Journal of
Clinical & Cellular Immunology

Laresgoiti-Servitje, J Clin Cell Immunol 2015, 6:5
DOI: 10.4172/2155-9899.1000361

Review Article Open Access

Pregnancy-Related MiRNAs Participate in the Regulation of the Immune System during the Gestational Period

Estibalitz Laresgoiti-Servitje[1,2*]

[1]*Basic Medical Sciences, TEC-ABC School of Medicine, Tecnológico de Monterrey, Mexico*

[2]*National Institute of Perinatology "Isidro Espinosa de Los Reyes", Mexico*

[*]**Corresponding author:** Estibalitz Laresgoiti-Servitje, TEC-ABC School of Medicine, American British Cowdray Medical Center, Carlos Graef Fernández 154-114, Mexico City, 05300, Mexico, Tel: +525511031741; E-mail: estibalitz.laresgoiti@itesm.mx

Received date: Jan 25, 2015; **Accepted date:** October 15, 2015; **Published date:** October 23, 2015

Abstract

Pregnancy is a wonderful and complex example of immunomodulation. The regulation that occurs during pregnancy involves hormones, major histocompatibility molecules, cytokines and different types of cells. Recent evidence shows a significant role for miRNAs in the regulation of the immune system´s cells during the gestational period. Placental miRNAs, found in both normal and complicated pregnancies, are primarily localized in four clusters. These are the chromosome 19-miRNA cluster (C19MC), the miR-371-3 cluster (also on chromosome 19), the chromosome 14-miRNA cluster (M14MC), and the miR-17-92 cluster.

Pregnancy-associated miRNAs may be involved in angiogenesis, trophoblast differentiation, and in the regulation of the immune system. However, their role has not been clearly elucidated. miRNAs hold promise as biomarkers in clinical settings, as altered miRNA expression may be present in pregnancy complications. Several miRNAs can regulate leukocytes because they target genes necessary for their development and/or function. Among them are miR-29a, miR-181, miR-125b, miR-17 and miR-92a.

Although many miRNAs related to healthy pregnancies or to pregnancy complications have been identified, there remains a lack of information regarding their target genes and the behavior of different miRNAs from the same cluster, particularly with regards to their ability to modulate immune system cells.

Keywords: miRNAs; Immune system; Pregnancy; $CD4^+$ T cells; Tregs; Th17

Introduction

MicroRNAs (miRNAs) are small non-coding RNAs that are expressed by several cell types and regulate gene expression via antisense complementarity to RNAs [1,2]. miRNAs play relevant roles in biological and pathological processes. Moreover, serum miRNA profiles may reflect physiological conditions, making them potential biomarkers for pregnancy disorders [3]. In recent years, miRNAs have acquired an important role as factors influencing trophoblast biology and immune regulation. Unfortunately, our understanding of how miRNAs participate in immune system regulation during pregnancy remains limited. This review aims to include recent research regarding the most frequently cited pregnancy-related miRNAs and the participation of some of these microRNAs in immune system regulation during the gestational period.

Pregnancy-Related miRNAs

Trophoblast cells are fetal cells localized at the feto-maternal interface that can express microRNAs [4]. Various miRNAs derived from the placenta are considered to be pregnancy-associated molecules that may reflect the state of the placenta [5,6]. Specific miRNAs have been described not only for the placenta but also for pregnancy disorders. These miRNAs may differ between first trimester and third trimester placentas [7]. miRNAs present during pregnancy are mainly clustered in four regions: the chromosome 19 miRNA cluster (C19MC) [8,9], the miR-371-3 cluster (also on chromosome 19), the chromosome 14 miRNA cluster (C14MC) located in the 14q32 domain [4,5,9], and the miR-17-92 cluster [7]. However Gu et al. found that third trimester placentas may also express miRNAs of the let-7 family, the miR-34 family, the miR-29 cluster, the miR-195 cluster, and miR-181c [7].

C19MC is the largest human microRNA cluster known and is mainly expressed in the placenta and undifferentiated cells [10], releasing miRNAs into the maternal circulation in placenta-derived exosomes [9,11]. Interestingly, this cluster is thought to be regulated by genomic imprinting, and only the paternally inherited allele is expressed in the placenta [12]. The human C19MC cluster comprises 54 miRNA genes [11]. On the other hand, 14MC includes 34 miRNAs, and the miR-371-3 cluster, only three [4]. Lastly, the miR-17-92 cluster, one of the best studied clusters, comprises miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1 and miR-92a-1 [13]. Different miRNA clusters that have been reported to be overexpressed during pregnancy, and examples of the miRNAs that comprise them, are presented in Table 1.

