REPRODUCTION
REVIEW

MicroRNAs: crucial regulators of placental development

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Abstract

MicroRNAs (miRNAs) are small non-coding single-stranded RNAs that are integral to a wide range of cellular processes mainly through the regulation of translation and mRNA stability of their target genes. The placenta is a transient organ that exists throughout gestation in mammals, facilitating nutrient and gas exchange and waste removal between the mother and the fetus. miRNAs are expressed in the placenta, and many studies have shown that miRNAs play an important role in regulating trophoblast differentiation, migration, invasion, proliferation, apoptosis, vasculogenesis/angiogenesis and cellular metabolism. In this review, we provide a brief overview of canonical and non-canonical pathways of miRNA biogenesis and mechanisms of miRNA actions. We highlight the current knowledge of the role of miRNAs in placental development. Finally, we point out several limitations of the current research and suggest future directions.

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Introduction

MicroRNAs (miRNAs) have been established as major regulators of gene expression and are involved in many biological processes (Vasudevan 2012, Jonas & Izaurralde 2015). Since their discovery in 1993, miRNAs have been of great interest to researchers and many new advances have been made in understanding their structure, regulation and mechanisms of action (Lee *et al.* 1993, Jonas & Izaurralde 2015). Most studies have shown that miRNAs suppress gene expression when bound to the 3′ untranslated region (UTR) of target mRNAs by inhibiting translation and reducing mRNA stability (Behm-Ansmant *et al.* 2006, Chen *et al.* 2010, Miao *et al.* 2016). However, additional modes of action for miRNAs, such as transcriptional regulation and activation of gene expression, have also been reported (Benhamed *et al.* 2012, Vasudevan 2012, Catalanotto *et al.* 2016, Miao *et al.* 2016).

The placenta is a transient organ essential for the survival and development of mammalian embryos (Rossant & Cross 2001). This organ plays critical roles in mediating the exchange of respiratory gases, nutrients and waste products between the mother and the fetus (Rossant & Cross 2001, Regnault *et al.* 2002, Wooding & Burton 2008). In addition, the placenta also acts as an endocrine organ and produces many pregnancy-associated hormones and growth factors that help in sustaining pregnancy, preventing fetus rejection by the mother's immune system and regulating fetal growth (Rossant & Cross 2001, Fu *et al.* 2013*a*, Ji *et al.* 2013).

Placental development is a spatially and temporally regulated process. This allows for increasing oxygen and nutrient demands required by the growing fetus to be met throughout gestation (Wooding & Burton 2008). Improper placental formation gives rise to many pregnancy-associated conditions such as preeclampsia and intrauterine growth restriction (Genbacev *et al.* 1996, Rossant & Cross 2001, Fu *et al.* 2013*a*). In recent years, the role of miRNAs in placentation has been increasingly recognized. In this review, we aim to provide an updated summary of the role of miRNAs in regulating various trophoblast activities and placental development. Dysregulation of miRNAs and their potential involvement in pregnancy complications has been discussed recently (Fu *et al.* 2013*a*, Mouillet *et al.* 2015, Escudero *et al.* 2016, Cai *et al.* 2017) and therefore will not be included in this review.

Overview of microRNAs

miRNAs are endogenous, small non-coding single-stranded RNAs, on average 22 nt in length, and are involved in multiple modes of gene regulation (Truesdell *et al.* 2012, Vasudevan 2012, Havens *et al.* 2014, Valinezhad Orang *et al.* 2014, Jonas & Izaurralde 2015, Catalanotto *et al.* 2016, Xiao *et al.* 2016). miRNAs are processed post- or co-transcriptionally from RNA polymerase II/III transcripts (Ha & Kim 2014). Approximately half of all known miRNA genes are intragenic, contained mostly within the introns and relatively few exons of protein coding genes (de Rie *et al.* 2017). The remaining miRNA genes are transcribed independent of a host gene via their own promoters (Kim & Kim 2007, Fuziwara & Kimura 2015).

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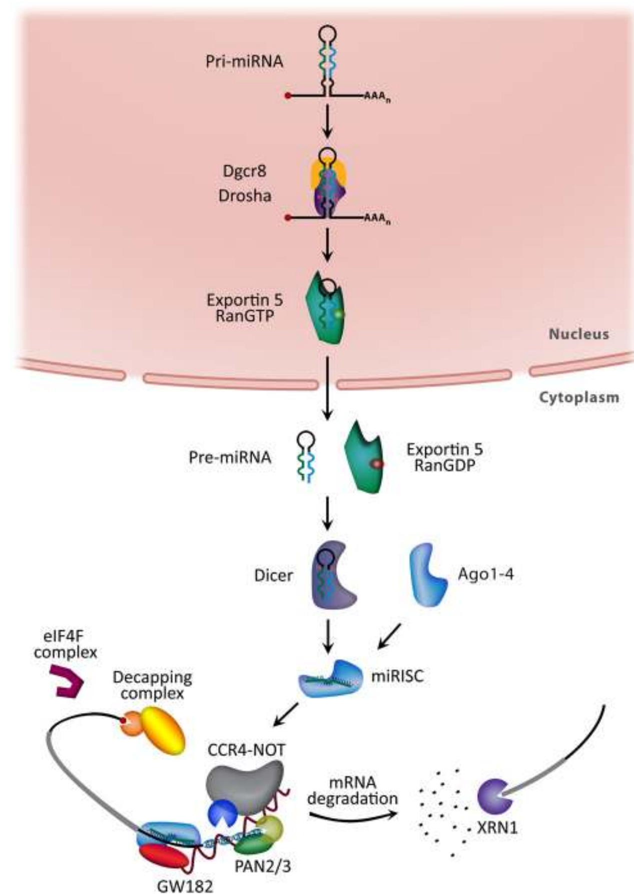

