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Minireview

The physiological role of interleukin-6 in the placenta and its pathological potential in pregnancy

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Summary. Interleukin-6 (IL-6) is a pleiotropic cytokine with pro-inflammatory and anti-inflammatory functions. Placentation and pregnancy progression depend on adequate interaction between the processes of proliferation, apoptosis, and invasion of trophoblast cells into the endometrium. Various cytokines and growth factors play important roles in regulating these processes, where IL-6 represents one of the major regulatory molecules influencing the trophoblast phenotype. In physiological circumstances, IL-6 is involved in angiogenesis and remodeling of endometrial blood flow, stimulates the production of placental hormones, and is one of the main regulators of inflammation response and immune homeostasis in the placenta. Elevated levels of IL-6 are indicated in women with infertility, preeclampsia, and placental neoplastic processes. Hypoxic conditions in the placenta play a pivotal role in modulating differentiation, invasion, and redox homeostasis of trophoblast and also seems to have a significant contribution to IL-6 effects. At the same time, IL-6 affects the oxidative state of trophoblasts, although the mechanisms of these outcomes are yet to be fully understood. Our experiments suggest the importance of hypoxic conditions in determining the effects of IL-6 in trophoblasts and the differential reactivity of JEG-3 cells in response to this cytokine. Additionally, increased levels of IL-6 in different systemic pathological states induce various disturbances of trophoblast cell homeostasis and could be one of the risk factors in the development of pregnancy disorders. Recently, increased IL-6 levels have been detected in COVID-19 cases as one of the major actors of the cytokine storm, raising the concerns of infection regarding the effects on the placenta and the offspring.

Keywords: cell migration, cytokine storm, hypoxia, interleukin-6, trophoblast homeostasis.

The development of the placenta, the unique organ between mother and fetus, is essential for a successful pregnancy and fetal health. Derived from extraembryonic tissues, the placenta develops during the first weeks of gestation, dynamically changing its structure and function (Hamilton and Boyd 1960). Optimal proliferation and invasion of trophoblasts into the endometrium are key events in the placentation process. The success of embryonic implantation depends on the adequate orchestration between proliferation and invasion of the trophoblast in the endometrium to establish the anchorage and blood supply of the fetus through the formation of the villous structures (Dubinsky et al. 2010), while the disturbed homeostasis of trophoblast cells leads to various pregnancy disorders resulting in shallow implantation and ischemia, affecting the redox metabolism and immune balance (Silva and Serakides 2016). The earliest stages of placenta development are conducted in a hypoxic environment. Due to the crucial importance of oxidative metabolism in various aspects of cell physiology, hypoxia in human trophoblast cells can induce a cellular phenotype different from the one present under normoxic conditions and conduct physiological trophoblast differentiation (Jain et al. 2014). Therefore, main-

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taining redox balance is essential for the optimal functioning of trophoblasts during both hypoxic and normoxic states. Studies have indicated the role of IL-6 in controlling the maternal immune system, which is a crucial participant in the establishment, progression, and maintenance of pregnancy (Munoz-Suano et al. 2011). Inflammation plays a pivotal role in regulating physiological and pathophysiological responses, while numerous immune and inflammatory cells reside in the placenta and play a crucial role in the inflammatory responses via cytokine secretion, which may affect placental development and function (Arck and Hecher 2013).

The developmental processes necessary for successful early stages of pregnancy, including extravillous trophoblast (EVT) invasion, involve a complex network of multiple cytokines and growth factors, with both stimulatory and inhibitory functions. Interleukin-6 (IL-6) is a pleiotropic cytokine with both pro-inflammatory and anti-inflammatory functions; many signalling pathways are affected by IL-6, resulting in numerous biological responses. One factor determining the biological effects of IL-6 in the placenta is its signaling. IL-6 acts through a classical pathway or trans-signaling mechanisms. Classical signaling, through the membrane-bound IL-6 receptor (mIL-6R), produces an anti-inflammatory effect; conversely, trans-signaling through the soluble IL-6 receptor (sIL-6R) generates a pro-inflammatory effect. In both cases, the binding between IL-6 and mIL-6R or sIL-6R is followed by homodimerization of β-subunit glycoprotein 130 (gp130), the signal transduction subunit. The soluble gp130 (sgp130) functions as a natural antagonist of IL6/sIL6R trans-signaling, neutralizing IL-6 bioactivity by blocking the IL-6/sIL-6R complex binding to gp130, thereby attenuating inflammation (Nasonov and Samsonov 2020).