C19MC			C14MC	miR-371-3	miR-17-92	let-7	miR-34	miR-29	miR-15/16	miR-181
miR-512-1	miR-523	miR-518e	miR-127-3p	miR-371	miR-17	let-7b	miR-34a	miR-29a	miR-195	miR-181a-1
miR-512-2	miR-518f	miR-518a-1	miR-134	miR-372	miR-18a	let-7d	miR-34b	miR-29b	miR-15a	miR-181a-2
miR-1323	miR-520b	miR-518d	miR-136	miR-373	miR-19a	let-7e	miR-34c	miR-29c	miR-15b	miR-181b-1
miR-498	miR-518b	miR-516-1	miR-299-5p		miR-20a	let-7g			miR-16-1	miR-181-b2
miR-520e	miR-526a-1	miR-518a-2	miR-337-5p		miR-19b-1	let-7c			miR-16-2	miR-181c
miR-512-1	miR-520c	miR-517c	miR-369-5p		miR-92a-1	let-7f				miR-181d
miR-515-1	miR-518c	miR-520h	miR-370			let-7i				
miR-519-e	miR-524	miR-521-1	miR-376a							
miR-520-f	miR-517a	miR-522	miR-379							
miR-515-2	miR-519d	miR-519a-1	miR-382							
miR-519c	miR-521-2	miR-527	miR-409-3p							
miR-1283-1	miR-520d	miR-516-1	miR-410							
miR-520a	miR-517b	miR-1283-2	miR-411							
miR-526b	miR-520g	miR-516-2	miR-431							
miR-519b	miR-516b-2	miR-519a-2	miR-487b							
miR-525	miR-526a-2		miR-539							
			miR-541							
			miR-543							
			miR-654-5p							
			miR-758							
			miR-889							

Table 1: miRNA clusters that include miRNAs known to be expressed during pregnancy.

Miura et al. indicated the presence of 82 miRNAs predominantly produced by the placenta, of which 24 significantly decreased after delivery. These were identified as "pregnancy-associated miRNAs". Of these, 87.5% were clustered on 19q13.42 or 14q32. The six miRNAs that presented the most significant reduction in plasma after pregnancy termination, and thus considered as placental-derived, were: miR-526b, miR-517c, miR-515-3p, miR-517a, miR-518b and miR-323p [6]. According to Morales-Prieto, miRNAs derived from the C19MC increase from the first to the third trimester. On the contrary, those from C14MC are upregulated in first trimester placentas [7] and decrease during the third trimester [4]. Kotlabova et al. identified seven miRNAs (miR-516-5p, miR-517, miR-518b, miR520b, miR-520h, miR-525, miR-526) with diagnostic potential based on their expression in the full-term placenta, their presence in maternal plasma throughout pregnancy and their absence in non-pregnant women [14]. Additionally, Luo et al. found five miRNAs specifically expressed in the placenta, some of them similar to those reported by other authors: miR 512-3p, miR-517a, miR-517a, miR-518a, and miR-519a [9]. Extracellular, chromosome 21-derived, miRNAs (miR-99a, miR-125b-2 and miR-155) can also be overexpressed in pregnant women compared to non-pregnant women [15].

Clearly much work is needed to understand which of these "pregnancy-related" miRNAs are in fact biologically relevant to pregnancy.

Another miRNA present in normal pregnancy human placentas is miR-126. This miRNA participates in angiogenesis and targets a negative regulator of vascular endothelial growth factor 1 (VEGF1). It has thus been proposed as a possible therapeutic target in preeclampsia [16]. Gu et al. showed that third trimester placentas have significantly upregulated miRNAs from let-7 and miR-34 families, and miR-29a, miR-195, and miR-181c, compared to those of first trimester placentas [7]. The miR-34 family targets the oncosuppressor protein p53, thus contributing to downstream effects of proliferation and induction of apoptosis. This family includes three members: miR-34a, 34b, and 34c [17]. The miR-29 family, comprising three miRNAs, up-regulates p53 and may induce apoptosis in a p53-independent manner [18]. On the other hand, dysregulation of miRNAs from the let-7 family, which includes seven miRNAs, has been related to a state of decreased cellular differentiation, and to cancer [19]. Lastly, miR-195 belongs to the miR-15/16 family and plays a role in cell cycle regulation and apoptosis [20].

miRNAs that regulate the innate and specific immune system are expressed throughout pregnancy. In contrast, miRNAs that promote cell differentiation and control cell cycle progression are mainly expressed in third trimester placentas [7]. Some miRNAs present during the third trimester can also modulate apoptotic pathways by targeting p53. The differential expression of miRNAs throughout pregnancy may reflect changes in placental physiology. However, the mechanisms regulating miRNA expression in human placenta are still not well understood.

miRNAs may also differ between healthy and abnormal pregnancies. Wessels et al. used a porcine model to compare miRNAs from endometrium associated with healthy embryos and trophoblast associated with healthy embryos, finding significantly higher expression of miR-27a, miR-29a, miR-29c, and miR-99a in healthy endometrium. Conversely, only miR-29c was increased in endometrium associated with arresting embryos, in relation to healthy embryos [21]. miRNAs have also been associated with preeclampsia, preterm labor, and intrauterine growth restriction, but these will not be discussed here.

