Chapter 3

Gene Expression Profiling of Placenta from Normal to Pathological Pregnancies

Soraya Mezouar and Jean-Louis Mege

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.80551

Abstract

The placenta is a unique temporary organ essential for growth of the fetus, which determines the success of pregnancy. Its originality relies on a combination of nutritive, endocrine and immunological functions that control maternal immune tolerance to fetus. In the present chapter, we review gene expression programs of placenta from placenta tissue to isolated cells using high throughput transcriptomic approach. Beside trophoblasts, we focused on immune cells including macrophages, dendritic cells and mast cells. From the gene expression signatures, we identify key pathways for the different trimesters of the normal pregnancy and pathological alterations including preeclampsia and gestational diabetes mellitus.

Keywords: placenta, pregnancy, preeclampsia, gestational diabetes mellitus, immune cells, gene regulation

1. Introduction

The placenta is a unique temporary organ and the central regulator of maternal-fetal environment [1]. It is a complex organ that needs to adapt constantly to maternal and fetal requirements during the progression of the pregnancy. The placenta is composed of several varieties of cells including trophoblasts, mesenchymal and endothelial cells and immune cells [2]. It is essential for materno-fetal exchange enabling the transfer of regulatory molecules to the fetus and fetal molecules to the maternal circulation [3]. The placenta is also involved in hormonal regulation [4, 5] and immunological defense of mother [6] and fetus [7]. The placenta synthetizes and secretes large number of molecules necessary for its development, metabolism

of mother and fetus growth [8]. These factors including placental hormones and growth factors lead to the regulation of gene expression critical for placenta plasticity and functions including angiogenesis, immune response, decidua invasion, endocrine regulation and fetal nutrition and growth [9].

The investigation of a complex organ such as placenta requires an approach without *a priori* that can be provided by high throughput methods such as microarray, ribonucleic acid-sequencing (RNA-Seq) and/or quantitative reverse transcription-polymerase chain reaction (qRT-PCR) technologies, which markedly changed our analysis of tissue physiology and pathophysiology. This field is expanding since the investigation of keywords including placenta, transcriptomic and gene expression on PubMed database revealed a progression of the number of publications per years from 1 in 2001 to 55 in 2017 (**Figure 1**). The transcriptomic studies have enabled identification of specific genes involved in the progression of the gestation and the outcome of complications. These gene signatures may be used as new biomarkers for maternal and fetal complications of pregnancy.

In this chapter, we will review the literature focusing on the gene expression profiling of placenta tissue and isolated cells during the progression of the gestation and pathological pregnancies.

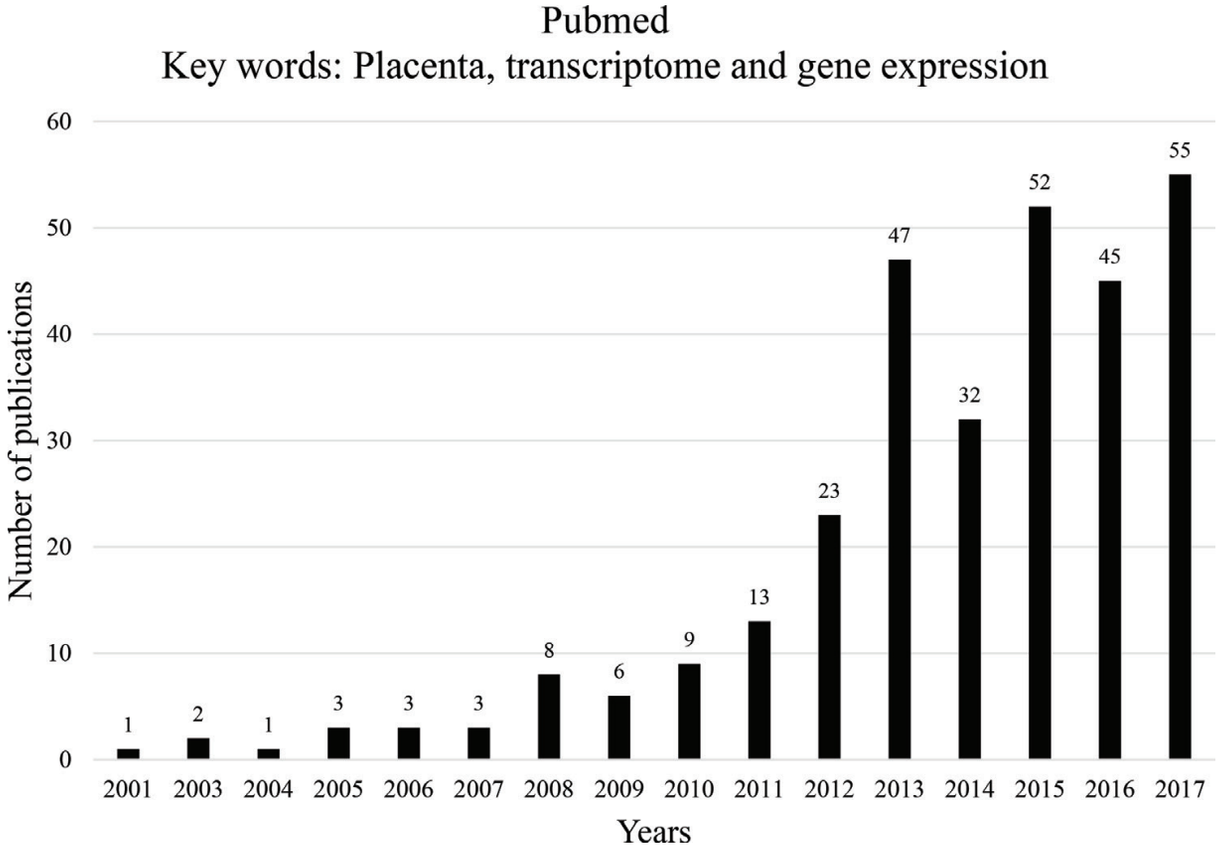

Figure 1. Number of publications associated with "placenta, transcriptome and gene expression".

2. Placenta transcriptome in normal pregnancy

2.1. Gene expression and anatomic organization of placenta

Human placenta is a feto-maternal organ composed of the fetal part (also known as chorion) and the maternal part (also known as decidua). The chorion is composed of trophoblasts, cytotrophoblasts and syncytiotrophoblasts, whereas the decidua contains enlarged endometrial stromal cells (epithelium) and leukocytes populations, thus suggesting that these two parts of placenta tissue are functionally different.

Few studies have investigated the transcriptomic profile of the different areas of the placenta tissue (**Table 1**). As shown in **Table 1**, two studies have investigated gene expression in amnion, chorion, decidua and villus parenchyma of at term placenta using microarray or RNA-sequencing. A core of gene expression patterns was observed in the different areas of the placenta; they are related to histology categories [10]. Microarray analysis revealed major differences among amnion, chorion and villus parenchyma. It showed that the gene encoding

Species	Placenta and gestational age	Technique	Results	References
Human	At term placentas (amnion, chorion, umbilical cord and section of villus parenchyma)	Microarray	• Differentially modulated genes are associated with placental trophoblast secretion, signal transduction, metabolism, immune regulation, cell adhesion and structure • Inter-individual differences are observed in gene expression between the mother and the fetal section of the placenta • The expression of a set of genes is related to the sex of the fetus	[10]
Human	At term placenta (amnion, chorion and decidua part)	RNA-sequencing	• 938, 865 and 944 genes are modulated in amnion, chorion and decidua tissues, respectively • 216 genes were commonly modulated among the three placenta tissues • Common genes were associated with placenta abnormalities including prolactin receptor, insulin-like growth factor 2 and a set of genes enriched with interleukin-1 pathway • Amnion: genes associated with cell adhesion and epidermal cell differentiation • Chorion: genes associated with angiogenesis, cell proliferation and Wnt receptor signaling • Decidua: genes associated with female pregnancy and wound healing	[11]

Table 1. Transcriptomic analysis of tissue component of the placenta.

Mucin 1 (MUC1) gene was strongly expressed in the amnion, whereas a cluster of up-modulated genes associated with signal transduction, cell differentiation and immunity categories was found in chorion. Among these genes, tissue remodeling genes, genes induced by interferon and major histocompatibility complex (MHC) genes were strongly up-modulated, suggesting a role for chorion in the plasticity and the immune tolerance of the placenta during pregnancy. Hypoxia-inducible factor (HIF)-1α, a transcription factor known to induce transcription of genes involved in glycolysis, erythropoiesis and angiogenesis [12], was expressed at low level in villus sections of placenta. In contrast, HIF-1α was up-modulated in amnion chorion and decidua [11]. It is likely that these discrepancies are related to exposition to different gradients of oxygen, which modulate HIF-1α expression.

Although these studies based on at term placentas are limited, they suggest that distinct tissue transcriptional programs exist in placenta. In addition, some inter-individual variations of the placenta structures have been observed during the second and the third trimester of the pregnancy [13]. Further investigations must include placentas at the different age of the gestation to precisely map gene expression in different areas of placenta during pregnancy.

2.2. Evolution of placenta gene expression during pregnancy

During pregnancy, the placenta gene expression is continuously modulated to adapt immune response to tolerance necessity and to modify metabolism according to pregnancy requirement. Hence, the early stages of the pregnancy are characterized by trophoblast invasion, which leads to placentation. During the mid-gestation, the placenta adapts its gene expression to maintain the fetal growth and the organ development. Finally, during the third trimester, placenta must provide enough nutriments for the growing of the fetus. Some evidence suggests that preterm birth is related to changes in gene expression during pregnancy [14].

The evolution of placenta gene expression during the different gestational stages is summarized in **Table 2**. The five studies investigated gene expression at different gestational ages in humans and mice. They identify common gene pathways involved in cell differentiation, immune response and angiogenesis (**Table 2**). In first trimester, the few genes that are found modulated are strongly involved in cell proliferation vascular development and angiogenesis. At mid-gestation several genes associated with cycle control, including cyclin family, are found up-modulated [17, 19]. There is an enrichment in gene ontology (GO) terms related to growth of the placenta, the set-up and the maturation of villous with blood vessels during first and second trimester as compared with third trimester [15, 20]. In addition, GO terms for cell differentiation and communication are also observed and are related to the organization of placenta structure and plasticity [21]. All studies observed a major change in the gene expression pattern at the end of the pregnancy. The third trimester is associated with the over-expression of genes involved in apoptosis, oxidative stress response and inflammatory process [17, 18], whereas the second and third trimesters share the up-modulation of genes associated with immune response. It has been recently shown that the gene expression program of placentas at the third trimester exhibits activation of the immune response and an increase of oxygen-rich maternal blood in placenta, which reflect labor and delivery route [22, 23].