Although it has been documented that IL-6 is expressed in human uteroplacental tissues, a relatively modest corpus of data exists on its role in the physiology of trophoblasts in pregnancy. IL-6 has an unequivocally important physiological significance in the normal functioning of the trophoblast and/or other types of uteroplacental cells, which, together with the growth factors of the placenta, may be one of the key molecules in the development of the fetus. The presence of interleukin-6 in the amniotic fluid increases during the progression of pregnancy. It is considered a physiological component, while some other cytokines, such as interleukin-1 and TNF-alpha, appear significantly only in pathological conditions (Opsjłn et al. 1993). IL-6 is abundantly expressed in the endometrium at the implantation phase, suggesting its function related to angiogenesis and vascular remodeling necessary for morphogenesis in early pregnancy. Throughout gestation, IL-6 is present since the early stages, expressed in the first-trimester abortion samples, with increased expression at the end of pregnancy (Champion et al. 2012; Pietro et al. 2020). The elevated levels of IL-6 in term placentas are related to the physiological processes of delivery since IL-6 stimulates uterine contractility through the stimulation of oxytocin expression (Fang et al. 2000).

Various studies imply that IL-6 may contribute to trophoblast growth and development by stimulating trophoblast growth factors. IL-6 enhanced the production of human chorionic gonadotropin (hCG), the main hormone responsible for maintaining the pregnancy by Jar, HCCM-5, and BeWo choriocarcinoma cell lines. IL-6 also regulates the secretion of placental lactogen and cytokines by EVT that attenuate hCG production, thereby further increasing hCG secretion to maintain a healthy pregnancy. However, these findings are yet to be confirmed in primary extravillous trophoblasts (Champion et al. 2012). Since the major downstream targets of IL-6 signalling are STAT3, MAPK, and c-Jun, early transcriptional activators involved in cellular growth and proliferation, IL-6 may up-regulate genes involved in trophoblast growth and differentiation, while some studies have also shown that STAT3 is a contributor to the trophoblast invasive capacities (Fitzgerald et al. 2005).

Being foremost the signal molecule of the immune system, the main paradigm of interleukin-6 role in the placenta implies its role in the regulation of immunological homeostasis of placental tissue. Throughout pregnancy, a specific immune-adaptive process occurs to properly implant the semi-allograft fetus without deteriorating rejection (Robertson 2010). Increased production of various anti-inflammatory cytokines like IL-4 and IL-10 provides an immune-tolerant microenvironment for implantation. Although pro-inflammatory processes promote essential physiological events such as placental invasion and parturition, increased expression of pro-inflammatory cytokines like IL-1, IL-6 and TNF-α is associated with increased rates of pregnancy complications like miscarriage and preterm delivery (PrabhuDas et al. 2015; Azizieh et al. 2018). IL-6 coordinates the balance of T-cell phenotypes, generating lymphocyte cell populations necessary for establishing immunological tolerance during pregnancy (Jasper et al. 2007). Accordingly, fine-tuning the balance between pro-inflammatory and anti-inflammatory cytokine actions is vital for a healthy pregnancy progression, where IL-6 is one of the main regulators. The main factor directing the type of IL-6 action is its concentration at a certain moment. The results obtained in our study suggest antiproliferative and cytotoxic effects on JEG-3 trophoblast cells in a time- and dose-depended manner, whereas physiological concentrations have not affected cell viability (Matić et al. 2022).