Figure 1 Overview of canonical microRNA biogenesis and mechanism. Canonical miRNA biogenesis is both Drosha- and Dicer-dependent. Following transcription, the primary (pri-) miRNA is identified and cleaved by the endoribonuclease, Drosha, to produce the precursor (pre-) miRNA. Nuclear export of the pre-miRNA is facilitated by the Exportin 5/RanGTP transport system. Once in the cytoplasm, the pre-miRNA is subject to terminal loop cleavage by the endoribonuclease Dicer. After cleavage, the mature miRNA duplex is loaded into the Argonaute family of proteins and the passenger strand is degraded, forming the miRNA-induced silencing complex (miRISC). The gene regulatory power of cytoplasmic miRISC typically culminates in gene silencing by mediating induction of translation inhibition, mRNA poly(A) deadenylation and mRNA degradation via interaction at the 3′ untranslated region of target mRNA. After target association and following recruitment of GW182 and associated proteins into miRISC, translation initiation is inhibited, preventing nascent protein translation of the target mRNA molecule. It is hypothesized that miRISC-induced dissociation of the translation initiation complex, eIF4F, from the 5′ cap of mRNA and/or its functional disruption suppresses translation initiation. Interaction of GW182 with poly(A) binding proteins (PABPC) and poly(A) deadenylase complexes PAN2/3 and CCR4-NOT localizes the 3′ mRNA tail to the miRISC complex, promoting efficient target mRNA deadenylation. Complete poly(A) deadenylation leads to decapping-protein 2 (DCP2)-mediated mRNA decapping, exposing the mRNA to 5′–3′ degradation via the exoribonuclease XRN1.

The vast majority of miRNAs are processed through the canonical biogenesis pathway (Kim *et al.* 2016) (Fig. 1). Canonical miRNA biogenesis begins with the detection of the primary miRNA transcript (pri-miRNA), contained within nascent RNA, by DiGeorge Critical Region 8 (DGCR8) and associated proteins through recognition of the RNA N6-methyladenylated GGAC motif (Alarcon *et al.* 2015). In complex with DGCR8 is the nuclear RNase III endonuclease Drosha which cleaves the pri-miRNA duplex proximal to the base of the characteristic hairpin structure of pri-miRNA. This produces the excised precursor (pre)-miRNA containing a 2 nucleotide 3′ overhang (Han *et al.* 2004). Together, Drosha and DGCR8 are termed the microprocessor complex (Denli *et al.* 2004).

Following pri-miRNA cleavage, the pre-miRNA is exported to the cytoplasm through an exportin 5 (XPO5)/RanGTP complex and then processed by the predominantly cytoplasmic RNase III endonuclease Dicer (Denli *et al.* 2004, Doyle *et al.* 2013). This cleavage, which removes the terminal loop, produces the mature miRNA duplex from pre-miRNA (Zhang *et al.* 2004). The labeling of the two strands of the miRNA duplex is based on the directionality of the strand in the pre-miRNA. The 5′ end of the pre-miRNA hairpin contains the 5p strand and the 3′ end the 3p strand (previously miRNA and miRNA*). Either the 5p or 3p strand of the miRNA duplex can be loaded into the Argonaute (AGO) family of proteins (AGO1–4 in humans) in an ATP-dependent manner (Yoda *et al.* 2010, Ha & Kim 2014); the strand that is loaded into AGO is termed the guide strand.

Several non-canonical miRNA biogenesis pathways have been elucidated (Ruby *et al.* 2007, Babiarz *et al.* 2008, Yang & Lai 2011, Abdelfattah *et al.* 2014, Ha & Kim 2014) and grouped into two general categories: Drosha/DGCR8-independent and Dicer-independent. These non-canonical pathways take advantage of the cellular machinery already in place to produce canonical miRNA by producing Drosha, Dicer and Argonaute substrates from discrete RNA sources such as small hairpin RNAs (shRNA), small nucleolar RNAs and splicing products (Yang & Lai 2011, Castellano & Stebbing 2013, Abdelfattah *et al.* 2014). Drosha/DGCR8-independent pre-miRNAs share a common trait in which separate processing mechanisms produce products which resemble Dicer substrates. For example, mirtrons encompass the group of pre-miRNAs produced from introns during mRNA splicing. Additionally, 7-methylguanosine (m^7G)-capped pre-miRNAs are transcribed such that the nascent RNA does not need Drosha cleavage and can be directly exported from the nucleus through exportin 1 (Xie *et al.* 2013). Moreover, the m^7G cap is thought to be the cause of a strong 3p strand bias. Dicer-independent miRNAs are processed from endogenous shRNA transcripts by Drosha and may be unique in their requirement for AGO2 to complete their processing within the cytoplasm. This group of pre-miRNAs is too short to be processed by Dicer, leading to the 5′ loading of the entire pre-miRNA into AGO2 (Abdelfattah *et al.* 2014). Slicing of the 3p strand and

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3′–5′ trimming creates a strong 5p strand bias. Although non-canonical miRNAs may elicit post-transcriptional silencing capabilities and undergo regulation independent of canonical miRNAs, the vast majority of miRNAs are processed through the canonical biogenesis pathway, requiring both Drosha and Dicer to complete their maturation (Kim *et al.* 2016). However, consistent with their canonical counterparts, these non-canonical miRNAs have been linked to various cellular programs such as proliferation, de/differentiation, immune response, neural development and cellular metabolism (Abdelfattah *et al.* 2014).