Additional miRNAs expressed during the gestational period that may exert immunomodulatory functions are described below.

miRNAs as Immunomodulators during Pregnancy

miRNAs that regulate innate and adaptive immune responses can be transferred by extracellular vesicles [22] and are strongly expressed throughout pregnancy [7]. It is believed that miRNAs belonging to C19MC have immunomodulatory functions that may prevent the fetus from being attacked by the mother's immune system [10]. Nonetheless, there is little information regarding the immunomodulatory mechanisms of these miRNAs.

Interestingly, by down-regulating miR-155, progesterone suppresses TLR-triggered immune responses during pregnancy via increased Socs1 expression [23]. miR-155 can also affect trophoblast migration and differentiation, and has been found to be upregulated in the preeclamptic placenta [24].

With regards to the miR-17-92a cluster, miR-17 and miR-19b also exert immunomodulatory abilities by targeting phosphatase and tensin homolog (PTEN), transforming growth factor β1 (TGF β-1) and TGF β-RII, mRNA [25]. Nevertheless, the role of miR-17 and 19b in pregnancy and pregnancy complications has not been consistent among studies. Doridot et al. found that increased expression may be associated with preeclampsia. This may be because miR-17 targets ephrin type B receptor 4 (EPHB4) and ephrin type B receptor 2 (EFNB2), two kinases involved in angiogenesis, resulting in the inhibition of spiral artery invasion by extravillous trophoblasts [26,27]. On the contrary, Ventura et al. showed that miR-17 and 19b are expressed at early stages of normal pregnancy, and that their down-regulation was associated with pregnancy loss [25]. Additionally, miR-17 is overexpressed in high-receptive endometria in a bovine embryo implantation model compared to low-receptive endometria [28]. Further studies are warranted to clarify which miRNAs from the 17-92 cluster, or which targets, may be participating in different pregnancy outcomes.

miR-29 can also participate in the regulation of innate and specific immune responses, as it may down-regulate interferon-γ (IFN-γ production by targeting IFN-γ mRNA in NK cells, $CD4^+$ and $CD8^+$ cells [29].

miRNAs Related to HLAs and NK Cells

Human leukocyte antigen G (HLA-G), which is a non-classical histocompatibility molecule that is highly expressed by trophoblast cells [30], can be down-regulated by miR-152, miR19a, and miR-148 [31-33]. HLA-C is also down-regulated by miR-148a [34]. Decreased expression of HLA-G by trophoblasts results in decreased leukocyte immunoglobulin-like receptor-B1 (LILRB1) recognition, preventing the subsequent inhibition of natural killer (NK) cell killing. It is noteworthy that in healthy placentas the levels of miR-152 and miR-148a are decreased compared with other tissues in which HLA-G is not expressed [35].

The immunomodulatory abilities of some miRNAs were initially described in cancer cells and transplants [36]. For example, it has been proposed that down-regulation of miR-152 in breast cancer cells may promote HLA-G expression and protect the tumor from NK cell lysis [32].

miR-181 promotes the development of NK cells through the suppression of nemo-like kinase, an inhibitor of Notch signaling [37]. miR-181 is up-regulated in third trimester placentas compared to the first trimester [7]. This finding is relevant, considering the importance of NK inhibition during the first trimester as part of pregnancy's required immunoregulation.

miRNAs as Regulators of $CD4^+$ T helper Lymphocyte Subsets

$CD4^+$ T lymphocyte subsets play a key role in immune system regulation during the gestational period. Initially, the Th1/Th2 paradigm was used to explain T lymphocyte behavior during pregnancy [38]. Although the predominance of Th2 cytokines and suppressed Th1-type cytokines during pregnancy has been reported by many authors [39-41], the sole use of these subsets to explain the behavior of the immune system during pregnancy over-simplifies the complex modulation that occurs. Clearly, a shift towards Th2 responses, overruling Th1-type immunity, is not sufficient to explain maternal tolerance to the fetus. Thus, the paradigm has been expanded into the Th1/Th2/Th17/Treg paradigm [39]. And it may expand further in the future to incorporate follicular helper T cells [42,43] and Th9 cells [44].

The presence of regulatory T lymphocytes ($CD4^+CD25^+FoxP3^+$ Tregs) is crucial for healthy pregnancies [45]. Four different Treg subsets have been described during pregnancy; these differ in their expression of CD45RA and HLA-DR molecules. $DRlow^+CD45RA^-$ and $DRhigh^+CD45RA^-$ Treg cells decrease in number, but not in suppressive activity, during the 10^{th} and 20^{th} weeks of pregnancy, and maintain the same levels until term. Moreover, the percentage of naïve $DR^-CD45RA^+$ Treg lymphocytes increases at week 10 and remains stable throughout pregnancy. Lastly, $DR^-CD45RA^-$ Tregs do not change in number during normal pregnancy [46]. It is believed that changes in the percentages of these subsets may participate in the development of pregnancy disorders [47]. Pregnancy promotes the expression of forkhead box P3 (FoxP3) in maternal $CD4^+$ T lymphocytes with fetal specificity. However, Th1 polarization may block pregnancy-induced Tregs against fetal antigens and lead to fetal loss [48].