Although an important regulator of placental physiology, IL-6 could be involved in numerous pregnancy-related pathological conditions. IL-6 has been related to infertility in

humans, with significantly increased serum concentrations of IL-6 reported in infertile compared with fertile women (Demir et al. 2009). IL-6 concentrations correlate with the extent of leukocyte infiltration in preterm placentas, confirming its major regulatory role in placental immune response (Chiesa et al. 2015). Significant increases in serum IL-6 concentrations and endometrial IL-6 mRNA levels have been recorded in women with preeclamptic pregnancy (Afshari et al. 2005; Jasper et al. 2007; Zhao et al. 2008). Increased levels of circulating IL-6 and soluble IL-6 receptor have been detected in women suffering recurrent miscarriages compared to control samples (Arruvito et al., 2009). Excessive production of IL-6 is also associated with adverse pregnancy outcomes such as the premature rupture of the membranes and chorioamnionitis (Qiu et al. 2018). In placental cancers, IL-6 stimulates the adhesion of trophoblastic cells to extravillous elements of the extracellular matrix (ECM), decreasing the expression of integrin and stimulating the production of metalloproteinase inhibitors (TIMP), thus allowing the tumor cell invasion process, enabling and maintaining the high proliferative and invasive phenotype of trophoblasts in choriocarcinomas (Bischof 2001). Recently, increased IL-6 levels have been detected in severe COVID-19 cases. It is considered one of the principal actors of the famous "cytokine storm" systematically affects many tissues, including the placenta (Jamilloux et al. 2020).

It has been widely proposed that one of the critical roles of IL-6 in uteroplacental physiology is the regulation of trophoblast invasion. Although IL-6 is associated with studies involving the progression and invasiveness of cells of certain cancer types, there is limited information on its role in trophoblast invasion. Besides certain studies that failed to confirm the effects of IL-6 on trophoblast cell invasiveness (Champion et al. 2012), the results obtained by Jovanović and Vićovac (2009) indicate the stimulatory effect of IL-6 on the invasive capacity of first-trimester villous CTB cells and HTR-8/SVneo trophoblast cell line due to up-regulation of certain types of trophoblast integrins, enabling the contact with the extracellular matrix components. Our study also shows the promigratory potential of IL-6 on the JEG-3 trophoblast cell line in normoxic conditions, implying the important contribution of this cytokine to trophoblast invasiveness by altering nitric oxide bioavailability (Matić et al. 2022). Additionally, Dubrinsky and coworkers have indicated the inhibition of migration capacity of JEG-3 choriocarcinoma cells after silencing the IL-6 expression, suggesting that endogenous IL-6 affects cell invasion in this cell type (Dubrinsky et al. 2010). Literature data imply that IL-6 may play a role in extravillous trophoblast invasiveness by raising the activity of trophoblast matrix metalloproteinases MMP-2 and MMP-9 (Meisser et al. 1999).

Since hypoxia represents a physiological condition of early pregnancy, it plays a pivotal role in modulating differentiation, invasion, and redox homeostasis of trophoblast. The average tension of oxygen in the early placenta is 5-6% around the 13th week of gestation and moderate hypoxia limits numerous processes of trophoblast physiology compared to normoxic conditions, enabling the optimal metabolic rate and invasive activity necessary for pregnancy progression at this phase (Yoshida et al. 2009). On the other hand, in severe hypoxia conditions, cells shift their metabolism from mitochondrial respiration to anaerobic glycolysis, resulting in the production of reactive oxygen species (ROS) and a decrease in ATP availability (Semenza 2007). It is important to consider that many *in vitro* experiments were conducted under normoxic conditions of 21% oxygen, where the hypoxic state regulates cellular phenotypes differently than normoxia (Ikejiri et al. 2011). The onset of oxidative stress, a phenomenon generated by a normal systemic inflammatory response, which results in higher amounts of circulating ROS, is widely present during pregnancy. ROS are generated at the decidual, trophoblast, and mesenchymal components of the maternal-foetal interface, and the essential physiological roles of ROS generation are cell signalling, regulation of cell survival, proliferation, adaptive homeostasis, and apoptosis, as well as host defence mechanisms such as phagocytosis and microbicidal activities (Bevilacqua et al. 2012; Davies 2016). Hypoxic states have been shown to decrease the invasive capacity of trophoblast cells compared with normoxia, while severe hypoxia increased the invasion capacity of HTR-8/SVneo trophoblast cells by up-regulating urokinase-type plasminogen activator suggesting its vital regulating effects (Graham et al. 1998; Yoshida et al. 2009). Moderate hypoxic conditions present in the physiological states of the placenta significantly decrease the IL-6 secretion via a major mediator of hypoxia, HIF1α, implicating that lower pressures of oxygen can protect the placental environment from the excessive cytokine-mediated immune response and limit the inflammatory conditions of trophoblast cells (Shirasuna et al. 2015). Hypoxia also directs trophoblasts' redox homeostasis, which is also involved in the rate of IL-6 secretion. Under 5% O_2 conditions, ROS production was significantly lower compared to normal culture conditions of 21% oxygen. On the contrary, ROS inducers stimulated IL-6 secretion dose-dependently, whereas some antioxidant treatments drastically decreased IL-6 secretion under hypoxia and normoxia. These data indicated that trophoblasts' redox status is a key factor in the induction of IL-6 secretion (Shirasuna et al. 2015). Our experiments suggest the crucial importance of hypoxic conditions in determining the effects of interleukin-6 in trophoblasts. The parameters of redox homeostasis, nitric oxide production, and cell viability showed different