Once AGO proteins are loaded and the miRNA duplex unwound, they form the minimal miRNA-induced silencing complex (miRISC) (Kawamata & Tomari 2010, Fabian & Sonenberg 2012). miRISC gains target specificity by recognition of miRNA response elements (MRE) on target RNA molecules, while the degree of complementarity determines, to some extent, the mode of regulation, i.e. direct or indirect gene silencing (Ameres *et al.* 2007, Jonas & Izaurralde 2015). A fully complementary miRNA:MRE promotes AGO2 endonuclease activity and cleavage of the target RNA molecule (Ameres *et al.* 2007). In turn, this also has the consequence of decreased miRNA stability as exact matches promote not only target cleavage but also degradation of the guide miRNA, although the mechanism is not well understood (Ameres & Zamore 2013). What is known is that the guide miRNA must first undergo the 3′ addition of adenosine or uracil which promotes 3′–5′ exonuclease activity, resulting in guide miRNA degradation (Krutzfeldt *et al.* 2005, Ameres *et al.* 2010).

In humans, the frequency of exact matches on target mRNA is rare (Jonas & Izaurralde 2015). The majority of validated MREs contain at least central mismatches to their guide miRNA, preventing AGO2 nuclease activity. As a consequence, AGO2 shifts from RNAi effector to mediator, and along with the non-endonucleolytic AGO family members act to recruit other proteins associated with mRNA stability. This has led to the detection of the miRNA seed region (nucleotides 2–8) that are crucial for many but not all miRNA:MRE interactions (Ellwanger *et al.* 2011, Xu *et al.* 2014, Miao *et al.* 2016). In most cases, miRNAs interact with the 3′ UTR of target mRNAs, resulting in translation inhibition and mRNA deadenylation and decapping (Huntzinger & Izaurralde 2011, Fabian & Sonenberg 2012, Meijer *et al.* 2013, Ipsaro & Joshua-Tor 2015).

To form an miRISC complex capable of post-transcriptional gene silencing, mRNA-bound miRISC recruits the GW182 family of proteins which acts as a scaffold to further recruit effector protein complexes (Behm-Ansmant *et al.* 2006). Both the PAN2–PAN3 and CCR4–NOT deadenylase complexes are recruited through the unstructured, tryptophan (W) repeats of GW182 (Christie *et al.* 2013, Jonas & Izaurralde 2015). PAN2–PAN3 initially catalyzes target mRNA poly(A) deadenylation which is promoted through the interaction of W-repeats to poly(A)-binding proteins (PABPC), bringing both the mRNA poly(A) tail and deadenylase into close proximity (Jonas & Izaurralde 2015). The CCR4–NOT complex completes the deadenylation process and is followed by mRNA decapping facilitated by decapping protein 2 (DCP2) and associated proteins (Behm-Ansmant *et al.* 2006). Decapped and deadenylated mRNA are then degraded from the 5′ end by the 5′–3′ exoribonuclease 1 (XRN1) (Braun *et al.* 2012) (Fig. 1).

While most miRNA studies focus on how miRNAs target mRNAs by binding to MREs at the 3′ UTR to suppress their expression, MREs have also been reported in the 5′ UTR. miRISC interactions within the 5′ UTR have been shown to both promote and suppress translation through mRNA-specific mechanisms, discussed in detail in Vasudevan (2012) and Valinezhad Orang *et al.* (2014). Moreover, cell-state-specific miRNA-mediated translational activation has been observed in human quiescent cells where nuclear AGO2 complexes with Fragile-x-mental-retardation-related protein 1 (FXR1) instead of GW182 (Truesdell *et al.* 2012). This complex was found to interact with nuclear mRNA targets which in turn led to translational activation following export to the cytoplasm (Truesdell *et al.* 2012).

Overview of placental development

Soon after fertilization, asymmetric cell division of the blastomere gives rise to different cell populations, an outer cell layer surrounding an inner cell population (Johnson & Ziomek 1981, Viswanathan *et al.* 2009). The blastocyst is formed when the outer cell layer differentiates into a layer of trophoblasts termed the trophectoderm (TE) and the inner cell population differentiates into the inner cell mass (ICM). The TE will later give rise to the placenta, while the ICM will develop into the embryo and the visceral endoderm (yolk sac) (Viswanathan *et al.* 2009, Maltepe & Fisher 2015).

With the trophectoderm formed, the blastocyst is ready for implantation (Caniggia *et al.* 2000). Implantation starts with the adhesion of the TE onto the receptive decidualized endometrium through a complex network of cell–cell communication events (Red-Horse *et al.* 2004). This leads to the invasion of the blastocyst through the extracellular matrix of the decidua by the proliferating and differentiating trophectoderm layer, embedding it deep into the uterine wall (Red-Horse *et al.* 2004, Noris *et al.* 2005, Wooding & Burton 2008).

Once the blastocyst is embedded within the uterine wall, the process of placenta formation, termed placentation, begins with the differentiation of the TE cells into the different trophoblast lineages (Red-Horse *et al.* 2004, Maltepe & Fisher 2015). Placentation in eutherian mammals is more complex compared to

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marsupial mammals (Moffett & Loke 2006, Carter 2007, Maltepe & Fisher 2015). Moreover, among eutherian mammals, placentation varies considerably in the degree of trophoblast invasiveness from minimal invasion occurring in epitheliochorial placentation (e.g. pigs and sheep), intermediate invasion in endotheliochorial placentation (e.g. dogs and cats) and maximal invasion in hemochorial placentation (e.g. humans and rodents) (Moffett & Loke 2006, Carter 2007, Wooding & Burton 2008).