Tregs are clearly talented players with regards to immunomodulation during pregnancy, and they may also be regulated by miRNAs. Unfortunately, the information regarding Treg-related genes targeted by miRNAs remains limited. miR-155 targets the transcription factor FoxP3, which contributes to the development of regulatory T cells, although it does not participate in their function [49]. Another miRNA cluster that is expressed in Treg cells is miR-17-92a [50], which comprises miR-17, miR-20, miR-18a, miR-19a, miR-19b, and miR-92a. From this cluster, miR-17 and miR-19b are able to inhibit inducible Treg (iTreg) differentiation in mice, by targeting PTEN, TGFβ-RII and cAMP responsive element binding protein 1 (CREB1), promoting Th1 responses through IFN-γ production [51]. Interestingly, miR-19a has been found to be overexpressed in the cervix of women who develop preterm birth [52] although this finding has not yet been related to altered Treg function [52]. On the other hand, miR-17 and 92a, which are highly expressed in Treg cells, are essential for the fitness of these cells, as they play a role in their ability to proliferate and their apoptotic pathways [50]. Unfortunately, the precise molecular pathways of these miRNAs in Tregs remain unknown.

Known roles for miRNAs, and/or pregnancy-related miRNAs, in the regulation of some cells of the immune system are described below:

miRNAs and Th17 cell function

Th17 cells are a subset of $CD4^+$ cells that produce interleukin 17 (IL-17) and express receptor-related orphan receptor (ROR) C2 [39,53]. They are involved in protection against microbes and participate in autoimmune diseases [54]. Santner-Nanan et al. first found a decreased number of Th17 cells during pregnancy compared with non-pregnant women [55]. Although many authors have not reported changes in numbers of Th17 cells throughout normal pregnancy [56], Lissauer et al., using a prospective analysis, reported a 60% decrease in the number of circulating Th17 lymphocytes after the first trimester of normal pregnancy [57]. This finding may reflect a possible role of these cells in implantation, an observation that may require further studies. These researchers also report that Th17 and Th1 cells are three and two times higher, respectively, in women with recurrent miscarriages compared to those with normal pregnancies [57].

It is known that miR-326 promotes Th17 differentiation by targeting Ets-1 [58,59]. In addition, miR-155 positively regulates Th17 differentiation and IL-17 production but not IL-10 or TGF-β secretion. This regulation is due to a decrease in the suppressor of cytokine signaling 1 (Socs1), a negative regulator of JAK-STAT signaling [60]. Further research regarding miRNAs that lead to Th17 differentiation during pregnancy is warranted.

Th9-related miRNAs

Th9 cells are involved in responses against helminth antigens and allergens [61,62]. These cells also participate in the pro-inflammatory process in allergic asthma [63] and promote $CD8^+$ T lymphocyte antitumor activity [64]. Nonetheless, information regarding miRNAs related to Th9 cells is scarce, and the role of Th9 lymphocytes in immune system regulation during pregnancy has not yet been studied.

B cell function and miRNAs

miR-125b, which may be overexpressed in plasma samples from pregnant women, inhibits B cell differentiation by binding the interferon regulatory protein-4 (IRF-4) and the B lymphocyte-induced maturation protein-1 (BLIMP-1), which are required for plasma cell differentiation [65]. Moreover, constitutive expression of miR-34a affects B cell development from the pro-B cell to the pre-B cell transition by targeting transcription factor Fox1 [66]. This may be relevant in pregnancy, considering that miRNAs from the miR-34 family can be up-regulated in the third trimester.

miRNAs related to dendritic cell function

Lastly, activated plasmacytoid (lymphoid) dendritic cells (BDCA-2+) promote Th2 differentiation in normal pregnancy [67]. These cells show high expression of a miRNA related to angiogenesis, miR-126, which controls the survival and function of dendritic cells. miR-126 regulates innate immunity by affecting the gene expression of TLR 7, 9 and VEGFR2 [68]. The presence of this miRNA is not only relevant for immune system regulation; it is also relevant for placental angiogenesis. The importance of miR-26 during pregnancy is supported by its decreased expression in patients with idiopathic recurrent pregnancy loss [69].

The role of some miRNAs that may affect immune system behavior during pregnancy is shown in Table 2.

Conclusion

Given the importance of miRNAs as regulators of multiple processes, it is a great advance to be able to identify miRNAs that may behave as biomarkers for normal pregnancy and disease. However, additional studies are required to clarify the role of these miRNAs in pregnancy, as well as their target genes and their final effects during normal pregnancy or pregnancy complications.

We are just starting to understand the complex regulation related to miRNAs.