Species	Placenta and gestational age	Technique	Results	References
Human	First trimester (45–59 days) Second trimester (109–115 days)	Microarray	• 500 genes common to the 1st and 2nd trimesters • 836 genes specific to the 1st trimester • 264 genes specific to the 2nd trimester • 1st or 2nd trimesters versus term: cell division, mitosis, DNA metabolism, pregnancy, response to chemical, immune response and regulation of cell cycle • Genes included in gestational regulation of the Wnt pathway	[15]
Human	First trimester (6–7 weeks) Third trimester (279 days)	qRT-PCR	• Cysteine dioxygenase (CDO) mRNA is up-modulated in at term placentas compared to 1st trimester placentas	[16]
Human	First (9–12 weeks) Third trimester	Microarray	• 7519 genes differentially expressed between 1st and 3rd trimesters • Biological processes up-regulated in 1st trimester: cell proliferation, cell differentiation and angiogenesis • Biological processes up-modulated in 3rd trimester: cell surface receptor-mediated signal transduction, G-protein mediated signaling, ion transport, neuronal activities and chemosensory perception • 3D separation observed for 17 imprinted genes of 1st and 3rd trimester placentas, suggesting epigenetic modifications	[17]
Human	Second (14–16 and 18–19, 21, 23–24 weeks) and third trimesters (37–40 weeks)	Microarray	• Little changes on gene expression observed during 14 to 24 weeks • 418 genes differentially modulated at the third trimester (37–40 weeks) compared to mid gestation (14–24 weeks) • These genes are involved in differentiation, motility, transcription, immunity, angiogenesis, extracellular matrix dissolution and lipid metabolism	[18]
Mice	Embryonic day 10.5, 12.5, 15.5 and 17.5	Microarray	• 599 genes differentially modulated • Up-regulation of genes associated with angiogenesis fatty acid metabolism and transport for E 10.5 compared to E 12.5 • Up-regulation of genes associated with hormonal control and ribosomal proteins for E 12.5 compared to E 10.5 • Up-regulation of genes associated with cell cycle and RNA metabolism for E 12.5 compared to E 15.5 • Up-regulation of genes associated with cellular transport for E 15.5 compared to E 12.5 • Up-regulation of genes associated with cell cycle control and RNA metabolism for E 17.5 compared to E 15.5	[19]

Table 2. Transcriptomic analysis of uncomplicated normal pregnancies at different ages of pregnancy.

2.3. Term labor and gene expression

The molecular mechanisms regulating the initiation of labor are still poorly understood. The key role of genes involved in prostaglandin synthesis and inflammatory responses in cervix, myometrium and chorio-membranes has been reported in laboring women as compared with non-laboring women [24]. **Table 3** summarized the studies evaluating placenta gene expression from preterm versus term labor with vaginal or cesarean deliveries. The commonly modulated genes are involved in immune response and apoptosis. Oros et al. showed a balance of immune modulators with an increased expression of tumor necrosis factor (TNF) and interleukin (IL)-6 and a decrease in interferon (IFN)-γ expression [26]. These results are likely related with cytokine production of at term placentas [30] and M1 polarization shift of macrophages [31]. Another study showed that gene expression associated with oxidative stress is elevated [25]. It has been previously observed that oxidative stress in placenta explants

Species	Placenta and gestational age	Technique	Results	References
Human	5–10 min before delivery (preterm labor or not)	Microarray	• Functional ontology analysis response to stress, cell surface receptor-linked signal transduction, regulation of transcription, immune system process, blood vessel development, death, cell-adhesion, cell-cell signaling, coagulation and oxygen and reactive oxygen species metabolism process	[25]
Human	Preterm (26–36 weeks) Term (>37 weeks) all with suspicion of preterm labor	qRT-PCR	• Increased expression of TNF, IL-6 and PGF • Decreased expression of IFN-γ and VEGFR1 • Term delivery after suspicion of preterm labor shows decreased VEGFA • Preterm delivery after suspicion of preterm labor shows decreased VEGFB	[26]
Human	Term (38–42 weeks) with vaginal delivery or cesarean	Microarray	• Up-regulated genes in placenta by labor are involved in angiogenic regulators, immune response, inflammatory response and apoptosis	[27]
Human	Term (34 weeks) with vaginal (laboring) delivery or cesarean (non-laboring)	Microarray	• 92 genes down- and 94 up-regulated genes in laboring placentas compared to no-laboring placentas • FOS, FOSb and GNGT1 are down-modulated in laboring placentas compared to non-laboring placentas	[28]
Human	Term and term nonlaboring cesarean deliveries	Microarray	• Labor is associated with up-modulated expression of MMP-1 gene in chorionic villus tissue • Genes involved in the extracellular matrix homeostasis are up-modulated such as fibronectin 1 and collagen XVII	[29]

Table 3. Transcriptomic analysis of uncomplicated pregnancies from preterm or term labor.

and production of inflammatory cytokines are related [25]. The TNF levels are elevated during labor, suggesting that TNF may be a biomarker of preterm labor [32, 33]. Based on gene expression in placenta, epidemiological analysis suggested a genetic predisposition to spontaneous preterm labor and preterm birth [34]. Nevertheless, additional investigation of transcriptomic analyses must be necessary to better understand the role of gene expression in term labor.

2.4. Placenta microRNAs in pregnancy

MicroRNAs are small non-coding 20–24 nucleotides that target and regulate numerous genes [35]. They are expressed by tissues and cells but can also circulate in blood. They can be used as biomarkers [36]. It has been reported that more than 500 microRNAs are produced by the human placenta and a part of them are placenta specific [37]. Their expression varies with the gestational stages; 191 microRNAs are differentially modulated in placentas from first versus third trimester [38]. During the first trimester, microRNAs are associated with angiogenesis, anti-apoptosis and oncogenesis categories, whereas microRNAs from third trimester are related to cell differentiation and tumor suppression categories. Luo et al. found that miR-378a-5p is up-modulated in first and second trimesters but not in third trimester in placenta tissue [39]. The variations of microRNAs expression during different gestational ages suggest that they may regulate specific functions during pregnancy. However, the studies investigating microRNAs in total tissue in normal pregnancy are scarce and further investigations are necessary to better characterize microRNA signature and their temporal expression pattern in the placenta at different ages of gestation.

3. Placenta transcriptome in pathological pregnancy

The alteration of gene expression pattern in placenta tissue may reflect metabolic disorders associated with pregnancy such as gestational diabetes mellitus or pathologies that compromise pregnancy success such as preeclampsia [40]. We will summarize main findings reported in preeclampsia and gestational diabetes mellitus that represent the two pathologies mainly investigated by transcriptomic analyses.

3.1. Preeclampsia

Preeclampsia is a severe placenta disease that occurs in 3–5% of pregnant women and is a source of complications for mother and fetus [41–43]. The preeclampsia is initiated at the time of trophoblast invasion and remodeling of the spiral arteries during the first and early second trimester of pregnancy [41, 44, 45]. Initial studies have shown that elevated levels of various placental proteins in maternal blood such as FLT1 (fms-related tyrosin kinase 1), sENG (soluble engolin) and PGF (placental growth factor) in early pregnancy may be predictive of preeclampsia development [46] but the presence of false negative rates limits their clinical use [47]. The use of high throughput methods such as microarray is likely useful to identify new biomarkers and potential therapeutic targets. **Table 4** summarizes transcriptional studies of

Species	Placenta and gestational age	Technique	Results	References
Human	At term preeclampsia or healthy	Microarray	• HLA-DRB1, but not HLA-A RQ and CSTM2 RQ genes, is up-regulated in placenta tissue from women with pre-eclampsia • HLA-A and HLA-DRB1 expression are related to the reduction of birthweight but not placenta weight	[48]
Human	At term preeclampsia or healthy	Microarray	• Increased glycogen phosphorylase gene in preeclampsia group compared to controls	[49]
Human	At term (>37 weeks) preeclampsia or healthy	Microarray	• Among 368 regulated genes in preeclampsia group compared to controls, 35% present an expression higher than 2.0 • Up-regulated genes are associated with cell-cycle or apoptosis functions • Up-regulation of immune-system activation-related genes • No differences of MHC complex in the two groups	[50]
Human	Term (32–40 weeks)	Microarray	• A few numbers of genes (21) are differentially expressed • Genes involved in transcriptional regulation, vaso-regulative pathways. Hypothetical protein and gene sequences with unknown functions	[51]
Human	Placenta with preeclampsia or from healthy donors (253–273 days)	Microarray	• Genes involved in cell proliferation, immune regulation, lipid biosynthesis, protein biosynthesis and transport, signal transduction are up-modulated • Genes previously involved in preeclampsia such as Flt-1, leptin, HTRA1 and SIGLEC6 are modulated	[52]
Human	Placenta with preeclampsia or from healthy donors (<32 weeks)	Microarray	• Modulation of genes involved in cell adhesion-related protein, obesity-related protein, transcription factor, immunological factor, protease inhibitor, neuro-mediator, endocrine-related protein, oncogenic factor and growth factor • Obese gene is the most up-modulated gene	[53]
Human	Placenta with preeclampsia, increased vascular resistance (notch) or from healthy donors	Microarray	• 148 genes are altered • Up-modulated genes associated with chemotaxis, NF-kappa B pathway are found in preeclampsia group compared to notch • Down-modulated genes associated with antigen processing and presentation (human leukocyte antigen B) are found in preeclampsia group compared to notch • Results suggest that progression of pre-eclampsia from notching is dependent of the development of inflammation	[54]