In humans, placentation consists, in part, of the differentiation and proliferation of the TE to form a branching network of villi that are in direct contact with the maternal circulation while simultaneously maintaining a barrier between the fetal and maternal blood (Kaufmann *et al.* 2004, Wooding & Burton 2008, Schmidt *et al.* 2015). The villi are the functional units of the placenta. They facilitate and respond to the demands of the developing fetus by regulating the exchange of gases, nutrients and wastes through the villus core, which consists of the mesenchyme and fetal blood vessels (Kaufmann *et al.* 2004). The tips of the branching villous network that come into direct contact with the endometrium are termed the anchoring villi, while the remaining villi, which float freely in the blood-filled intervillous space, are called the floating villi (Maltepe *et al.* 2010).

The highly proliferative, undifferentiated cytotrophoblast (CTB) progenitor cells of the placental villi differentiate into two general pathways. CTBs can either fuse to form a multinucleated monolayer of syncytiotrophoblasts (STBs) that enclose the villous stroma, or differentiate into invasive extravillous trophoblasts (EVTs) that infiltrate the endometrium and a portion of the myometrium (Cartwright *et al.* 2010). STBs function as a barrier, or more precisely, as an interface between fetal and maternal blood as well as in the production of pregnancy-associated hormones and growth factors important for placental and fetal development and growth (Fu *et al.* 2013*a*). The mechanisms that facilitate CTB fusion and production of the STB layer are still under investigation; however, formation of gap junctions, activation of apoptotic pathways and the expression of endogenous retroviral proteins such as syncytin appear to be key mechanisms (Wooding & Burton 2008).

In the EVT pathway, the proliferating CTBs of the anchoring villi form a column that attaches to the uterine epithelium and subsequently differentiates into interstitial EVTs (Anin *et al.* 2004, Ji *et al.* 2013). Interstitial EVTs (iEVTs) invade the decidua and one-third of the myometrium where they further differentiate into the multinucleated placental bed giant cells (Fu *et al.* 2013*a*). Endovascular EVTs (enEVTs) acquire endothelial-like characteristics and invade the maternal spiral arteries to replace the endothelial cells. This results in the transformation of spiral arteries into distended, thin-walled vessels to ensure continuous maternal blood flow to the placenta and to maintain sufficient oxygen and nutrient supplies for the growing embryo (Anin *et al.* 2004, Lyall *et al.* 2013). Recently, endoglandular EVTs (egEVT) have been identified as a potential third subtype of EVTs (Moser *et al.* 2010, 2015). Initial findings suggest that egEVT disintegrate uterine glands and open the gland lumen to the intervillous space releasing glandular secretions that may impact placentation (Burton *et al.* 2007, Moser *et al.* 2015).

Many studies on human placental development, including the miRNAs work discussed in the following sections, have been carried out using *in vitro* models, such as immortalized trophoblast and choriocarcinoma cell lines, primary cultures of trophoblasts and/or villous explants from first trimester placenta. Rodents, especially mice, have also been used as a model. It is important to recognize that each of these models have pros and cons. Although cell lines are easy to work with, especially with respect to transient and stable transfection of genes, there are significant differences in gene expression signatures between cell lines and primary trophoblasts (Bilban *et al.* 2010). For example, chromosome 19 miRNA cluster (C19MC) members are not expressed in HTR8/SVneo cells, while chromosome 14 miRNA cluster (C14MC) members cannot be detected in JEG-3 cells (Mouillet *et al.* 2011, Morales-Prieto *et al.* 2014). Primary CTBs have been used mainly to study the differentiation of CTB to STB, but these cells have a limited life span and can only be used to study the short-term effects of transiently transfected miRNAs. Villous explants maintain the cellular architecture and mimic more closely the *in vivo* environment (Miller *et al.* 2005). However, only the short-term effect of miRNA overexpression or inhibition can be examined. The mouse model provides some insights into the *in vivo* functions of miRNAs, but it should be noted that there are significant differences between the mouse and human placentation that can affect the transferability of findings to humans (Wildman *et al.* 2006, Carter 2007, Maltepe & Fisher 2015, Schmidt *et al.* 2015, Grigsby 2016). For example, trophoblast invasion during early mouse placentation is shallow as it only extends into the decidua, whereas in humans, it proceeds to the myometrium (Carter 2007, Maltepe & Fisher 2015, Schmidt *et al.* 2015). Also, mouse trophoblasts express major histocompatibility complex (MHC)-K, -D and -L, while human trophoblasts express human leukocyte antigen G (HLA-G) or HLA-C. This leads to different interaction dynamics between uterine immune cells and invading trophoblasts (Chaouat & Clark 2015, Schmidt *et al.* 2015). Importantly, there are different miRNA expression profiles between human and mouse placentas. Specifically, C19MC is expressed only in primates with no orthologs found in rodents (Morales-Prieto *et al.* 2014), while miRNAs of the *Sfmbt2* cluster are rodent-specific (Zheng *et al.* 2011, Schmidt *et al.*

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2015, Inoue *et al.* 2017). Also, C14MC in humans shows a divergence in rodents where it is located on chromosome 12 and lacks multiple members found in humans (Seitz *et al.* 2004). Therefore, in the following discussion, we will point out which model(s) was used in each study.