Interestingly, different miRNAs from the same cluster may promote contrasting behaviors from immune system cells. Thus, the assessment of putative miRNA target genes is essential to understand immune system modulation by miRNAs.

It is noteworthy that many clusters known as "pregnancy-related" comprise miRNAs that participate in the regulation of the immune system, but many others that also contribute to leukocyte behavior during pregnancy are not within these reported clusters. This shows that we have not yet deciphered the full spectrum of pregnancy-related miRNAs.

Even though this review concentrates on pregnancy-related miRNAs and their participation in the regulation of the immune system, several other factors, such as cytokines and hormones, also participate in the regulation of Tregs and other $CD4^+$ cell subsets during pregnancy. Further studies of the miRNAs present at the maternal-fetal interface or in pregnant women's plasma that can regulate leukocytes will enhance our understanding of immune system modulation during pregnancy.

miRNA	Targets	Function of miRNA	Model	Reference	Normal pregnancy status
miR-148	HLA-G	Down-regulates HLA-G expression	JEG-3 cells Human placenta (extravillous trophoblast)	[32,35]	Down-regulated
miR-148a	HLA-C	Down-regulates HLA-C expression	Cell line	[34]	Down-regulated
miR-152	HLA-G	Down-regulates HLA-G expression	Human placenta (extravillous trophoblast)	[35]	Down-regulated
miR-181	Suppression of nemo-like kinase	Development of NK cells	Human CD34+cells Human placenta	[37]	Down-regulated in 1st trimester Up-regulated in 3rd trimester
miR-155	FoxP3	Promotes development of Treg cells in thymus and spleen	miR-155 deficient mice	[49]	Down-regulated (progesterone down-regulates miR-155)
miR-155	Socs1	Promotes Th17 differentiation and IL-17 production	BALB/c T cells	[60]	Down-regulated (progesterone down-regulates miR-155)
miR-17 and 19b	miR-19b: PTEN miR-17: TGFβRII and CREB1	Inhibit iTreg differentiation	Mice	[51]	Some miRNAs of this cluster are up-regulated in normal pregnancy
miR-17 and 19b	PTEN, TGFβ−RII and TGFβ1	Block target mRNA	Villous human samples	[25]	Some miRNAs of this cluster are up-regulated in normal pregnancy
miR-17, 92a	Presumed to target multiple signaling molecules	Regulate proliferation and apoptosis of Tregs	miR-17-92 cluster deficient mice	[50]	Up-regulated in normal pregnancy
miR-19a	HLA-G	Down-regulates HLA-G expression	BALB/c mice	[33]	Down-regulated
miR-326	Ets-1	Down-regulates Ets expression and promotes Th17 differentiation	Patients with multiple sclerosis and mice with experimental autoimmune encephalomyelitis	[58,59]	Unknown Presumed to be down-regulated in normal pregnancy
miR-29a	IFN-γ mRNA	Down-regulates IFN-γ in NK, CD4+ an CD8+ cells	Mice infected with Listeria monocytogenes and Mycobaterium bovis	[29]	Up-regulated in normal third trimester placentas
miR-29a	p85-αvδχδχ42	Up-regulates p53, promotes apoptosis in p53 independent manner	HeLa cells Porcine model Human placentas	[7,18,21]	Up-regulated in endometrium and trophoblast associated with normal pregnancy Up-regulated in normal third trimester placentas
miR-125b	IRF-4 and BLIMP-1	Affects plasma cell differentiation	Pregnant human plasma samples	[65]	Up-regulated
miR-126	TLR7, 9 and VEGFR2	Survival and function of plasmacytoid dendritic cells Promotes angiogenesis	Knockout mice	[68,69]	Present in normal pregnancy Decreased in idiopathic recurrent pregnancy loss
miR-34a	Foxp1	Blocks B cell development	C57BL/6 mice, WEHI-231 cells and 70Z/3 cells	[66]	miRNA-34 family up-regulated in third trimester

Table 2: miRNAs that may affect immune system behavior during pregnancy.