Species	Placenta and gestational age	Technique	Results	References
Human	Placenta with preeclampsia or from healthy donors (39 weeks)	RNA-Seq	• 53 differently expressed genes are modulated • Perturbation of pathways involved in vascular function and immunological balance in preeclampsia group • Some identified-genes have been previously reported (e.g. leptin) or not previously associated with preeclampsia	[55]
Human	Placenta with preeclampsia or from healthy donors (35–39 weeks)	Microarray	• 58 genes are modulated and associated with immune system, inflammation, oxidative stress, signaling, growth and development pathways • Some genes identified have been previously reported (leptin) or not previously associated with preeclampsia (CYP11A and CDKN1C)	[56]
Human	Placenta with preeclampsia (31–39 weeks), preterm labor (24–33 weeks) or from healthy donors (37–39 weeks)	Microarray	• 20 miRNAs and 120 mRNAs are differentially modulated in preeclampsia and preterm group compared to healthy donors • Functional analysis shows a common activity of these genes associated to cellular activities	[57]
Human	Placenta with preeclampsia (mean 34.2 weeks), with small for gestational age (mean 34.5 weeks) or both (mean 33.9 weeks)	Microarray	• No significant difference between preeclampsia and small-for gestational-age groups • Increased anti-angiogenic gene expressions are observed	[58]
Human	Placenta with preeclampsia or from healthy donors (mean 37.5 and 39.8 weeks, respectively)	Microarray	• Differentially expressed genes associated with inflammation, immune regulation and cell motivity are found	[59]
Human	Placenta with preeclampsia or from healthy donors (mean 34.6 and 38.6 weeks, respectively)	Microarray	• 896 differentially expressed genes are found • Up-regulation of HTRA4, LHB and β-hCG • Decreased of NOX4 gene	[60]
Human	Placenta with preeclampsia or from healthy donors (34–37 weeks)	Microarray	• 2109 differentially expressed genes are found • Down-modulation of CD4 • Up-regulation of LEP, FLT1, PAPPA2, INHA, SIAE and ENG	[61]

Species	Placenta and gestational age	Technique	Results	References
Human	At term placenta with preeclampsia or from healthy donors	Microarray	• 213 and 82 genes are found up- and down-modulated, respectively • Differentially expressed genes are observed between early and late onset preeclampsia • Up-regulation of FLT1, PAPPA2, CGB5, LEP and INHBA • Down-modulation of PDGFD, BHLHB3 and BMP5	[62]
Human	Variable	Meta-gene analysis on microarray experiment in published studies	• Differential expression of autophagy-associated genes is found in microarray datasets from separate published studies	[63]
Human	Term	Meta-gene analysis on microarray experiment in published studies	• The most highly affected pathways in preeclampsia placenta are Wnt, ErbB, PPAR, Hedgehog signaling pathways, mRNA surveillance pathway and ubiquitin mediated proteolysis. • Identification of specific genes for preeclampsia: LEP, HTRA4, SPAG4, LHB, TREM1, FSTL3, CGB, INHA, PROCR and LTF genes	[64]

Table 4. Transcriptomic analysis of pregnancy with preeclampsia.

placenta from women with preeclampsia. Most studies use at term placentas and report a number of modulated genes varying from 20 to more than 2000.

Among the up-modulated genes, those associated with the regulation of the immune response are most frequently reported in transcriptomic analysis of preeclampsia placentas (**Table 4**). These findings may be related to the up-regulated gene expression profile of circulating cells from pregnant women with preeclampsia [65–67] and to the observation of increased levels of inflammatory cytokines including IL-6, IL-8 and TNF [68, 69]. Indeed, using microarray approach on blood samples, we observed a specific transcriptional signature of genes up-modulated in severe preeclampsia including genes associated with ribosome and complement functions [67]. In addition, we had identified VSIG4 (V-set and immunoglobulin domain containing 4) as a biomarker of severe preeclampsia.

Among genes associated with immune response, three studies reported the modulation of human leukocyte antigen (HLA) genes [48, 54, 59]. HLA-A, HLA-B and HLA-DRB1 are up-modulated in placentas from preeclampsia as compared to control group. The molecules, HLA-A and HLA-DRB1 have been associated with preeclampsia outcome [48, 70, 71] and have been related to reduced birth weight but not to placenta weight. Clinical observations show that both birth weight [72] and placenta weight [73] are decreased in pregnant women with preeclampsia.

Gene associated with hypoxia and oxidative stress are frequently found in placenta from women with preeclampsia. The placental hypoxia associated to preeclampsia is due to shallow implantation, impaired trophoblast invasion or vascularization of placenta arteries [40, 74]. The hypoxia leads to low birth weight and newborn diseases [75]. The gene encoding leptin has emerged as a potential biomarker of preeclamptic placentas from transcriptomic analyses [52, 56, 76]. This gene is known to be up-modulated in placenta from patients who experience chronic hypoxic ischemia [77]. Other genes involved in hypoxia are down-modulated in preeclampsia: this is the case for the gene encoding a glutathione reductase, an antioxidant protein, whereas the gene encoding the thioredoxin peroxidase is up-regulated [78]. In contrast, Zhang et al. found no modulation of genes encoding enzymes involved in oxidative stress as compared to controls [79].

The transcription analysis enables the identification of several up-modulated genes including genes involved in apoptosis processes [50], activin-A, inhibin A [80], soluble sENG [61], soluble sFlt-1 [61] and placental growth factor PGF [81]. In these studies, three angiogenic genes are found differently expressed: they include sFLT1 (also known as vascular endothelial growth factor, VEGF), PGF and sENG that are up-modulated in preeclampsia and associated with severe preeclampsia [61, 62, 82, 83]. In a case-control clinical study, the level of sFLT1 increases and that of PGF decreases during normal pregnancy; this response is more pronounced in women who develop preeclampsia [46]. Thus, it has been proposed that sFLT1 could be used as biomarker for predicting the development of preeclampsia [84]. However, these genes are not found in all transcriptomic studies of preeclamptic placentas [85]. This discrepancy may be explained by the clinical heterogeneity of preeclampsia, placenta sampling sites, gestational weeks, sex of the child, labor and the method of delivery. These parameters restrict the use of these genes as biomarkers for diagnosis or prognosis of preeclampsia.

3.2. Gestational diabetes mellitus

Placenta is an endocrine organ that provides glucose to fetus. A pathological state of insulin resistance leading to glucose intolerance is called gestational diabetes mellitus (GDM) [86]. The mother may develop hemorrhage, hypertension, infection, difficulty in labor and increased risk of mortality [87]. The placentas from GDM patients exhibit histological alterations and elevation of its size and weight at third trimester. This may be due to insufficient production of placental hormones [88]. To better understand the role of placenta in the development of GDM, transcriptomic analyses of placenta from pregnant women with a GDM or mice model of diabetes have been conducted in some studies (**Table 5**). Few genes are differentially modulated and they are predominantly related to extracellular matrix remodeling, immune response and regulation of apoptosis categories.

Among the immune response category, genes such as TNF are up-modulated. TNF is known to be involved in insulin resistance, obesity and diabetes [95, 96]. Although TNF levels are increased in GDM and type 1 diabetes [97], no relation was found between placenta TNF mRNA amounts and the levels of this cytokine in maternal blood with GDM [98–100].

Species	Placenta and gestational age	Transcriptomic technique	Results	References
Mouse (Streptozotocin induced-diabetes)	E 10.5	Microarray	• 158 genes are modulated in diabetic placentas compared to controls (47% down-and 54% up-modulated genes) • Functional category: extracellular matrix, hormones, cell surface receptor, signal transduction, transcription factors, metabolism, channel, cytoskeleton and RNA binding • Diabetes-induced molecular changes and abnormal differentiation of cells, modification of growth and junctional zone and labyrinth	[89]
Human	Placenta with GDM (38 weeks)	Microarray	• Increased expression of genes involved in markers and mediators of inflammation • Increased expression of genes involved in stress-activated and inflammatory responses • Increased expression of genes encoding interleukins, leptin and TNF receptors • Gene modulation is associated with extracellular matrix component and angiogenic activators	[90]
Human	Placenta with GDM or from healthy donors (mean 37.7–38.4 weeks)	Microarray	• 66 genes are up-modulated in GDM placentas • Modulated genes are associated with cell functions (activation), immune response, organ development and regulation of cell death • Modulated genes including LEP, CEBPA and MIF have been previously described • Up-modulation of AQP3, LEP, FLT1, ADFP, CEBPA and MIF genes • AQP3 is a new gene associated with GDM outcome	[91]
Mouse (60% calories-by-fat diet induced-diabetes)	E 12.5	nCounter nanostring	• Altered gene expression in the fetal brain • GDM mice present repressed genes associated with neuro-developmental, cholinergic signaling, IFN/antiviral response, growth, cell cycle regulation and apoptosis • GDM mice present increased expression of genes associated with inflammation	[92]

Species	Placenta and gestational age	Transcriptomic technique	Results	References
Human	At term placenta with GDM or from healthy donors	Microarray	• Up-regulation of miR-508-3p and down-modulation of miR-27a, miR-9, miR-137, miR-92a, miR-33a, miR-30d, miR-362-5p and miR-502-5p • This gene signature targets EGFR, PI3K and AKT genes involved in placental development and fetal growth	[93]
Human	Placenta with GDM or from healthy donors (38 weeks)	Microarray	• 435 genes are modulated • 18.5% of modulated genes are involved in stress-activated and inflammatory responses • Up-regulation of interleukins (IL-1R), leptin, and TNF receptors	[90]
Human	Placenta with GDM (23–41 weeks)	Microarray	• 243 genes present an altered expression • TNF, IL-1β, LEP, IFN-γ and HLA-G are differentially modulated • Gene modulation is associated with cytokine-cytokine receptor interaction	[94]

Table 5. Transcriptomic analysis of pregnancy with gestational diabetes mellitus.

Transcriptional studies reveal strong association of leptin (LEP) with GDM [90, 101, 102]. LEP is up-modulated in placenta and could be a cause or a result of glucose uptake in placentas from women with GDM [102, 103]. Elevated circulating levels of LEP are found in GDM but LEP is also found in others pathological pregnancies such as preeclampsia. The changes in LEP concentration are associated with the modulation of cytokines such as TNF [102].

Finally, common modulated genes are found in transcriptome analyses of placental gene expression in term pregnancy complications, suggesting that they could be associated more to a dysfunction of the placenta than to a specific complication. As examples, FLT1 (fms-related tyrosine kinase 1) or PAPPA2 (Pappalysin-2) are commonly modulated in placenta disorders and could be used as biomarkers.

3.3. miRNAs in complicated pregnancy

Some investigations highlight dysregulation of microRNAs in preeclampsia and GDM, suggesting their role in pathological pregnancies [104]. In preeclampsia, the upregulation of miR-210, miR-20b, miR-29b, miR-16, miR-155 and miR-675 is associated with angiogenesis and trophoblast invasion [44, 105–110]. In contrast, down-modulation of miR-378a-5p, miR-376 and miR-195 is related to the promotion of trophoblast invasion and proliferation [39, 111]. However, some discrepancies are observed according to transcriptomic studies. For example, several studies showed that miR-210 represents the most up-regulated microRNAs in preeclampsia, whereas other studies found no change in placenta from preeclampsia compared to healthy donors [57].