miRNAs in trophectoderm development and implantation

Many studies carried out in mice suggest that miRNAs play a role in trophectoderm development. Examination of mouse miRNA expression patterns during trophectoderm specification has revealed let-7, miR-21, miR-29c, miR-96, miR-125a, miR-214, miR-297, miR-376a and miR-424 as candidates that may play a role in this process (Viswanathan *et al.* 2009, Nosi *et al.* 2017). In mouse embryonic stem cells (ESC), overexpression of miR-15b, miR-322 and miR-467 suppressed their embryonic fate and led to the induction of a trophoblast stem-cell (TSC)-like phenotype. Further analysis revealed that these miRNAs target transcription factors *Sall1*, *Sall4*, *Pou5f1* and *Nanog* (Nosi *et al.* 2017), that are important for the maintenance of ESC self-renewal and pluripotency. In addition, the miR-302/367 cluster was found to promote TE differentiation in humans by targeting bone morphogenetic protein (BMP) inhibitors *TOB2, DAZAP2* and *SLAIN1* (Lipchina *et al.* 2011); BMP4 is a member of the transforming growth factor beta (TGFB) superfamily and is involved in promoting TE differentiation (Xu *et al.* 2002, Wu *et al.* 2008). In a human pulmonary artery cell line, miR-302 was also shown to target BMP4 receptor 2, while BMP signaling led to the transcriptional downregulation of the miRNA-302/367 gene cluster (Kang *et al.* 2012), which if it also occurs in trophoblasts could create an interesting signal-buffering dynamic.

Limited evidence obtained so far has suggested that miRNAs play a role in regulating implantation. First, studies in mice have shown that miRNAs are differentially expressed between implantation sites and inter-implantation sites in the endometrium (Chakrabarty *et al.* 2007, Hu *et al.* 2008, Geng *et al.* 2014). Further studies revealed that overexpression of miR-145 impaired the attachment of mouse embryos to endometrial epithelial cells by targeting insulin-like growth factor 1 receptor (*Igf1r*) (Kang *et al.* 2015). Finally, Dicer knockdown in mouse blastocysts altered miRNAs expression and resulted in a lower implantation rate (Cheong *et al.* 2014). In humans, a number of miRNAs in the endometrium, including miR-145, were also found to be differentially expressed between women who repeatedly fail to have successful implantation and fertile women (Revel *et al.* 2011). These findings suggest a possible role of miRNAs in regulating implantation; however, more studies are required to understand the functions of miRNAs and their underlying mechanisms in this process.

Another important aspect of successful implantation is the interaction between the fetal blastocyst and the maternal immune cells. Early in pregnancy, maternal uterine natural killer (uNK) cells, T cells, B cells, macrophages and dendritic cells are recruited into the endometrium at the site of implantation to help regulate placental and fetal development (Szekeres-Bartho 2002, Bidarimath *et al.* 2014, Zhang *et al.* 2016*a*). As mentioned earlier, human EVT expresses a limited variety of MHC molecules, mostly HLA-G and HLA-C (Bidarimath *et al.* 2014, Schmidt *et al.* 2015, Hackmon *et al.* 2017). HLA-G interacts with the maternal killer immunoglobulin-like receptors expressed by uNK cells, resulting in the activation of uNK cytokine production but not its cytotoxicity response (Rajagopalan *et al.* 2006). This in turn promotes maternal immunological tolerance and placental development and vascularization (Bidarimath *et al.* 2014, Ratsep *et al.* 2015). Both miR-148a and miR-152 were found to bind the 3′ UTR of *HLA-G*, amplified from the JEG-3 human trophoblast cell line, downregulating its expression and thereby reducing HLA-G mediated inhibition of natural killer cells cytotoxicity (Manaster *et al.* 2012). These findings suggest that miRNAs play a role in regulating maternal immunological tolerance to invading EVT. In addition, miRNAs have also been shown to help regulate other maternal immune cells such as macrophages, endometrial dendritic cells and T cells in the pregnant uterus and have been extensively reviewed in Robertson and Moldenhauer (2014), Mori *et al.* (2016), Schjenken *et al.* (2016) and Robertson *et al.* (2017).

Interestingly, miRNAs were also shown to promote antiviral immunity in both trophoblast and non-trophoblast cells. In alignment with the role of placenta to protect the developing fetus, trophoblasts are the first line of defense against external factors that can impair fetal development. Therefore, it is not surprising that primary human trophoblasts are highly resistant to viral infection (Delorme-Axford *et al.* 2013). More importantly, they can confer this resistance to other types of cells when these cells uptake exosomes naturally secreted by primary trophoblasts; the exosomes were found to contain members of C19MC, miR-512-3p, miR-516b-5p and miR-517-3p (Bayer *et al.* 2015). These C19MC miRNAs initiated autophagy in recipient cells without leading to cell death which was suggested to impair viral replicability (Delorme-Axford *et al.* 2013, Bayer *et al.* 2015). Thus, miRNAs play a dynamic role to not only promote decidual immune tolerance in support of the growing fetus but also protect both mother and fetus from viral infection (Mouillet *et al.* 2014, Ouyang *et al.* 2014).

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miRNAs in trophoblast differentiation, migration and invasion

Several studies have suggested that miRNAs are important regulators of CTB to STB differentiation. Microarray analyses of miRNA expression profiles in primary trophoblast before and after their differentiation into STB have revealed that multiple members of C19MC such as miR-515-5p, miR-518f, miR-519c-3p and miR-519e-5p were significantly downregulated during CTB to STB differentiation (Zhang *et al.* 2016*b*). Further investigation showed that miR-515-5p targeted several genes that play critical roles in STB differentiation, including human glial cell missing-1 (*GCM1*) (Yu *et al.* 2002, Liang *et al.* 2010, Wakeland *et al.* 2017) and frizzled 5 (*FZD5*) (Lu *et al.* 2013) and significantly reduced cell fusion (Zhang *et al.* 2016*b*). Another miRNA gene cluster is the miR-17–92 family that is located on chromosome 13 and encodes six miRNAs (miR-17, miR-18a, miR-19a, miR-19b-1, miR-20a and miR-92a) (Concepcion *et al.* 2012). Multiple members of the miRNA-17–92 cluster, and its paralog cluster miR-106a–363, have been found to silence GCM1 in primary cultures of human trophoblasts. These miRNAs are downregulated during CTB to STB differentiation, thereby promoting the differentiation process (Kumar *et al.* 2013). Studies from our laboratory have demonstrated that miR-378a-5p suppressed BeWo cell fusion and STB marker gene expression by targeting cyclin G2 (*CCNG2*), suggesting that it inhibits STB differentiation (Nadeem *et al.* 2014).

