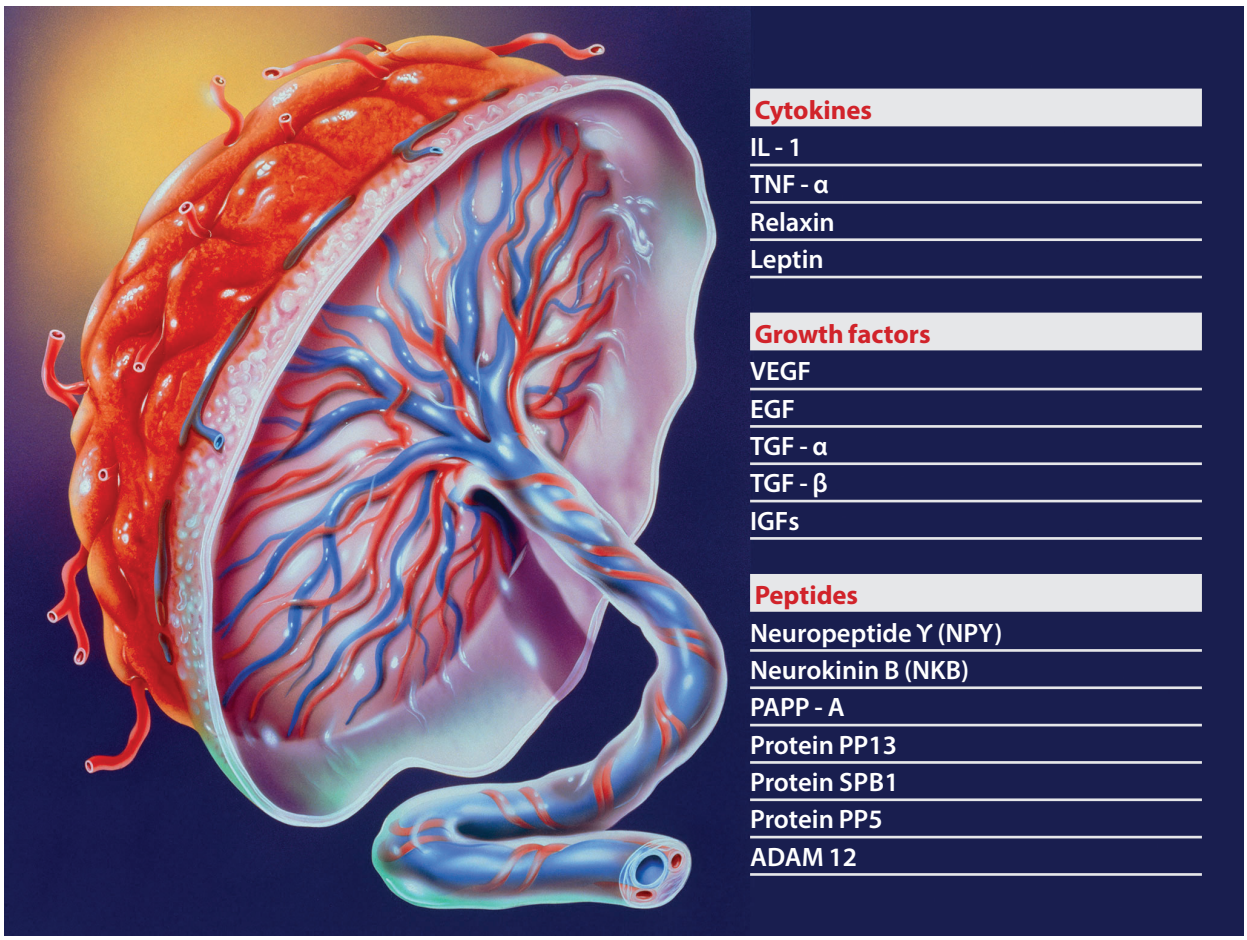

Figure. Cytokines, growth factors and peptides secreted by the human placenta

proteins, cytokines, steroid hormones, growth factors and placental alterations of all hypothalamic and pituitary hormones), is crucial. These factors either regulate the secretion of regional placental hormones or penetrate into the fetal or maternal circulation. The placental hormonic activity already starts from the stage of blastocyst formation, its function being the creation of a favorable environment for fetal development during pregnancy, and the programming of the series of events leading to labor[1,2].

The aim of this review is to analyze the functions of all placenta - produced cytokines, growth factors and peptides, as recorded in recently published data in the field of pregnancy pathology.