Altered circulating levels of specific microRNAs have been reported in compromised pregnancies. For example, the low detection of miR-376c level in blood of 16–18 weeks pregnant women is related with the outcome of preeclampsia [112]. In similar conditions, three miRNAs, including miR-132, miR-29a and miR-222, are decreased in blood from women at 16–19 gestational weeks who were diagnosed a GDM at 25–28 weeks of gestation [113]. Thus, despite the promising perspectives to use microRNAs in diagnosis of complicated pregnancies, future studies are needed to provide a proof of concept.

4. Gene expression of placental immune cells

Beside the investigation of gene expression in whole placenta, several studies investigated transcriptomic profiles of isolated placental cells including immune and nonimmune cells. We focused here only on immune cells. Placental immune cells are necessary for development of the placenta bed and the semi-allogeneic tolerance of the fetal-placental unit. In addition, they are involved in the regulation of trophoblast invasion, angiogenesis and spiral artery remodeling. The distribution of immune placental cells is markedly distinct from that of circulating immune cells: NK cells and macrophages are found at high density, whereas lymphocytes, dendritic cells and mast cells are less represented. Therefore, we studied the transcriptomic response of macrophages, dendritic cells and mast cells.

4.1. Macrophages

Placental macrophages include decidual and Hofbauer cells from decidua (basalis) or villous stroma, respectively. They are the most abundant cells that persist throughout pregnancy [114, 115]. They play a central role in maintaining a homeostasis during pregnancy by controlling imbalance between anti- and pro-inflammatory features of placenta environment [116, 117]. Indeed, the pro-inflammatory (M1) polarization of macrophages or the prevention of M2 polarization (anti-inflammatory and/or immunoregulatory properties) leads to spontaneous abortion or miscarriage [118], inadequate remodeling of the uterine vessels during placentation and protection against infection [119].

4.1.1. First and second trimesters

After placentation, placental macrophages exhibit a M2 profile during the first and second trimesters. This M2 profile contributes to the anti-inflammatory environment of the first part of pregnancy and the prevention of the rejection of the fetus by maternal immune system [120]. The first study of gene expression pattern in human first trimester decidual macrophages was conducted in 2008 [121]. The authors identified 14,000 genes modulated in placental macrophages compared to blood monocytes. Genes involved in immunomodulation and remodeling categories are associated with M2 phenotype. Hence, the genes encoding CCL18, CD209, insulin-like growth factor-1 (IGF-1), mannose receptor c type (MRC)-1 and fibronectin-1 are up-modulated. Houser et al. investigated the polarization of macrophage subsets isolated from decidua from first trimester (6–12 weeks) [122]. They identified two

distinct macrophage subsets according to CD11c expression, namely $CD11c^{low}$ and $CD11c^{high}$ subsets. Both subsets expressed two M2 markers, CD209 (DC-SIGN) and CD206 (mannose receptor). Genes involved in invasion, mobility, inflammatory process and lipid metabolism are enriched in the two subsets, but genes involved in antiapoptotic pathways are found only in $CD11^{high}$ macrophages. In contrast, $CD11c^{low}$ macrophages express genes involved in growth regulation and development, and extracellular communication. These findings are in agreement with those of Svensson et al. who found two macrophage subsets, ICAM-3^{high} and ICAM-3^{low}, in macrophages from first trimester (7–12 weeks) [123]. Both macrophage populations express genes and cytokines associated with M2 profile and are related to CD11c expression.

4.1.2. Third trimester (term placentas)

The third trimester is associated to a pro-inflammatory environment. This inflammatory state is due to the synchronization of immune-endocrine cross-talk, based on especially estrogens [124], which favors M1 polarization of macrophages [125]. Indeed, a low level of estradiol is sufficient to promote macrophage M1 polarization, as measured by the secretion of inflammatory cytokines such as IL-1β, IL-6 and TNF. The investigation of DNA of at term placenta macrophages reveals the methylation of inflammatory genes including TLR9, IL-1β, IL-12RB2, CD48 and FGR and the hypomethylation of M2 genes including CCL2, CCL13, CCL14 and CD209 [126]. Using microarray analysis, we previously investigated the polarization of macrophages from at term placentas in comparison to macrophage-derived monocytes [127]. We did not find a polarization of at term placenta macrophages. Indeed, both M1 (CXCL9, EDN1, IL-15, IL-15RA and IL-2RA) and M2 (FN1, CTSC and CCL23) genes were up-modulated. Interestingly, we reported for the first time the ability of placental macrophages to formed multinuclear giant cells (MGCs). These MGCs present functional enrichment in genes associated with cytoskeleton reorganization and immune response. In addition, as observed in placental macrophages, MGCs are not polarized. Taking together, although the third trimester is associated with an inflammatory environment, the activation of placental macrophages does not reproduce the classical model of M1/M2 polarization.

4.1.3. Placenta macrophages in pathological pregnancy

Placental macrophages are likely associated with number of pregnancy complications. Here, we focused on three pathological conditions, preeclampsia, GDM and chorioamnionitis, in which the involvement of macrophages is documented [128] .

4.1.3.1. Preeclampsia

Although alterations of macrophages are suspected in preeclampsia, the studies of placenta macrophages during preeclampsia are controversial [116, 129]. Some studies reported a decreased [115, 130, 131] or an increased [132–135] number of placental macrophages. In addition, they produce inflammatory cytokines and anti-inflammatory cytokines [136, 137]. It has been also reported that the count of M2 macrophages is decreased in the decidua of

preeclamptic placentas [132]. The transcriptomic and protein expression of CD74, a HLA class II molecule, are decreased in placental macrophages of preeclampsia women. This down-regulation of CD74 interferes with trophoblast-macrophage cross-talk [138]. Prins et al. investigated macrophages in early decidua from women who later developed preeclampsia [139]. They observed an increased expression of CD68 mRNA, but decreased CD206/CD68 mRNA ratio, suggesting that the number of M2 macrophages is affected before the onset of preeclampsia. This finding may be related to the increased number of M1 macrophages in preeclamptic placenta found by other authors [140]. A better comprehension of the rupture of the M1/M2 balance may provide insight into understanding of preeclampsia pathogenesis.

4.1.3.2. Gestational diabetes mellitus

The inflammation associated with GDM leads to macrophage infiltration into placenta, suggesting a key role of these cells during this metabolic complication of pregnancy. The number of macrophages is increased in placentas from women with GDM as compared to normal pregnancy [141]. Placental macrophages, isolated from an experimental model of diabetes (rats receiving an injection of streptozotocin), change from M2 to M1 inflammatory profile under high glucose stimulation [142]. Similarly, isolated placental macrophages from diabetic women present a M1 or an atypical M2 profile [142]. Immunohistochemistry and PCR approaches show that the mRNA expression levels of TNF and IL-6 are higher in placentas from women with GDM than in controls, suggesting an inflammatory profile of placenta macrophages. Further studies are needed to define the role of inflammatory macrophages in GDM.

4.1.3.3. Chorioamnionitis

During pregnancy, placenta could be the target of infectious agents. The chorioamnionitis, mainly due to ascending polymicrobial infection, is a severe complication of the pregnancy leading to an acute inflammation of the membrane and chorion [143]. In human placenta, we observed a decreased number of macrophages expressing CD14, CD68 and CD163 in at term placentas from women with chorioamnionitis compared to placenta from normal pregnancies [127]. Our results are in agreement with other reports [144, 145]. In addition, isolated macrophages from placenta with chorioamnionitis exhibit an altered inflammatory response with decreased production of IL-10 [127]. Other reports describe a M2 profile of macrophages from chorioamnionitis placentas [146]. These findings underline the role of placenta macrophages in the control of infection in pregnant women.

4.2. Dendritic cells

Dendritic cells are found at the feto-maternal interface and in decidua basalis [147]. They represent approximately 2% of leukocytes from placenta and their number does not vary through gestation. Both mature dendritic cells (expressing CD83) and immature dendritic cells (expressing CD14 and DC-SIGN) have been identified in placenta tissue [148].

We previously isolated decidual dendritic cells from at term placentas of healthy women by combining negative selection with anti-CD14 antibodies and positive selection with anti-CD11c antibodies [149]. We found that 1525 genes are differentially modulated with a specific transcriptional profile as compared to monocyte-derived dendritic cells. It mainly consists of the up-modulation of genes involved in immunomodulatory cytokines, estrogen and progesterone gene pathway. The investigation of gene expression programs in placenta dendritic cells is emerging and will require additional investigation to associate gene expression and dendritic cells subsets in normal and pathological pregnancy.

4.3. Mast cells

Mast cells are found in human placentas [150] and it has been reported that mast cells and their products, especially histamine, could participate in the placenta development. Indeed, histamine is involved in trophoblast invasion and growth [151] and the cross-talk with trophoblasts *via* the expression of adhesion molecules by trophoblasts [152]. The alteration of these specific adhesion molecules is associated with the impairment of placenta invasion and the outcome of preeclampsia. A decreased number of mast cells have been reported in preeclampsia, GDM and intrauterine growth retardation [151, 153]. To our knowledge, no data about gene expression in placenta mast cells has been published. We isolated placenta mast cells from at term women using positive selection with CD117 and IgE antibodies. In a comparative study with a mast cell line (human mast cells, HMC-1.2), we found that a large number of genes are up-modulated in placenta mast cells. The functional analysis reveals an enrichment with three categories, FcεRI signaling, immune response and reproduction processes. In this latter category, we identified specific genes of Wnt pathway and a set of genes involved in the response to estrogen and progesterone (manuscript in preparation). These preliminary results highlight the originality of placenta mast cells among placenta innate immune cells.

4.4. Common transcriptomic signature of macrophages, dendritic cells and mast cells

To identify a common signature of these three placenta immune cells, we performed a retro-analysis of microarray data deposited in Gene Expression Omnibus at the National Center for Biotechnology Information. We evaluated the transcriptomic signatures of macrophages, dendritic cells and mast cells from at term placentas of healthy women and compared them to those of monocytes, monocyte-derived dendritic cells and the cell line HMC-1, respectively. As depicted in **Figure 2A**, the hierarchical clustering reveals two major branches that distinguish cells of placenta origin from the others (ANOVA, $p < 0.001$). Focusing on common modulated genes, we observed that 479 (**Figure 2B**) and 5671 (**Figure 2C**) genes are up- and down-regulated, respectively. Interestingly, 45% of down-modulated genes are associated with pregnancy versus 10% of up-modulated genes. Thus, these data suggest that innate immune cells express a core of genes that reflect the influence of placenta microenvironment.