References

1. Bidarimath M, Khalaj K, Wessels JM, Tayade C (2014) MicroRNAs, immune cells and pregnancy. Cell Mol Immunol 11: 538-547.
2. Lee RC, Feinbaum RL, Ambros V (1993) The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell 75: 843-854.
3. Gilad S, Meiri E, Yogev Y, Benjamin S, Lebanony D, et al. (2008) Serum microRNAs are promising novel biomarkers. PLoS One 3: e3148.
4. Morales-Prieto DM, Chaiwangyen W, Ospina-Prieto S, Schneider U, Herrmann J, et al. (2012) MicroRNA expression profiles of trophoblastic cells. Placenta 33: 725-734.
5. Morales-Prieto DM, Ospina-Prieto S, Chaiwangyen W, Schoenleben M, Markert UR (2013) Pregnancy-associated miRNA-clusters. J Reprod Immunol 97: 51-61.
6. Miura K, Miura S, Yamasaki K, Higashijima A, Kinoshita A, et al. (2010) Identification of pregnancy-associated microRNAs in maternal plasma. Clin Chem 56: 1767-1771.
7. Gu Y, Sun J, Groome LJ, Wang Y (2013) Differential miRNA expression profiles between the first and third trimester human placentas. Am J Physiol Endocrinol Metab 304: E836-843.
8. Luo L, Ye G, Nadeem L, Fu G, Yang BB, et al. (2012) MicroRNA-378a-5p promotes trophoblast cell survival, migration and invasion by targeting Nodal. J Cell Sci 125: 3124-3132.
9. Luo SS, Ishibashi O, Ishikawa G, Ishikawa T, Katayama A, et al. (2009) Human villous trophoblasts express and secrete placenta-specific microRNAs into maternal circulation via exosomes. Biol Reprod 81: 717-729.
10. Bullerdiek J, Flor I (2012) Exosome-delivered microRNAs of "chromosome 19 microRNA cluster" as immunomodulators in pregnancy and tumorigenesis. Mol Cytogenet 5: 27.
11. Donker RB, Mouillet JF, Chu T, Hubel CA, Stolz DB, et al. (2012) The expression profile of C19MC microRNAs in primary human trophoblast cells and exosomes. Mol Hum Reprod 18: 417-424.
12. Noguer-Dance M, Abu-Amero S, Al-Khtib M, Lefèvre A, Coullin P, et al. (2010) The primate-specific microRNA gene cluster (C19MC) is imprinted in the placenta. Hum Mol Genet 19: 3566-3582.
13. Mogilyansky E, Rigoutsos I (2013) The miR-17/92 cluster: a comprehensive update on its genomics, genetics, functions and increasingly important and numerous roles in health and disease. Cell Death Differ 20: 1603-1614.
14. Kotlabova K, Doucha J, Hromadnikova I (2011) Placental-specific microRNA in maternal circulation – identification of appropriate pregnancy-associated microRNAs with diagnostic potential. J Reprod Immunol 89: 185-191.
15. Kotlabova K, Doucha J, Chudoba D, Calda P, Dlouha K, et al. (2013) Extracellular chromosome 21-derived microRNAs in euploid & aneuploid pregnancies. Indian J Med Res 138: 935-943.
16. Yan T, Liu Y, Cui K, Hu B, Wang F, et al. (2013) MicroRNA-126 regulates EPCs function: implications for a role of miR-126 in preeclampsia. J Cell Biochem 114: 2148-2159.
17. Misso G, Di Martino MT, De Rosa G, Farooqi AA4, Lombardi A, et al. (2014) Mir-34: a new weapon against cancer? Mol Ther Nucleic Acids 3: e194.
18. Park SY, Lee JH, Ha M, Nam JW, Kim VN (2009) miR-29 miRNAs activate p53 by targeting p85 alpha and CDC42. Nat Struct Mol Biol 16: 23-29.
19. Roush S, Slack FJ (2008) The let-7 family of microRNAs. Trends Cell Biol 18: 505-516.
20. Zhou Y, Jiang H, Gu J, Tang Y, Shen N, et al. (2013) MicroRNA-195 targets ADP-ribosylation factor-like protein 2 to induce apoptosis in human embryonic stem cell-derived neural progenitor cells. Cell Death Dis 4: e695.
21. Wessels JM, Edwards AK, Khalaj K, Kridli RT, Bidarimath M, et al. (2013) The microRNAome of pregnancy: deciphering miRNA networks at the maternal-fetal interface. PLoS One 8: e72264.