Cytokines: their multiple and crucial functions

Cytokines are produced from the cells of trophoblast, macrophages and endothelial placental cells. They play an important role in the mechanisms of villus formation and differentiation. The main placenta-produced cytokines are: tumor necrosis factor - α (TNF - α), interleukins 1, 2 and 6 (IL - 1, IL - 2, IL - 6), interferon (IFN), relaxin and leptin.

IL - 1

Interleukin 1 is produced by decidual cells. Its intraamniotic levels are increased in the event of membrane rupture or preterm delivery associated with inflammation. IL - 1 stimulates T - lymphocytes for the production of IL - 2. Both IL - 1 and IL - 2 are important regulators of the placental immunological function and actively participate in the immunobiological interactions between the mother and the fetus. Another action of IL - 1 is to increase the

levels of prostaglandin F2α (PGF2α) which leads to the synthesis of corticotropin releasing hormone (CRH) receptors. It has been proposed that IL - 1 develops synergic action with epidermal growth factor (EGF)[1,3].

TNF - α

The cytokine TNF - α stimulates, like IL - 1, the production of prostaglandins. It acts in the amniotic fluid or the decidua and influences cellular development and prostaglandins production. Several bacterial toxins, such as lipopolysaccharide S (LPS) that acts in the decidua, lead to the secretion of TNF - α. It has also been determined that TNF - α expresses cytostatic but no cytolytic action in human amniotic cells, while it additionally stimulates the production of PGF2α in the decidua and prostaglandin E2 (PGE2) in the amniotic fluid. Finally, TNF - α cooperates within the uterine environment with factor NF - κB, both of an important role in the functional withdrawal of progesterone, an event essential for the initiation of labor. In addition, NF - κB stimulates the production of prostaglandins.

Relaxin

It is produced by the chorionic membranes, the decidua and the placenta. Relaxin receptors are localized in cells of the syncytiotrophoblasts. Relaxin participates in the action of collagenase within the chorionic membranes: it stimulates prostaglandins production, while it is also thought to play a role in the initiation of the procedure of labor.

Leptin

It is produced by the placenta and participates in the procedures of implantation and in the regulation of fetal development and placental function. The regulation of transplancental substance delivery is possibly achieved via the control of both nitric monoxide (NO) production and lipids catabolism. Of note, the production of leptin is increased in cases of pre - eclampsia and gestational diabetes mellitus, leading to the hypothesis of a potential correlation between these pathological conditions and leptin. Finally, recently published data support the notion that a strong correlation exists between estrogen levels and leptin production during the early stages of pregnancy. Any disturbance of these mechanisms is potentially associated with pre - eclampsia and intrauterine growth restriction[4].

Growth factors and their critical roles

The placenta is responsible for the production of several growth factors which include: tumor growth factor α (TGF - α), insulin - like growth factor (IGF), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), platelet - derived growth factor β (PDGF - β), platelet - derived endothelial cell growth factor (PD - ECGF) and fibroblasts growth factor (FGF).

VEGF

Vascular endothelial growth factor is a glycoprotein, with at least five isomorphes, which regulates angiogenesis and lymphangiogenesis. It controls proliferation and endothelial cells and monocytes migration as well as vascular permeability.

Endocrine gland - derived vascular endothelial growth factor (EG-VEGF) represents an isomorphe produced by the placenta and other tissues and is characterized by endocrine function. It is considered that the expression of EG - VEGF and its receptors is regulated by chorionic gonadotropin whose levels peak between the 8th and 11th week of gestation. It is a restraining factor, limiting the pathological invasion of the trophoblast.

Both VEGF - A and VGEF - B as well as placental growth factor (PIGF) represent three other isomorphes of VEGF which actively participate in the procedure of angiogenesis during pregnancy. Finally, PIGF plays a role in inflammatory reactions, attracting and stimulating monocytes. It is expressed at high levels throughout pregnancy, regulating the development and proliferation of the trophoblast[5-8].

EGF

EGF comprises a family of growth factors consisting of transmembrane proteins that act via specific

receptors of ErbB, their function being the regulation of cellular proliferation, migration and differentiation. Several members of the EGF family are expressed during the period of implantation and enhance the synthesis of chorionic gonadotropin and progesterone.

The heparin - binding epidermal growth factor (HB - EGF) is exclusively expressed during the period of implantation and can be found at the blastocysts' attachment positions[9,10].

TGF - α

Tumor growth factor - α has the same chemical structure as EGF and acts via common receptors (ErbB). It has angiogenic properties and is expressed in endometrial epithelial cells, promoting the synthesis of prostaglandins[1].

TGF - β

The tumor growth factor - β family includes activin, inhibin and follistin.