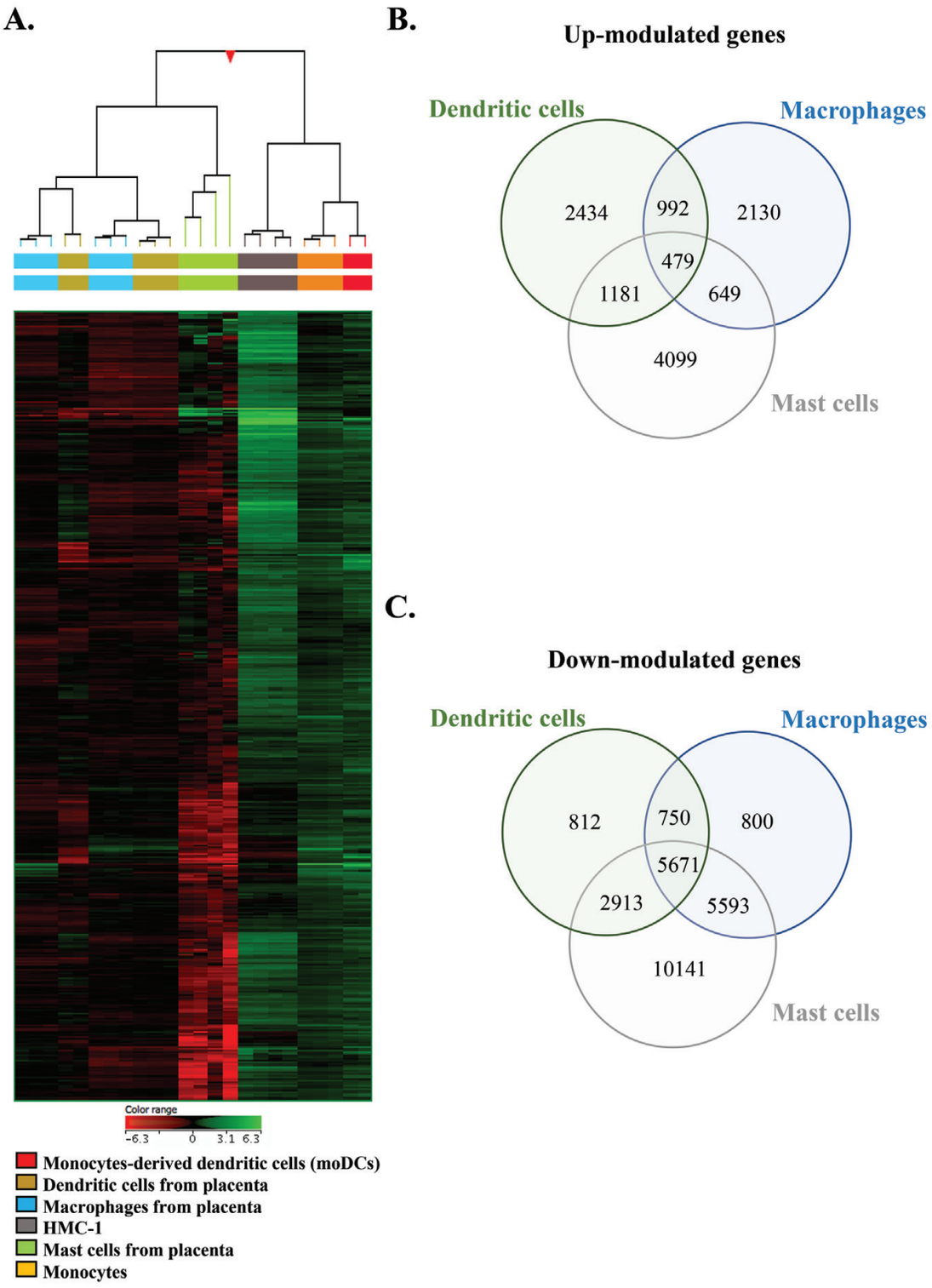

Figure 2. Transcriptomic analysis of dendritic cells, macrophages and mast cells from placenta tissue compared to controls including monocytes-derived dendritic cells, monocytes-derived macrophages and HMC-1 cell line, respectively. (A) Hierarchical clustering of placental cells showing the up- (red) and down- (green) modulated genes. Venn diagrams were realized to show the number of (B) up- and (C) down-modulated genes in common from dendritic cells (green), macrophages (blue) and mast cells (gray) from placenta.

5. Conclusion

Transcriptional analysis of placenta reveals the modulation of a very large number of genes and pathways, allowing a better understanding of tissue and cell mechanisms of normal and pathological pregnancy. The development of RNA-Seq, with a better genomic coverage and more sensitivity than microarray, and single cell technology will permit promises to detect genes with low expression level and to reveal differential new gene expression for normal and complicated pregnancies. Thus, this study reveals only the visible part of an iceberg and suggests that the immersed part must be further investigated.

Acknowledgements

We are very thankful to Dr. Christian Capo for his help and councils regarding the redaction of the manuscript. Soraya Mezouar was supported by a "Fondation pour la Recherche Médicale" postdoctoral fellowship (reference: SPF20151234951). This work was supported by the French Government under the "Investissements d'avenir" (investments for the future) program managed by the "Agence Nationale de la Recherche" (reference: Méditerranée Infection 10-IAHU-03).

Author contributions

Soraya Mezouar and Jean-Louis Mege conceived and wrote the paper.

Declaration of interest

The authors declare no competing interests.

Author details

Soraya Mezouar[1]* and Jean-Louis Mege[1,2]

*Address all correspondence to: soraya.mezouar@univ-amu.fr

1 Aix-Marseille University, Institut de Recherche pour le Développement (IRD), Assistance Publique-Hôpitaux de Marseille (AP-HM), Microbes Evolution PHylogeny and Infections (MEPHI), Institut Hospitalo-Universitaire (IHU)—Méditerranée Infection, Marseille, France

2 Assistance Publique-Hôpitaux de Marseille (AP-HM), Institut Hospitalo-Universitaire (IHU)—Méditerranée Infection, UF Immunologie, Marseille, France

References

[1] Roberts RM, Green JA, Schulz LC. The evolution of the placenta. Reproduction. 2016; **152**:R179-R189

[2] Wang Y, Zhao S. Vascular Biology of the Placenta; Integrated Systems Physiology: From Molecules to Function to Disease. San Rafael (CA): Morgan & Claypool Life Sciences; 2010

[3] Gude NM, Roberts CT, Kalionis B, King RG. Growth and function of the normal human placenta. Thrombosis Research. 2004;**114**:397-407

[4] Cole LA. Hyperglycosylated HCG, a review. Placenta. 2010;**31**:653-664

[5] Handwerger S, Freemark M. The roles of placental growth hormone and placental lactogen in the regulation of human fetal growth and development. Journal of Pediatric Endocrinology & Metabolism. 2000;**13**:343-356

[6] Moffett A, Loke C. Immunology of placentation in eutherian mammals. Nature Reviews. Immunology. 2006;**6**:584-594

[7] Simister NE. Placental transport of immunoglobulin G. Vaccine. 2003;**21**:3365-3369

[8] Petraglia F, Imperatore A, Challis JRG. Neuroendocrine mechanisms in pregnancy and parturition. Endocrine Reviews. 2010;**31**:783-816

[9] Garnica AD, Chan WY. The role of the placenta in fetal nutrition and growth. Journal of the American College of Nutrition. 1996;**15**:206-222

[10] Sood R, Zehnder JL, Druzin ML, Brown PO. Gene expression patterns in human placenta. Proceedings of the National Academy of Sciences of the United States of America. 2006;**103**:5478-5483

[11] Kim J, Zhao K, Jiang P, Lu Z, Wang J, Murray JC, et al. Transcriptome landscape of the human placenta. BMC Genomics. 2012;**13**:115

[12] Zimna A, Kurpisz M. Hypoxia-inducible factor-1 in physiological and pathophysiological angiogenesis: Applications and therapies. BioMed Research International. 2015;**2015**:549412. DOI: 10.1155/2015/549412

[13] Jauniaux E, Poston L, Burton GJ. Placental-related diseases of pregnancy: Involvement of oxidative stress and implications in human evolution. Human Reproduction Update. 2006;**12**:747-755

[14] Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008;**371**:75-84

[15] Mikheev AM, Nabekura T, Kaddoumi A, Bammler TK, Govindarajan R, Hebert MF, et al. Profiling gene expression in human placentae of different gestational ages: An OPRU network and UW SCOR study. Reproductive Sciences. 2008;**15**:866-877

[16] Korneeva KL, Rodriguez RR, Ralchenko SV, Martunovska OV, Frolova AO, Martsenyuk OP, et al. Expression of genes, encoding the enzymes of cysteine metabolism in human placenta in the first and third trimesters of uncomplicated pregnancy. Ukrainian Biochemical Journal. 2016;**88**:88-98

[17] Sitras V, Fenton C, Paulssen R, Vårtun Å, Acharya G. Differences in gene expression between first and third trimester human placenta: A microarray study. PLoS One. 2012; **7**:e33294

[18] Winn VD, Haimov-Kochman R, Paquet AC, Yang YJ, Madhusudhan MS, Gormley M, et al. Gene expression profiling of the human maternal-fetal interface reveals dramatic changes between midgestation and term. Endocrinology. 2007;**148**:1059-1079

[19] Gheorghe C, Mohan S, Longo LD. Gene expression patterns in the developing murine placenta. Journal of the Society for Gynecologic Investigation. 2006;**13**:256-262

[20] Kingdom J, Huppertz B, Seaward G, Kaufmann P. Development of the placental villous tree and its consequences for fetal growth. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2000;**92**:35-43

[21] Uusküla L, Männik J, Rull K, Minajeva A, Kõks S, Vaas P, et al. Mid-gestational gene expression profile in placenta and link to pregnancy complications. PLoS One. 2012; **7**:e49248