22. Fernández-Messina L, Gutiérrez-Vázquez C, Rivas-García E, Sánchez-Madrid F, de la Fuente H (2015) Immunomodulatory role of microRNAs transferred by extracellular vesicles. Biol Cell 107: 61-77.
23. Sun Y, Cai J, Ma F, Lü P, Huang H, et al. (2012) miR-155 mediates suppressive effect of progesterone on TLR, TLR4-triggered immune response. Immunol Lett 146: 25-30.
24. Fu G, Brkic J, Hayder H, Peng C (2013) MicroRNAs in Human Placental Development and Pregnancy Complications. Int J Mol Sci 14: 5519-5544.
25. Ventura W, Koide K, Hori K, Yotsumoto J, Sekizawa A, et al. (2013) Placental expression of microRNA-17 and -19b is down-regulated in early pregnancy loss. Eur J Obstet Gynecol Reprod Biol 169: 28-32.
26. Chen DB, Wang W (2013) Human placental microRNAs and preeclampsia. Biol Reprod 88: 130.
27. Doridot L, Miralles F, Barbaux S, Vaiman D (2013) Trophoblasts, invasion, and microRNA. Front Genet 4: 248.
28. Ponsuksili S, Tesfaye D, Schellander K, Hoelker M, Hadlich F, et al. (2014) Differential Expression of miRNAs and Their Target mRNAs in Endometria Prior to Maternal Recognition of Pregnancy Associates with Endometrial Receptivity for In Vivo- and In Vitro-Produced Bovine Embryos. Biol Reprod 91: 135.
29. Ma F, Xu S, Liu X, Zhang Q, Xu X, et al. (2011) The microRNA miR-29 controls innate and adaptive immune responses to intracellular bacterial infection by targeting interferon-γ. Nat Immunol 12: 861-869.
30. Hunt JS, Petroff MG, McIntire RH, Ober C (2005) HLA-G and immune tolerance in pregnancy. FASEB J 19: 681-693.
31. Kempers AC, Van Dijk M, Oudejans C (2012) How miRNAs affect the expression of human leukocyte antigen G in pregnancy. Am J Immunol 8: 136-145.
32. Zhu XM, Han T, Wang XH, Li YH, Yang HG, et al. (2010) Overexpression of miR-152 leads to reduced expression of human leukocyte antigen-G and increased natural killer cell mediated cytolysis in JEG-3 cells. Am J Obstet Gynecol 202: 592.
33. Castelli EC, Moreau P, Oya e Chiromatzo A, Mendes-Junior CT, Veiga-Castelli LC, et al. (2009) In silico analysis of microRNAS targeting the HLA-G 3' untranslated region alleles and haplotypes. Hum Immunol 70: 1020-1025.
34. Kulkarni S, Savan R, Qi Y, Gao X, Yuki Y, et al. (2011) Differential microRNA regulation of HLA-C expression and its association with HIV control. Nature 472: 495-498.
35. Manaster I, Goldman-Wohl D, Greenfield C, Nachmani D, Tsukerman P, et al. (2012) MiRNA-mediated control of HLA-G expression and function. PLoS One 7: e33395.
36. Veit TD, Chies JA (2009) Tolerance versus immune response -- microRNAs as important elements in the regulation of the HLA-G gene expression. Transpl Immunol 20: 229-231.
37. Cichocki F, Felices M, McCullar V, Presnell SR, Al-Attar A, et al. (2011) Cutting edge: microRNA-181 promotes human NK cell development by regulating Notch signaling. J Immunol 187: 6171-6175.
38. Laresgoiti-Servitje E, Gómez-López N, Olson DM (2010) An immunological insight into the origins of pre-eclampsia. Hum Reprod Update 16: 510-524.
39. Saito S, Nakashima A, Shima T, Ito M (2010) Th1/Th2/Th17 and regulatory T-cell paradigm in pregnancy. Am J Reprod Immunol 63: 601-610.
40. Miyazaki S, Tsuda H, Sakai M, Hori S, Sasaki Y, et al. (2003) Predominance of Th2-promoting dendritic cells in early human pregnancy decidua. J Leukoc Biol 74: 514-522.
41. Saito S, Sakai M, Sasaki Y, Tanebe K, Tsuda H, et al. (1999) Quantitative analysis of peripheral blood Th0, Th, Th2 and the Th1:Th2 cell ratio during normal human pregnancy and preeclampsia. Clin Exp Immunol 117: 550-555.