Activin is composed of two units of inhibin and presents the following types: activin - A (βA - βA), activin - B (βB - βB) and activin - AB (βA - βB). Activin - A, which is found in maternal serum, induces the placental production of prostaglandins and oxytocin via a paracrine pathway, thus presenting an action opposite to that of inhibin. Activin - B is present in the amniotic fluid and umbilical cord serum.

Inhibin down - regulates the secretion of follicular stimulating hormone (FSH) from the pituitary gland and increases the placental production of gonadotropin releasing hormone (GnRH) and progesterone. Finally, inhibin, via its reaction with GnRH, leads to the increased secretion of chorionic gonadotropin (hCG).

Follistin is expressed in syncytiotrophoblast, chorion, amnion and decidua, presenting an action that restrains activin[1,11].

IGFs

Both IGF - I and IGF - II are produced by the placenta. Their density is increased during pregnancy. They are characterized as mediators in the procedure of decidua development, they cooperate with EGF, they stimulate the production of placental lactogen and progesterone, while they also limit the production of estrogens. Finally, the IGFs participate in the transmembrane circulation of glucose and aminoacids, regulating fetal and placental development[12].

Peptides and their important contribution

The placenta produces peptides that contribute to the harmonious function of the fetal - maternal - placental unit, the normal development of the fetus and the physiological stimulation of the mechanisms that characterize the initiation of labor.

Neuropeptide Y (NPY)

It is secreted by the placenta in the maternal and fetal circulation, but also in the amniotic fluid. The levels of NPY do not present significant changes during pregnancy; however, they progressively increase at labor, their levels peaking during the advanced stages. Immediately after delivery NPY levels decrease, this underlining the placental origin of the peptide. Receptors for NPY are present in all placental villi cells. It has been hypothesized that NPY actions consist in stimulating the production of CRH via an autocrine mechanism, and participating in myometrial activity, as the receptors that are bound to NPY and are localized in the myometrium increase the intracellular concentration of calcium[1,13].

Neurokinin B (NKB)

It is secreted by the placenta. Its levels are increased during pregnancy, while after labor they undergo an immediate decrease, clearly indicating the placental origin of this peptide. NKB acts via a paracrine mechanism, toning the placental vessels and leading to their relaxation, and regulating myometrial activity and stimulating uterine contractions[13,14].

PAPP - A

It is a glycoprotein, produced by the syncytiotrophoblast, which is detected approximately 33 days after

fertilization. The pregnancy - associated plasma protein A (PAPP - A) is the main protease of IGFBP - 4, which, via proteolysis, increases the regional placental bioavailability of IGF. IGF acts in the trophoblast, regulating steroidogenesis and the transmembrane circulation of glucose and aminoacids.

Determination of the levels of PAPP - A in combination with a first trimester ultrasound calculation of nuchal translucency are prognostic factors for a prompt prenatal diagnosis of fetal chromosomal abnormalities. It has been found that pregnant women with small placental extension and increased alpha - fetoprotein (αFP) present low levels of PAPP - A, this being associated with increased risk for intrauterine growth restriction (IUGR) and a preterm or stillbirth delivery. Finally, it is possible that PAPP - A participates in the mechanisms of blood coagulation[15-17].

Protein PP13

It is a dimer produced by the placenta. It can be used as early marker - in combination with PAPP - A for the diagnosis of pre - eclampsia and HELLP syndrome[16].

Protein SPB1

It is produced by the syncytiotrophoblast and undergoes progressively increasing concentration throughout pregnancy. It inhibits the multiplication of lymphocytes, thus shielding the fetus from the potential of immunological rejection[2].

Protein PP5

It is also produced by the syncytiotrophoblast and also progressively increases concentration throughout gestation. It is considered to act as a natural inhibitor of blood coagulation[2].

ADAM 12

Disintegrin and metalloproteinase 12 (ADAM12) are a family of placenta - produced glycoproteins. During the first trimester of pregnancy, they are considered to be a reliable marker, in combination with other factors, for a prompt prenatal diagnosis of chromosomal abnormalities[18].

Conclusions

The human placenta has a dual role of either intermediate barrier or active messenger between the mother and the fetus. Among the substances that it produces, the roles of cytokines, growth factors and peptides are central as they act via endocrine, paracrine and autocrine pathways for the normal progression of pregnancy and labor. The wide spectrum of severe complications which are noted in the event of a disturbance of their levels or normal functions includes pre - eclampsia, preterm birth and IUGR, this clearly demonstrating the significance of these factors for the physiology of pregnancy.

Conflict of interest

All authors declare no conflict of interest.

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