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

Estibaliz Laresgoiti-Servitje 1,2*
1Basic Medical Sciences, TEC-ABC School of Medicine, Tecnológico de Monterrey, Mexico
2National Institute of Perinatology “Isidro Espinosa de Los Reyes”, Mexico

*Corresponding author: Estibaliz 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: estibaliz.laresgoiti@itesm.mx

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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 fetomaternal 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 (M14MC) 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.
Table 1: miRNA clusters that include miRNAs known to be expressed during pregnancy.

<table>
<thead>
<tr>
<th>C19MC</th>
<th>C14MC</th>
<th>miR-371-3</th>
<th>miR-17-92</th>
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<th>miR-29</th>
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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 preclampsia, 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 preclampic 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+CD25FoxP3+ 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 D RHigh‘CD45RA-’ Treg cells decrease in number, but not in suppressive activity, during the 10th and 20th 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, TGFB-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 TGFB-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.
<table>
<thead>
<tr>
<th>miRNA</th>
<th>Targets</th>
<th>Function of miRNA</th>
<th>Model</th>
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<td>Human placenta (extravillous trophoblast)</td>
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<td>Down-regulated (progesterone down-regulates miR-155)</td>
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<td>Socs1</td>
<td>Promotes Th17 differentiation and IL-17 production</td>
<td>BALB/c T cells</td>
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<td>Down-regulated (progesterone down-regulates miR-155)</td>
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<td>Up-regulated in normal third trimester placentas</td>
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<td>Up-regulates p53, promotes apoptosis in p53 independent manner</td>
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<td>Up-regulated in endometrium and trophoblast associated with normal pregnancy</td>
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<td>Affects plasma cell differentiation</td>
<td>Pregnant human plasma samples</td>
<td>[65]</td>
<td>Up-regulated</td>
</tr>
<tr>
<td>miR-126</td>
<td>TLR7, 9 and VEGFR2</td>
<td>Survival and function of plasmacytoid dendritic cells</td>
<td>Knockout mice</td>
<td>[68,69]</td>
<td>Present in normal pregnancy Decreased in idiopathic recurrent pregnancy loss</td>
</tr>
<tr>
<td>miR-34a</td>
<td>Foxp1</td>
<td>Blocks B cell development</td>
<td>C57BL/6 mice, WEHI-231 cells and 702/3 cells</td>
<td>[66]</td>
<td>miRNA-34 family up-regulated in third trimester</td>
</tr>
</tbody>
</table>

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


43. An I-F, Zhang X-H, Sun X-T, Zhao L-H, Li S, et al. (2015) Unexplained infertility patients have increased serum IL-4, IL-6, IL-8, TNFα, IFNγ and increased Th1/CD4+ T cell ratio: increased Th1 and IL-21 strongly correlate with presence of autoantibodies. Immunol Invest 44: 164-173.