response patterns to IL-6 treatment compared to normoxic values. JEG-3 trophoblasts are much more sensitive to elevated IL-6 levels, measured by MTT cell viability assay in normoxia than in hypoxic conditions, which implies that a hypoxic state may protect trophoblast cells from the excessive production of aggressive oxygen radicals. Also, in a hypoxic state, IL-6 exerts prooxidative effects, while physiological concentrations induce antioxidative properties under normal oxygen tension. These data suggest that early pregnancy could represent the most vulnerable phase of deteriorating effects of increased IL-6 concentrations present in different pathological conditions (Matić et al. 2022). These results suggest that not only is IL-6 controlled by redox status, and it is involved in regulating oxidative metabolism in the placenta.

Recently, the appearance of COVID-19 infection intensifies the focus of inflammation consequences in pregnancy, and various complications were significantly higher in infected pregnant women compared to healthy subjects. Numerous inflammation markers, including IL-6, are significantly higher in pregnant women with COVID-19, although no significant difference in the levels of IL-6 was observed between the pregnancy trimesters (Tanacan et al. 2021). As an essential component of the cytokine storm, interleukin-6 plays a decisive role in determining the clinical course of the infection, and in addition to, interleukin-8 (IL-8) and TNF-α are considered as independent markers of the severity of the clinical course of COVID-19 (Tanaka et al. 2016; Velazquez-Salinas et al. 2019). The registered increase of IL-6 levels in COVID-19 is variable in different studies. Still, it is multiple times higher compared to the physiological levels and several times higher compared the average levels registered in preeclampsia (Chen et al. 2020; Santa Cruz et al. 2021). The results of our current study indicate the intense disturbance of cell redox homeostasis, strong cytotoxic effect on JEG-3 trophoblasts cells, and outstanding increased migration capacity. COVID-19 The levels of the interleukin-6 present in severe COVID-19 cases undoubtedly indicate a high-risk factor for pregnancy disorders, which is expected and in concordance with the literature, although the precise mechanisms of the recorded effects have yet to be investigated. Preeclampsia-like syndrome has been reported in women with severe COVID-19 and could be a consequence of the cytokine storm (Mendoza et al. 2020). Placental viral infections may activate maternal and foetal immune systems. High concentrations of inflammatory cytokines lead to redox disturbances, diminishing nitric oxide bioavailability and releasing the potent vasoconstrictor endothelin-1 (ET-1), worsening initial symptoms (Racicot et al. 2014; Moghaddas Sani et al. 2019). This raises the concerns of severe complications in preeclamptic pregnancies already loaded with elevated IL-6 levels with SARS-CoV-2 infection, making the time-efficient therapeutic limiting of inflammation rate vital for successful delivery.

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