[22] PrabhuDas M, Bonney E, Caron K, Dey S, Erlebacher A, Fazleabas A, et al. Immune mechanisms at the maternal-fetal interface: perspectives and challenges. Nature Immunology. 2015;**16**:328-334

[23] Saben J, Kang P, Zhong Y, Thakali KM, Gomez-Acevedo H, Borengasser SJ, et al. RNA-Seq analysis of the rat placentation site reveals maternal obesity-associated changes in placental and offspring thyroid hormone signaling. Placenta. 2014;**35**:1013-1020

[24] Romero R, Espinoza J, Kusanovic JP, Gotsch F, Hassan S, Erez O, et al. The preterm parturition syndrome. BJOG: An International Journal of Obstetrics & Gynaecology. 2006;**113 Suppl 3**:17-42

[25] Cindrova-Davies T, Yung H-W, Johns J, Spasic-Boskovic O, Korolchuk S, Jauniaux E, et al. Oxidative stress, gene expression, and protein changes induced in the human placenta during labor. The American Journal of Pathology. 2007;**171**:1168-1179

[26] Oros D, Strunk M, Breton P, Paules C, Benito R, Moreno E, et al. Altered gene expression in human placenta after suspected preterm labour. Placenta. 2017;**55**:21-28

[27] Peng H-H, Kao C-C, Chang S-D, Chao A-S, Chang Y-L, Wang C-N, et al. The effects of labor on differential gene expression in parturient women, placentas, and fetuses at term pregnancy. The Kaohsiung Journal of Medical Sciences. 2011;**27**:494-502

[28] Sitras V, Paulssen RH, Grønaas H, Vårtun A, Acharya G. Gene expression profile in labouring and non-labouring human placenta near term. Molecular Human Reproduction. 2008;**14**:61-65

[29] Vu T-D, Feng Y, Placido J, Reznik SE. Placental matrix metalloproteinase-1 expression is increased in labor. Reproductive Sciences. 2008;**15**:420-424

[30] Paradowska E, Blach-Olszewska Z, Gejdel E. Constitutive and induced cytokine production by human placenta and amniotic membrane at term. Placenta. 1997;**18**:441-446

[31] Brown MB, von Chamier M, Allam AB, Reyes L. M1/M2 macrophage polarity in normal and complicated pregnancy. Frontiers in Immunology. 2014;**5**:606

[32] Romero R, Mazor M, Brandt F, Sepulveda W, Avila C, Cotton DB, et al. Interleukin-1 alpha and interleukin-1 beta in preterm and term human parturition. American Journal of Reproductive Immunology. 1992;**27**:117-123

[33] Opsjłn SL, Wathen NC, Tingulstad S, Wiedswang G, Sundan A, Waage A, et al. Tumor necrosis factor, interleukin-1, and interleukin-6 in normal human pregnancy. American Journal of Obstetrics and Gynecology. 1993;**169**:397-404

[34] Varner MW, Esplin MS. Current understanding of genetic factors in preterm birth. BJOG: An International Journal of Obstetrics & Gynaecology. 2005;**112**:28-31

[35] Bartel DP. MicroRNAs: Genomics, biogenesis, mechanism, and function. Cell. 2004; **116**:281-297

[36] Soifer HS, Rossi JJ, Saetrom P. MicroRNAs in disease and potential therapeutic applications. Molecular Therapy. 2007;**15**:2070-2079

[37] Morales-Prieto DM, Ospina-Prieto S, Schmidt A, Chaiwangyen W, Markert UR. Elsevier trophoblast research award lecture: Origin, evolution and future of placenta MiRNAs. Placenta. 2014;**35**(Suppl):S39-S45

[38] Cai M, Kolluru GK, Ahmed A. Small molecule, big prospects: MicroRNA in pregnancy and its complications. Journal of Pregnancy. 2017;**2017**:6972732

[39] Luo L, Ye G, Nadeem L, Fu G, Yang BB, Honarparvar E, et al. MicroRNA-378a-5p promotes trophoblast cell survival, migration and invasion by targeting nodal. Journal of Cell Science. 2012;**125**:3124-3132

[40] Huppertz B. Placental pathology in pregnancy complications. Thrombosis Research. 2011;**127**(Suppl 3):S96-S99

[41] Steegers EAP, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet. 2010; **376**:631-644

[42] Roberts JM, Escudero C. The placenta in preeclampsia. Pregnancy Hypertension. 2012; **2**:72-83

[43] Lain KY, Roberts JM. Contemporary concepts of the pathogenesis and management of preeclampsia. Journal of the American Medical Association. 2002;**287**:3183-3186

[44] Roberts JM, Hubel CA. The two stage model of preeclampsia: Variations on the theme. Placenta. 2009;**30**:S32-S37. Suppl A

[45] Huppertz B. Placental origins of preeclampsia: Challenging the current hypothesis. Hypertension. 2008;**51**:970-975

[46] Levine RJ, Maynard SE, Qian C, Lim K-H, England LJ, Yu KF, et al. Circulating angiogenic factors and the risk of preeclampsia. The New England Journal of Medicine. 2004; **350**:672-683

[47] Kleinrouweler CE, Wiegerinck MMJ, Ris-Stalpers C, Bossuyt PMM, van der Post JAM, von Dadelszen P, et al. Accuracy of circulating placental growth factor, vascular endothelial growth factor, soluble fms-like tyrosine kinase 1 and soluble endoglin in the prediction of pre-eclampsia: A systematic review and meta-analysis. BJOG: An International Journal of Obstetrics & Gynaecology. 2012;**119**:778-787

[48] Small HY, Akehurst C, Sharafetdinova L, McBride MW, McClure JD, Robinson SW, et al. HLA gene expression is altered in whole blood and placenta from women who later developed preeclampsia. Physiological Genomics. 2017;**49**:193-200

[49] Tsoi SCM, Cale JM, Bird IM, Kay HH. CDNA microarray analysis of gene expression profiles in human placenta: Up-regulation of the transcript encoding muscle subunit of glycogen phosphorylase in preeclampsia. Journal of the Society for Gynecologic Investigation. 2003;**10**:496-502

[50] Pang Z-J, Xing F-Q. DNA microarrays detect the expression of apoptosis-related genes in preeclamptic placentas. Journal of Perinatal Medicine. 2004;**32**:25-30

[51] Hoegh AM, Borup R, Nielsen FC, Sørensen S, Hviid TVF. Gene expression profiling of placentas affected by pre-eclampsia. Journal of Biomedicine & Biotechnology. 2010;**2010**:787545. DOI: 10.1155/2010/787545

[52] Kang JH, Song H, Yoon JA, Park DY, Kim SH, Lee KJ, et al. Preeclampsia leads to dysregulation of various signaling pathways in placenta. Journal of Hypertension. 2011;**29**:928-936

[53] Reimer T, Koczan D, Gerber B, Richter D, Thiesen HJ, Friese K. Microarray analysis of differentially expressed genes in placental tissue of pre-eclampsia: Up-regulation of obesity-related genes. Molecular Human Reproduction. 2002;**8**:674-680

[54] Centlow M, Wingren C, Borrebaeck C, Brownstein MJ, Hansson SR. Differential gene expression analysis of placentas with increased vascular resistance and pre-eclampsia using whole-genome microarrays. Journal of Pregnancy. 2011;**2011**:472354

[55] Kaartokallio T, Cervera A, Kyllönen A, Laivuori K, Kere J, Laivuori H, et al. Gene expression profiling of pre-eclamptic placentae by RNA sequencing. Scientific Reports. 2015; (5):14107

[56] Enquobahrie DA, Meller M, Rice K, Psaty BM, Siscovick DS, Williams MA. Differential placental gene expression in preeclampsia. American Journal of Obstetrics and Gynecology. 2008;**199**:566.e1-566.e11

[57] Mayor-Lynn K, Toloubeydokhti T, Cruz AC, Chegini N. Expression profile of MicroRNAs and MRNAs in human placentas from pregnancies complicated by preeclampsia and preterm labor. Reproductive Sciences. 2011;**18**:46-56

[58] Toft JH, Lian IA, Tarca AL, Erez O, Espinoza J, Eide IP, et al. Whole-genome microarray and targeted analysis of angiogenesis-regulating gene expression (ENG, FLT1, VEGF, PlGF) in placentas from pre-Eclamptic and small-for-gestational-age pregnancies. The Journal of Maternal-Fetal & Neonatal Medicine. 2008;**21**:267-273

[59] Founds SA, Conley YP, Lyons-Weiler JF, Jeyabalan A, Hogge WA, Conrad KP. Altered global gene expression in first trimester placentas of women destined to develop preeclampsia. Placenta. 2009;**30**:15-24

[60] Lapaire O, Grill S, Lalevee S, Kolla V, Hösli I, Hahn S. Microarray screening for novel preeclampsia biomarker candidates. Fetal Diagnosis and Therapy. 2012;**31**:147-153

[61] Tsai S, Hardison NE, James AH, Motsinger-Reif AA, Bischoff SR, Thames BH, et al. Transcriptional profiling of human placentas from pregnancies complicated by preeclampsia reveals disregulation of sialic acid acetylesterase and immune signalling pathways. Placenta. 2011;**32**:175-182

[62] Sitras V, Paulssen RH, Grønaas H, Leirvik J, Hanssen TA, Vårtun A, et al. Differential placental gene expression in severe preeclampsia. Placenta. 2009;**30**:424-433

[63] Goldman-Wohl D, Cesla T, Smith Y, Greenfield C, Dechend R, Staff AC, et al. Expression profiling of autophagy associated genes in placentas of preeclampsia. Placenta. 2013; **34**:959-962

[64] Brew O, Sullivan MHF, Woodman A. Comparison of Normal and pre-eclamptic placental gene expression: A systematic review with meta-analysis. PLoS One. 2016;**11**:e0161504

[65] Chaiworapongsa T, Romero R, Whitten A, Tarca AL, Bhatti G, Draghici S, et al. Differences and similarities in the transcriptional profile of peripheral whole blood in early and late-onset preeclampsia: Insights into the molecular basis of the phenotype of preeclampsiaa. Journal of Perinatal Medicine. 2013;**41**:485-504

[66] Dahlstrøm B, Esbensen Y, Vollan H, Oian P, Bukholm G. Genome profiles in maternal blood during early onset preeclampsia and towards term. Journal of Perinatal Medicine. 2010;**38**:601-608