Many studies have reported that miRNAs regulate EVT differentiation, migration and invasion by targeting key pathways known to regulate these processes. Early placentation occurs in a hypoxic environment, and oxygen tension has been reported to regulate many cellular processes in the placenta, including proliferation, EVT differentiation and invasion (Chang *et al.* 2018). However, the precise role of oxygen tension in EVT differentiation and invasion is still not well understood. Earlier studies have suggested that hypoxic conditions during early pregnancy are in part responsible for the high rate of trophoblast proliferation and inhibition of EVT invasion (Red-Horse *et al.* 2004). As the trophoblasts invade deeper into the uterus, where oxygen levels are higher, they shift from a more proliferative phenotype to a more migratory and invasive phenotype (Genbacev *et al.* 1997, Kaufmann & Castellucci 1997, Knofler 2010). However, hypoxia was recently found to promote EVT differentiation in a hypoxia-inducible factor (HIF)-dependent manner while inhibiting STB differentiation in primary cultures of human CTB (Wakeland *et al.* 2017). Thus, it is proposed that low oxygen induces the differentiation into immature EVT, but further maturation of EVT and invasion increase with rising oxygen tension (Chang *et al.* 2018).

Since hypoxia plays an important role in early placental development, studies have investigated its effects on miRNA expression and function (Donker *et al.* 2007, Mouillet *et al.* 2010, Fu *et al.* 2013*a*). They have revealed a group of miRNAs that are upregulated under hypoxia, a subset of which, hypoxamirs, and are under direct regulation of hypoxia-induced transcription factors (Kulshreshtha *et al.* 2007). MiR-210 is the most well-studied example of hypoxamirs, upregulated directly by HIF1A (Camps *et al.* 2008); additionally, it is regulated by a hypoxia-responsive transcription factor, nuclear factor kappa-B subunit p50 (NFKB1), in primary human trophoblasts (Zhang *et al.* 2012). It was reported that miR-210 inhibited migration and invasion in primary CTBs (Zhang *et al.* 2012), HTR8/SVneo cell line (Luo *et al.* 2016), and primary ETVs (Anton *et al.* 2013) by targeting ephrin-A3 (*EFNA3*), homeobox-A9 (*HOXA9*) (Zhang *et al.* 2012), and thrombospondin type I domain containing 7A (*THSD7A*) (Luo *et al.* 2016) or by activating the MAPK pathway (Anton *et al.* 2013). However, knockout of mir-210 did not result in significant changes in fetal or placental weight and non-severe hypoxia (12% O_2) did not increase miR-210 in these mice, suggesting that miR-210 may be dispensable for fetal-placental development under normoxic and non-severe hypoxic conditions (Krawczynski *et al.* 2016). Thus, the role of miR-210 in hypoxia-regulated placental development requires further investigation.

miRNAs also regulate EVT differentiation and invasion by modulating growth factor signaling. An important family of growth factors in placental development is the TGFB superfamily. Many miRNAs have been found to enhance EVT migration and invasion by targeting members of the TGFB family. For example, miR-376c targeted both activin receptor-like kinase 7 (*ALK7*) and *ALK5* to impede TGFB/Nodal signaling (Fu *et al.* 2013*b*), while miR-378a-5p targeted the ligand Nodal (Luo *et al.* 2012) to promote migration and invasion in HTR8/SVneo cells and EVT outgrowth in first trimester placental villous explants. Similarly, miR-195 enhanced trophoblast invasion by targeting activin receptor type-2B, a type II receptor for Nodal and activin, in HTR8/SVneo cells (Wu *et al.* 2016).

Using HTR8/SVneo, JEG-3 or BeWo trophoblast cell lines, several studies have suggested that miRNAs also regulate EVT motility by targeting other genes involved in regulating cell invasion. Both miR-346 and miR-582-3p targeted endocrine-gland-derived vascular endothelial growth factor (*EG-VEGF*) as well as matrix metalloproteinase 2 (*MMP2*) and *MMP9*, and strongly inhibited the migratory and invasive abilities of trophoblasts (Su *et al.* 2017). Similarly, miR-93 (Pan *et al.* 2017) and miR-204 (Yu *et al.* 2015), which targeted *MMP2* and *MMP9*, respectively, inhibit cell invasion. Members of the C19MC, miR-519d-3p (Ding *et al.* 2015) and miR-520g (Jiang *et al.* 2017*a*) also targeted *MMP2* and inhibited migration and invasion, while miR-520c-3p inhibited invasion by suppressing *CD44*, which is needed for the interaction between EVTs and decidual

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extracellular matrix (Takahashi *et al.* 2017). On the other hand, miR-21 promoted not only migration and invasion but also cell proliferation (Chaiwangyen *et al.* 2015). Among its targets is phosphatase and tensin homolog (*PTEN*), a known inhibitor of the AKT pathway. PTEN dephosphorylates phosphatidylinositol-3,4,5-trisphosphate ($PI(3,4,5)P_3$), leading to inactivation of AKT which is involved in trophoblast cell motility (Chaiwangyen *et al.* 2015). MiR-34a inhibited invasion by targeting *MYC* (Sun *et al.* 2015). MiR-20a is another such miRNA where it inhibited not only trophoblast motility but also cell proliferation by targeting forkhead box protein A1 (*FOXA1*) (Wang *et al.* 2014). As all these studies were only done in cell lines, the significance of these miRNAs in EVT differentiation and invasion requires validation using additional model systems.