42. Zhang X, Mozeleski B, Lemoine S, Dériaud E, Lim A, et al. (2014) CD4 T cells with effector memory phenotype and function develop in the sterile environment of the fetus. Sci Transl Med 6: 238ra72.
43. An L-F, Zhang X-H, Sun X-T, Zhao L-H, Li S, et al. (2015) Unexplained infertility patients have increased serum IL-, IL-4, IL-6, IL-8, IL-, TNFa, IFNγ and increased Tfh/CD4 T cell ratio: increased Tfh and IL-21 strongly correlate with presence of autoantibodies. Immunol Invest 44: 164-173.
44. Liao W, Spolski R, Li P, Du N, West EE, et al. (2014) Opposing actions of IL-2 and IL-21 on Th9 differentiation correlate with their differential regulation of BCL6 expression. Proc Natl Acad Sci U S A 111: 3508-3513.
45. Guerin LR, Prins JR, Robertson SA (2009) Regulatory T-cells and immune tolerance in pregnancy: a new target for infertility treatment? Hum Reprod Update 15: 517-535.
46. Steinborn A, Schmitt E, Kisielewicz A, Rechenberg S, Seissler N, et al. (2012) Pregnancy-associated diseases are characterized by the composition of the systemic regulatory T cell (Treg) pool with distinct subsets of Tregs. Clin Exp Immunol 167: 84-98.
47. Loewendorf AI, Nguyen TA, Yesayan MN, Kahn DA (2014) Normal human pregnancy results in maternal immune activation in the periphery and at the uteroplacental interface. PLoS One 9: e96723.
48. Xin L, Ertelt JM, Rowe JH, Jiang TT, Kinder JM, et al. (2014) Cutting edge: committed Th1 CD4+ T cell differentiation blocks pregnancy-induced Foxp3 expression with antigen-specific fetal loss. J Immunol 192: 2970-2974.
49. Kohlhaas S, Garden OA, Scudamore C, Turner M, Okkenhaug K, et al. (2009) Cutting edge: the Foxp3 target miR-155 contributes to the development of regulatory T cells. J Immunol 182: 2578-2582.
50. Skinner JP, Keown AA, Chong MM (2014) The miR-17 ~ 92a cluster of microRNAs is required for the fitness of Foxp3+ regulatory T cells. PLoS One 9: e88997.
51. Jiang S, Li C, Olive V, Lykken E, Feng F, et al. (2011) Molecular dissection of the miR-17-92 cluster's critical dual roles in promoting Th1 responses and preventing inducible Treg differentiation. Blood 118: 5487-5497.
52. Elovitz MA, Brown AG, Anton L, Gilstrop M, Heiser L, et al. (2014) Distinct cervical microRNA profiles are present in women destined to have a preterm birth. Am J Obstet Gynecol 210: 221.
53. Polese B, Gridelet V, Araklioti E, Martens H, Perrier d'Hauterive S, et al. (2014) The Endocrine Milieu and CD4 T-Lymphocyte Polarization during Pregnancy. Front Endocrinol (Lausanne) 5: 106.
54. Annunziato F, Cosmi L, Santarlasci V, Maggi L, Liotta F, et al. (2007) Phenotypic and functional features of human Th17 cells. J Exp Med 204: 1849-1861.
55. Santner-Nanan B, Peek MJ, Khanam R, Richarts L, Zhu E, et al. (2009) Systemic increase in the ratio between Foxp3+ and IL-17-producing CD4+ T cells in healthy pregnancy but not in preeclampsia. J Immunol 183: 7023-7030.
56. Nakashima A, Ito M, Yoneda S, Shiozaki A, Hidaka T, et al. (2010) Circulating and decidual Th17 cell levels in healthy pregnancy. Am J Reprod Immunol 63: 104-109.
57. Lissauer D, Goodyear O, Khanum R, Moss PA, Kilby MD (2014) Profile of maternal CD4 T-cell effector function during normal pregnancy and in women with a history of recurrent miscarriage. Clin Sci (Lond) 126: 347-354.
58. Du C, Liu C, Kang J, Zhao G, Ye Z, et al. (2009) MicroRNA miR-326 regulates TH-17 differentiation and is associated with the pathogenesis of multiple sclerosis. Nat Immunol 10: 1252-1259.
59. Saito S, Nakashima A, Ito M, Shima T (2011) Clinical implication of recent advances in our understanding of IL-17 and reproductive immunology. Expert Rev Clin Immunol 7: 649-657.
60. Yao R, Ma YL, Liang W, Li HH, Ma ZJ, et al. (2012) MicroRNA-155 modulates Treg and Th17 cells differentiation and Th17 cell function by targeting SOCS1. PLoS One 7: e46082.
61. Anuradha R, George PJ, Hanna LE, Chandrasekaran V, Kumaran P, et al. (2013) IL-4-, TGF-ß-, and IL-1-dependent expansion of parasite antigen-specific Th9 cells is associated with clinical pathology in human lymphatic filariasis. J Immunol 191: 2466-2473.
62. Geginat J, Paroni M, Maglie S, Alfen JS, Kastirr I, et al. (2014) Plasticity of human CD4 T cell subsets. Front Immunol 5: 630.
63. Staudt V, Bothur E, Klein M, Lingnau K, Reuter S, et al. (2010) Interferon-regulatory factor 4 is essential for the developmental program of T helper 9 cells. Immunity 33: 192-202.
64. Lu Y, Hong S, Li H, Park J, Hong B, et al. (2012) Th9 cells promote antitumor immune responses in vivo. J Clin Invest 122: 4160-4171.
65. Gururajan M, Haga CL, Das S, Leu CM, Hodson D, et al. (2010) MicroRNA 125b inhibition of B cell differentiation in germinal centers. Int Immunol 22: 583-592.
66. Rao DS, O'Connell RM, Chaudhuri AA, Garcia-Flores Y, Geiger TL, et al. (2010) MicroRNA-34a perturbs B lymphocyte development by repressing the forkhead box transcription factor Foxp1. Immunity 33: 48-59.
67. Darmochwal-Kolarz D, Rolinski J, Tabarkiewicz J, Leszczynska-Gorzelak B, Buczkowski J, et al. (2003) Myeloid and lymphoid dendritic cells in normal pregnancy and pre-eclampsia. Clin Exp Immunol 132: 339-344.
68. Agudo J, Ruzo A, Tung N, Salmon H, Leboeuf M, et al. (2014) The miR-126-VEGFR2 axis controls the innate response to pathogen-associated nucleic acids. Nat Immunol 15: 54-62.
69. El-Shorafa HM, Sharif FA (2013) Dysregulation of micro-RNA contributes to the risk of unexplained recurrent pregnancy loss. Int J Reprod Contracept Obstet Gynecol 2: 330-335.