[67] Textoris J, Ivorra D, Amara AB, Sabatier F, Ménard J-P, Heckenroth H, et al. Evaluation of current and new biomarkers in severe preeclampsia: A microarray approach reveals the VSIG4 gene as a potential blood biomarker. PLoS One. 2013;**8**:e82638

[68] Jonsson Y, Rubèr M, Matthiesen L, Berg G, Nieminen K, Sharma S, et al. Cytokine mapping of sera from women with preeclampsia and normal pregnancies. Journal of Reproductive Immunology. 2006;**70**:83-91

[69] Sharma A, Satyam A, Sharma JB. Leptin, IL-10 and inflammatory markers (TNF-α, IL-6 and IL-8) in pre-eclamptic, normotensive pregnant and healthy non-pregnant women. American Journal of Reproductive Immunology. 2007;**58**:21-30

[70] Capittini C, Pasi A, Bergamaschi P, Tinelli C, De Silvestri A, Mercati MP, et al. HLA haplotypes and birth weight variation: Is your future going to be light or heavy? Tissue Antigens. 2009;**74**:156-163

[71] Lynge Nilsson L, Djurisic S, Hviid TVF. Controlling the immunological crosstalk during conception and pregnancy: HLA-G in reproduction. Frontiers in Immunology. 2014;**13**(5):198. DOI: 10.3389/fimmu.2014.00198

[72] Misra DP. The effect of the pregnancy-induced hypertension on fetal growth: A review of the literature. Paediatric and Perinatal Epidemiology. 1996;**10**:244-263

[73] Dahlstrøm B, Romundstad P, Øian P, Vatten LJ, Eskild A. Placenta weight in pre-eclampsia. Acta Obstetricia et Gynecologica Scandinavica. 2008;**87**:608-611

[74] Nishizawa H, Ota S, Suzuki M, Kato T, Sekiya T, Kurahashi H, et al. Comparative gene expression profiling of placentas from patients with severe pre-eclampsia and unexplained Fetal growth restriction. Reproductive Biology and Endocrinology. 2011;**9**:107

[75] Zamudio S. The placenta at high altitude. High Altitude Medicine & Biology. 2003; **4**:171-191

[76] Mise H, Sagawa N, Matsumoto T, Yura S, Nanno H, Itoh H, et al. Augmented placental production of leptin in preeclampsia: Possible involvement of placental hypoxia. The Journal of Clinical Endocrinology and Metabolism. 1998;**83**:3225-3229

[77] Trollmann R, Klingmüller K, Schild RL, Rascher W, Dötsch J. Differential gene expression of somatotrophic and growth factors in response to in vivo hypoxia in human placenta. American Journal of Obstetrics and Gynecology. 2007;**197**:601.e1-601.e6

[78] Vanderlelie J, Gude N, Perkins A. Antioxidant gene expression in preeclamptic placentae: A preliminary investigation. Placenta. 2008;**29**:519-522

[79] Zhang J, Masciocchi M, Lewis D, Sun W, Liu A, Wang Y. Placental anti-oxidant gene polymorphisms, enzyme activity, and oxidative stress in preeclampsia. Placenta. 2008;**29**: 439-443

[80] Lindheimer MD, Woodruff TK. Activin A, inhibin A, and pre-eclampsia. Lancet. 1997; **349**:1266-1267

[81] Carty DM, Delles C, Dominiczak AF. Novel biomarkers for predicting preeclampsia. Trends in Cardiovascular Medicine. 2008;**18**:186-194

[82] Maynard SE, Min J-Y, Merchan J, Lim K-H, Li J, Mondal S, et al. Excess placental soluble Fms-like tyrosine kinase 1 (SFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. The Journal of Clinical Investigation. 2003;**111**:649-658

[83] Venkatesha S, Toporsian M, Lam C, Hanai J, Mammoto T, Kim YM, et al. Soluble Endoglin contributes to the pathogenesis of preeclampsia. Nature Medicine. 2006;**12**:642-649

[84] Widmer M, Villar J, Benigni A, Conde-Agudelo A, Karumanchi SA, Lindheimer M. Mapping the theories of preeclampsia and the role of angiogenic factors: A systematic review. Obstetrics and Gynecology. 2007;**109**:168-180

[85] Kleinrouweler CE, van Uitert M, Moerland PD, Ris-Stalpers C, Post JAM, van der, Afink GB. Differentially expressed genes in the pre-Eclamptic placenta: A systematic review and meta-analysis. PLoS One. 2013;**8**:e68991

[86] Stanley K, Fraser R, Bruce C. Physiological changes in insulin resistance in human pregnancy: Longitudinal study with the hyperinsulinaemic euglycaemic clamp technique. BJOG: An International Journal of Obstetrics & Gynaecology;**105**:756-759

[87] Kim C. Gestational diabetes: Risks, management, and treatment options. International Journal of Women's Health. 2010;**2**:339-351

[88] Al-Badri MR, Zantout MS, Azar ST. The role of adipokines in gestational diabetes mellitus. Therapeutic Advances in Endocrinology and Metabolism. 2015;**6**:103-108

[89] Salbaum JM, Kruger C, Zhang X, Delahaye NA, Pavlinkova G, Burk DH, et al. Altered gene expression and spongiotrophoblast differentiation in placenta from a mouse model of diabetes in pregnancy. Diabetologia. 2011;**54**:1909-1920

[90] Radaelli T, Varastehpour A, Catalano P, Hauguel-de Mouzon S. Gestational diabetes induces placental genes for chronic stress and inflammatory pathways. Diabetes. 2003;**52**:2951-2958

[91] Enquobahrie DA, Williams MA, Qiu C, Meller M, Sorensen TK. Global placental gene expression in gestational diabetes mellitus. American Journal of Obstetrics and Gynecology. 2009;**200**:206.e1-206.13

[92] Money KM, Barke TL, Serezani A, Gannon M, Garbett KA, Aronoff DM, et al. Gestational diabetes exacerbates maternal immune activation effects in the developing brain. Molecular Psychiatry. 2017

[93] Li J, Song L, Zhou L, Wu J, Sheng C, Chen H, et al. A MicroRNA signature in gestational diabetes mellitus associated with risk of macrosomia. Cellular Physiology and Biochemistry. 2015;**37**:243-252

[94] Zhao Y-H, Wang D-P, Zhang L-L, Zhang F, Wang D-M, Zhang W-Y. Genomic expression profiles of blood and placenta reveal significant immune-related pathways and categories in Chinese women with gestational diabetes mellitus. Diabetic Medicine. 2011;**28**:237-246

[95] Uysal KT, Wiesbrock SM, Marino MW, Hotamisligil GS. Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. Nature. 1997;**389**:610-614

[96] Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: Direct role in obesity-linked insulin resistance. Science. 1993;**259**:87-91

[97] Desoye G, Mouzon SH. The human placenta in gestational diabetes mellitus: The insulin and cytokine network. Diabetes Care. 2007;**30**:S120-S126

[98] Basu S, Haghiac M, Surace P, Challier J-C, Guerre-Millo M, Singh K, et al. Pre-gravid obesity associates with increased maternal endotoxemia and metabolic inflammation. Obesity (Silver Spring). 2011;**19**:476-482

[99] Challier J-C, Bintein T, Bessières B, Mouzon SH. Médecine de la Reproduction, Gynécologie Endocrinologie. Diabète et obésité: évolutions placentaires. 2008;**10**:7

[100] Oliva K, Barker G, Riley C, Bailey MJ, Permezel M, Rice GE, et al. The effect of pre-existing maternal obesity on the placental proteome: Two-dimensional difference gel electrophoresis coupled with mass spectrometry. Journal of Molecular Endocrinology. 2012;**48**:139-149

[101] Lappas M, Yee K, Permezel M, Rice GE. Release and regulation of leptin, resistin and adiponectin from human placenta, fetal membranes, and maternal adipose tissue and skeletal muscle from normal and gestational diabetes mellitus-complicated pregnancies. The Journal of Endocrinology. 2005;**186**:457-465

[102] Qiu C, Williams MA, Vadachkoria S, Frederick IO, Luthy DA. Increased maternal plasma leptin in early pregnancy and risk of gestational diabetes mellitus. Obstetrics and Gynecology. 2004;**103**:519-525

[103] Henson MC, Castracane VD. Leptin: Roles and regulation in primate pregnancy. Seminars in Reproductive Medicine. 2002;**20**:113-122

[104] Barchitta M, Maugeri A, Quattrocchi A, Agrifoglio O, Agodi A. The role of MiRNAs as biomarkers for pregnancy outcomes: A comprehensive review. International Journal of Genomics. 2017;**2017**:8067972. DOI: 10.1155/2017/8067972

[105] Pineles BL, Romero R, Montenegro D, Tarca AL, Han YM, Kim YM, et al. Distinct subsets of MicroRNAs are expressed differentially in the human placentas of patients with preeclampsia. American Journal of Obstetrics and Gynecology. 2007;**196**:261.e1-261.e6

[106] Gao W-L, Liu M, Yang Y, Yang H, Liao Q, Bai Y, et al. The imprinted H19 gene regulates human placental trophoblast cell proliferation via encoding MiR-675 that targets nodal modulator 1 (NOMO1). RNA Biology. 2012;**9**:1002-1010

[107] Zhang Y, Diao Z, Su L, Sun H, Li R, Cui H, et al. MicroRNA-155 contributes to preeclampsia by down-regulating CYR61. American Journal of Obstetrics and Gynecology. 2010;**202**:466.e1-466.e7

[108] Wang W, Feng L, Zhang H, Hachy S, Satohisa S, Laurent LC, et al. Preeclampsia up-regulates angiogenesis-associated microRNA (i.e., MiR-17, -20a, and -20b) that target Ephrin-B2 and EPHB4 in human placenta. The Journal of Clinical Endocrinology and Metabolism. 2012;**97**:E1051-E1059

[109] Li P, Guo W, Du L, Zhao J, Wang Y, Liu L, et al. MicroRNA-29b contributes to pre-eclampsia through its effects on apoptosis, invasion and angiogenesis of trophoblast cells. Clinical Science. 2013;**124**:27-40

[110] Hu Y, Li P, Hao S, Liu L, Zhao J, Hou Y. Differential expression of MicroRNAs in the placentae of Chinese patients with severe pre-eclampsia. Clinical Chemistry and Laboratory Medicine. 2009;**47**:923-929

[111] Bai Y, Yang W, Yang H, Liao Q, Ye G, Fu G, et al. Downregulated MiR-195 detected in preeclamptic placenta affects trophoblast cell invasion via modulating ActRIIA expression. PLoS One. 2012;**7**:e38875