miRNAs in trophoblast proliferation and apoptosis

Proliferation and apoptosis are important mechanisms of proper placental development; disruption of the equilibrium between cell division and death impairs placental function (Levy *et al.* 2000). A recent *in vivo* study in mice has demonstrated the critical role of the miR-290 cluster in placental cell proliferation and placental growth; deletion of the miR-290 cluster resulted in the reduction of trophoblast progenitor cell proliferation and placental size (Paikari *et al.* 2017). In addition, many *in vitro* studies have shown that miRNAs regulate trophoblast proliferation and apoptosis. For example, miR-378a-5p (Luo *et al.* 2012) and miR-376c (Fu *et al.* 2013*b*) enhanced HTR8/SVneo cell proliferation and survival and EVT outgrowth in villous explants by inhibiting Nodal/TGFB signaling. On the other hand, miR-195 inhibited apoptosis through targeting of inducible nitric oxide synthase (*iNOS*) in HTR8/SVneo cells (Wang *et al.* 2017). Furthermore, overexpression of miR-377 and let-7a, which are upregulated in term placenta samples versus first trimester samples, decreased trophoblast proliferation by reducing ERK and/or MYC expression in first trimester placental explants (Farrokhnia *et al.* 2014). Together, these studies suggest a potential regulatory link between miRNAs and proliferation in human trophoblasts.

Studies using multiple human trophoblast cell lines suggested a role of miRNAs in the regulation of apoptosis. The miR-29 family (miR-29a/b/c) promoted apoptosis by targeting myeloid cell leukemia-1 (*MCL1*), an apoptosis regulator and a member of the BLC2 family (Li *et al.* 2013, Gu *et al.* 2016). Overexpression of miR-18a increased apoptosis by inducing the expression of estrogen receptor alpha (ESR1) (Zhu *et al.* 2015), while miR-128a induced apoptosis via the mitochondrial pathway by downregulating *BAX* (Ding *et al.* 2016) and miR-30a-3p by inhibiting *IGF1* (Niu *et al.* 2018). On the other hand, miR-101 targeted endoplasmic reticulum protein 44 (*ERP44*) to suppress ER-stress-induced apoptosis (Zou *et al.* 2014). Again, as majority of these studies were carried out using only cell lines, more studies are required to confirm the involvement of these miRNAs in trophoblast cell proliferation and apoptosis.

miRNAs in placental vascular development

Placenta vascularization is essential to meet the metabolic demands of the rapidly growing fetus. Delayed or reduced vascular development of the placenta can result in compromised pregnancies (Reynolds & Redmer 2001). Placental vascular formation includes vasculogenesis, the *de novo* synthesis of vessels within the villi core and angiogenesis, the formation of new vessels from preexisting ones (Huppertz & Peeters 2005, Demir *et al.* 2007). Recently, deletion of the miR-290 cluster in mice has been reported to cause disorganization of the vasculature in the labyrinth (Paikari *et al.* 2017), providing strong evidence that miRNAs are important regulators of placenta vascular development.

Several miRNAs have also been suggested to play a role in vasculogenesis and angiogenesis. It was reported that miR-126 promotes proliferation, differentiation and migration of human endothelial progenitor cells by targeting an anti-angiogenic factor *PIK3R2* (Yan *et al.* 2013). Also, in pregnant rats, miR-126 was found to increase vascular sprouting, as well as placental and fetal weights (Yan *et al.* 2013). The importance of miR-126 in placenta vascular development is further supported by the finding that downregulation of miR-126 contributes to endothelial dysfunction (Yan *et al.* 2013).

VEGF is a highly regulated pro-angiogenic factor known to initiate vasculogenesis in the placenta, induce endothelial cell proliferation and migration and inhibit apoptosis (Wang & Zhao 2010). Several miRNAs have been reported to target *VEGF*. For example, miR-16 directly targeted *VEGF* to inhibit HUVEC proliferation, migration and tube formation (Zhu *et al.* 2016). Also, overexpressing miR-16 in mice placentas decreased placental and fetal weights and inhibited the total placental vasculature and capillary number (Zhu *et al.* 2016). Similarly, miR-136 (Ji *et al.* 2017), miR-200c, -20a and -20b (Hu *et al.* 2016) also targeted *VEGF*, and may exert inhibitory effects on angiogenesis. However, whether these miRNAs affect placental vascular development has not been investigated. In CD34+ endothelial cells isolated from human umbilical cord blood, miR-210 was induced by VEGF and exerted proangiogenic effects (Alaiti *et al.* 2012), suggesting that miR-210 may play a role in placental angiogenesis.

miRNAs in trophoblast cellular metabolism

Early in pregnancy, and before spiral artery plug dissolution, placental and fetal nutrients and oxygen supply is dependent on endometrial secretions and maternal plasma (Murray 2012). As a consequence,

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first trimester placenta has a relatively low oxygen concentration (1–3%) (Pringle *et al.* 2010, Murray 2012) and placental cells use glycolysis and lactic acid fermentation for ATP synthesis as their primary metabolic fuel source to conserve oxygen supplies for fetal tissues (Murray 2012, Kolahi *et al.* 2017). Moreover, HIF1A downregulates mitochondrial oxygen consumption (Papandreou *et al.* 2006) to reduce ROS production at complex 3 of the electron transport chain (ETC) in the mitochondria (Colleoni *et al.* 2013). The hypoxia-induced miR-210 has been reported to regulate cellular metabolism. Using primary human trophoblasts, it was found that overexpression of miR-210 reduced, while inhibition of miR-210 increased, mitochondrial respiration (Muralimanoharan *et al.* 2012). Iron-sulfur complex assembly proteins (ISCU) and cytochrome-c oxidase assembly protein (COX10), which play important roles in the mitochondria ETC and tricarboxylic acid cycle, have been shown to be targeted by miR-210 in human endothelial and cancer cell lines (Chan *et al.* 2009, Chen *et al.* 2010). In trophoblasts, miR-210 was also found to directly target *ISCU* and to reduce the expression of ISCU and COX10 (Muralimanoharan *et al.* 2012, Colleoni *et al.* 2013), suggesting that these genes are involved in miR-210-regulated trophoblast mitochondrial adaptation to low oxygen.

In addition to miR-210, several other miRNAs are also involved in mitochondrial biogenesis and function. For example, miR-130b-3p was found to decrease signals for mitochondrial biogenesis and adaptation to oxidative stress through targeting of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (*PGC1A*), a major regulator of mitochondrial biogenesis and energy metabolism (Jiang *et al.* 2017*b*). Also, miR-143 overexpression in primary human trophoblasts upregulated mitochondrial complexes 1, 2 and 3 but not 4 and 5 (Muralimanoharan *et al.* 2016), thus improving mitochondrial function. It also targeted hexokinase-2, a rate-limiting enzyme of glycolysis, and as a result reduced the glycolysis rate in trophoblasts (Muralimanoharan *et al.* 2016). Together, these miRNAs may help regulate trophoblast metabolic adaptation to change in oxygen levels throughout gestation.

Concluding remarks

The placenta is an essential organ for pregnancy. The proper development of placenta requires precise regulation by many signaling molecules, including miRNAs. Increasing evidence suggests that miRNAs play important roles in regulating many key processes in placental development, such as trophoblast differentiation, migration, invasion, proliferation, apoptosis, vasculogenesis/angiogenesis and cellular metabolism (Fig. 2). Although several recent *in vivo* studies in animal models have provided strong evidence that miRNAs are critical regulators of placental development (Ito *et al.* 2015, Zhu *et al.* 2016, Paikari *et al.* 2017), there are differences in placental development and placental miRNA expression profiles between mice and humans. Therefore, applications of findings from different animal models into humans should be treated with caution. Furthermore, most reported miRNA studies in placenta were performed using human cell lines derived from immortalized first trimester trophoblasts or choriocarcinoma, while only a

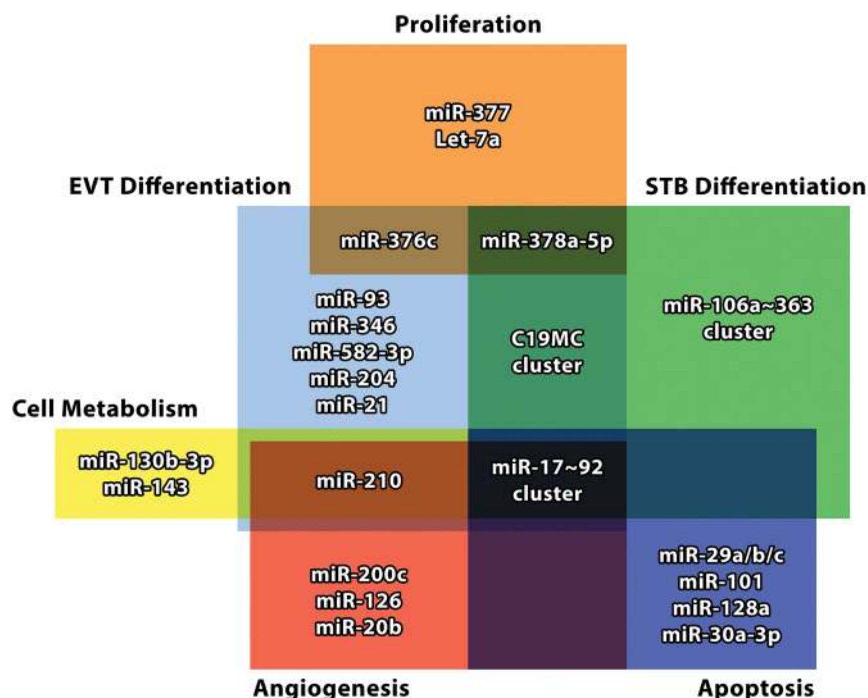

Figure 2 MicroRNAs involved in placental development. Proper development and functioning of the placenta requires precise control of trophoblast proliferation, apoptosis, differentiation, cellular metabolism, as well as vasculogenesis/angiogenesis. Many miRNAs have been suggested to play a regulatory role in one or more of these processes and are listed in this Venn diagram.

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smaller proportion of studies used primary cultures of trophoblasts, placental explants and/or clinical samples. There are also reports of differential miRNA expression patterns between primary cells and immortalized trophoblast cell lines. Therefore, the use of multiple model systems should be emphasized.

Most studies conducted today focus on one or a few target genes. Since miRNAs target many genes, the use of multi-omics approaches to investigate gene networks responsible for the regulatory functions of miRNAs in the placenta will provide a better understanding of how miRNAs are involved in regulating placental development. Finally, all miRNA studies in placenta focused on canonical 3′ UTR-mediated gene silencing. As our understanding of the different miRNA biogenesis pathways and modes of miRNA action continues to expand, their novel contributions to modulating cellular activities during pregnancy should also be investigated.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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