[112] Fu G, Ye G, Nadeem L, Ji L, Manchanda T, Wang Y, et al. MicroRNA-376c impairs transforming growth factor-β and nodal signaling to promote trophoblast cell proliferation and invasion. Hypertension. 2013;**61**:864-872

[113] Zhao C, Dong J, Jiang T, Shi Z, Yu B, Zhu Y, et al. Early second-trimester serum MiRNA profiling predicts gestational diabetes mellitus. PLoS One. 2011;**6**:e23925

[114] Bulmer JN, Johnson PM. Macrophage populations in the human placenta and Amniochorion. Clinical and Experimental Immunology. 1984;**57**:393-403

[115] Williams PJ, Searle RF, Robson SC, Innes BA, Bulmer JN. Decidual leucocyte populations in early to late gestation normal human pregnancy. Journal of Reproductive Immunology. 2009;**82**:24-31

[116] Nagamatsu T, Schust DJ. The contribution of macrophages to normal and pathological pregnancies. American Journal of Reproductive Immunology. 2010;**63**:460-471

[117] Svensson-Arvelund J, Ernerudh J. The role of macrophages in promoting and maintaining homeostasis at the fetal-maternal interface. American Journal of Reproductive Immunology. 2015;**74**:100-109

[118] Guenther S, Vrekoussis T, Heublein S, Bayer B, Anz D, Knabl J, et al. Decidual macrophages are significantly increased in spontaneous miscarriages and over-express FasL: A potential role for macrophages in trophoblast apoptosis. International Journal of Molecular Sciences. 2012;**13**:9069-9080

[119] Liu T, Zhang Q, Liu L, Xu X, Chen H, Wang H, et al. Trophoblast apoptosis through polarization of macrophages induced by Chinese toxoplasma Gondii isolates with different virulence in pregnant mice. Parasitology Research. 2013;**112**:3019-3027

[120] Zhang Y-H, He M, Wang Y, Liao A-H. Modulators of the balance between M1 and M2 macrophages during pregnancy. Frontiers in Immunology. 2017;**8**:120

[121] Gustafsson C, Mjösberg J, Matussek A, Geffers R, Matthiesen L, Berg G, et al. Gene expression profiling of human decidual macrophages: Evidence for immunosuppressive phenotype. PLoS One. 2008;**3**:e2078

[122] Houser BL, Tilburgs T, Hill J, Nicotra ML, Strominger JL. Two unique human decidual macrophage populations. Journal of Immunology. 2011;**186**:2633-2642

[123] Svensson J, Jenmalm MC, Matussek A, Geffers R, Berg G, Ernerudh J. Macrophages at the fetal-maternal interface express markers of alternative activation and are induced by M-CSF and IL-10. Journal of Immunology. 2011;**187**:3671-3682

[124] Li M, Piao L, Chen C-P, Wu X, Yeh C-C, Masch R, et al. Modulation of decidual macrophage polarization by macrophage colony-stimulating factor derived from first-trimester decidual cells. The American Journal of Pathology. 2016;**186**:1258-1266

[125] Bouman A, Heineman MJ, Faas MM. Sex hormones and the immune response in humans. Human Reproduction Update. 2005;**11**:411-423

[126] Kim SY, Romero R, Tarca AL, Bhatti G, Kim CJ, Lee J, et al. Methylome of fetal and maternal monocytes and macrophages at the feto-maternal interface. American Journal of Reproductive Immunology. 2012;**68**:8-27

[127] Amara AB, Gorvel L, Baulan K, Derain-Court J, Buffat C, Vérollet C, et al. Placental macrophages are impaired in chorioamnionitis, an infectious pathology of the placenta. Journal of Immunology. 2013;**191**:5501-5514

[128] Tang Z, Abrahams VM, Mor G, Guller S. Placental Hofbauer cells and complications of pregnancy. Annals of the New York Academy of Sciences. 2011;**1221**:103-108

[129] Wetzka B, Nüsing R, Charnock-Jones DS, Schäfer W, Zahradnik HP, Smith SK. Cyclooxygenase-1 and -2 in human placenta and placental bed after normal and pre-eclamptic pregnancies. Human Reproduction. 1997;**12**:2313-2320

[130] Tang Z, Buhimschi IA, Buhimschi CS, Tadesse S, Norwitz E, Niven-Fairchild T, et al. Decreased levels of folate receptor-β and reduced numbers of fetal macrophages (Hofbauer cells) in placentas from pregnancies with severe pre-eclampsia. American Journal of Reproductive Immunology. 2013;**70**:104-115

[131] Bürk MR, Troeger C, Brinkhaus R, Holzgreve W, Hahn S. Severely reduced presence of tissue macrophages in the basal plate of pre-eclamptic placentae. Placenta. 2001; **22**:309-316

[132] Schonkeren D, van der Hoorn M-L, Khedoe P, Swings G, van Beelen E, Claas F, et al. Differential distribution and phenotype of decidual macrophages in preeclamptic versus control pregnancies. The American Journal of Pathology. 2011;**178**:709-717

[133] Reister F, Frank HG, Kingdom JC, Heyl W, Kaufmann P, Rath W, et al. Macrophage-induced apoptosis limits endovascular trophoblast invasion in the uterine wall of pre-eclamptic women. Laboratory Investigation. 2001;**81**:1143-1152

[134] Wilczyński JR, Tchórzewski H, Banasik M, Głowacka E, Wieczorek A, Lewkowicz P, et al. Lymphocyte subset distribution and cytokine secretion in third trimester decidua in normal pregnancy and preeclampsia. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2003;**109**:8-15

[135] Kim J-S, Romero R, Cushenberry E, Kim YM, Erez O, Nien JK, et al. Distribution of CD14+ and CD68+ macrophages in the placental bed and basal plate of women with preeclampsia and preterm labor. Placenta. 2007;**28**:571-576

[136] Rein DT, Breidenbach M, Hönscheid B, Friebe-Hoffmann U, Engel H, Göhring U-J, et al. Preeclamptic women are deficient of interleukin-10 as assessed by cytokine release of trophoblast cells in vitro. Cytokine. 2003;**23**:119-125

[137] Hennessy A, Pilmore HL, Simmons LA, Painter DM. A deficiency of placental IL-10 in preeclampsia. Journal of Immunology. 1999;**163**:3491-3495

[138] Przybyl L, Haase N, Golic M, Rugor J, Solano ME, Arck PC, et al. CD74-downregulation of placental macrophage-trophoblastic interactions in preeclampsia. Circulation Research. 2016;**119**:55-68

[139] Prins JR, Faas MM, Melgert BN, Huitema S, Timmer A, Hylkema MN, et al. Altered expression of immune-associated genes in first-trimester human decidua of pregnancies later complicated with hypertension or foetal growth restriction. Placenta. 2012; **33**:453-455

[140] Faas MM, Spaans F, De Vos P. Monocytes and macrophages in pregnancy and preeclampsia. Frontiers in Immunology. 2014;**5**:298

[141] Yu J, Zhou Y, Gui J, Li A-Z, Su X-L, Feng L. Assessment of the number and function of macrophages in the placenta of gestational diabetes mellitus patients. Journal of Huazhong University of Science and Technology Medical sciences. 2013;**33**:725-729

[142] Sisino G, Bouckenooghe T, Aurientis S, Fontaine P, Storme L, Vambergue A. Diabetes during pregnancy influences Hofbauer cells, a subtype of placental macrophages, to acquire a pro-inflammatory phenotype. Biochimica et Biophysica Acta. 2013;**1832**: 1959-1968

[143] Czikk MJ, McCarthy FP, Murphy KE. Chorioamnionitis: From pathogenesis to treatment. Clinical Microbiology and Infection. 2011;**17**:1304-1311

[144] Toti P, Arcuri F, Tang Z, Schatz F, Zambrano E, Mor G, et al. Focal increases of Fetal macrophages in placentas from pregnancies with histological chorioamnionitis: Potential role of fibroblast monocyte chemotactic Protein-1. American Journal of Reproductive Immunology. 2011;**65**:470-479

[145] Vinnars M-TN, Rindsjö E, Ghazi S, Sundberg A, Papadogiannakis N. The number of CD68(+) (Hofbauer) cells is decreased in placentas with chorioamnionitis and with advancing gestational age. Pediatric and Developmental Pathology. 2010;**13**:300-304

[146] Joerink M, Rindsjö E, van Riel B, Alm J, Papadogiannakis N. Placental macrophage (Hofbauer cell) polarization is independent of maternal allergen-sensitization and presence of chorioamnionitis. Placenta. 2011;**32**:380-385

[147] Tagliani E, Erlebacher A. Dendritic cell function at the maternal-fetal interface. Expert Review of Clinical Immunology. 2011;**7**:593-602

[148] Kämmerer U, Eggert AO, Kapp M, McLellan AD, Geijtenbeek TBH, Dietl J, et al. Unique appearance of proliferating antigen-presenting cells expressing DC-SIGN (CD209) in the decidua of early human pregnancy. The American Journal of Pathology. 2003;**162**:887-896

[149] Gorvel L, Ben Amara A, Ka MB, Textoris J, Gorvel J-P, Mege J-L. Myeloid decidual dendritic cells and immunoregulation of pregnancy: Defective responsiveness to *Coxiella burnetii* and *Brucella abortus*. Frontiers in Cellular and Infection Microbiology. 2014;**4**:179

[150] Purcell WM, Hanahoe TH. A novel source of mast cells: The human placenta. Agents and Actions. 1991;**33**:8-12

[151] Szukiewicz D, Szukiewicz A, Maslinska D, Poppe P, Gujski M, Olszewski M. Mast cells and histamine in intrauterine growth retardation—Relation to the development of placental microvessels. Inflammation Research. 1999;**48**(Suppl 1):S41-S42

[152] Szewczyk G, Pyzlak M, Smiertka W, Klimkiewicz J, Szukiewicz D. Histamine stimulates Alphav-Beta3 integrin expression of the human trophoblast through the H(1) receptor. Inflammation Research. 2006;**55**(Suppl 1):S79-S80

[153] Szukiewicz D, Szukiewicz A, Maslinska D, Szewczyk G, Watroba M. Mast cell-derived vascular endothelial growth factor (VEGF) and microvascular density in diabetic placentae. Inflammation Research. 2003;**52**(Suppl 1):S09-S10

IntechOpen