Published in final edited form as:

Birth Defects Res A Clin Mol Teratol. 2011 August ; 91(8): 737–743. doi:10.1002/bdra.20782.

Expression patterns of placental microRNAs

Jean-Francois Mouillet¹, Tianjiao Chu¹, and Yoel Sadovsky^{1,2}

¹Magee-Womens Research Institute, Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh

²Department of Microbiology and Molecular Genetics, University of Pittsburgh

Abstract

Among different types of small RNA molecules, distinct types of microRNAs (miRNAs) are expressed in many cell types, where they modulate RNA stability and translation, thus controlling virtually every aspect of tissue development, proliferation, differentiation, and function. Aberrant miRNA expression has been linked to discrete pathological processes. As the placenta plays a pivotal role in governing fetal development, it is not surprising that the placenta expresses numerous types of miRNAs. Whereas many of these miRNAs are ubiquitously expressed, certain miRNA species are largely unique to the placenta. Research in the field of placental miRNAs is in its early phase, with most studies centering on cataloging placental miRNA species or examining differences in placental miRNA expression between placentas from normal pregnancies and those from pregnancies complicated by pathologies that are associated with placental dysfunction. Recent research endeavors ventured to assess the function of miRNAs in cultured placental trophoblasts, using *in vitro* conditions that model relevant pathophysiological processes. The impact of miRNA-mediated repression on the trophoblast transcriptome, particularly in response to genetic and environmental perturbations, remains largely unknown. Further in depth studies are required to unravel the functional significance of miRNAs in molding placental robustness, which must constantly adapt to altered maternal physiological status in order to sustain optimal support to the developing embryo. In this review we summarize the current information about placental miRNAs expression, and the lingering challenges in this field.

Keywords

MicroRNA; placenta; trophoblast; hypoxia; fetal growth restriction; normalization

Introduction

The recent discovery of a multitude of small non-coding RNAs, which modulate gene expression and genome architecture, has drastically impacted our understanding of gene regulatory networks. Among these small regulatory RNAs, microRNAs (miRNAs), which are abundant in animal, plants, and viruses, represent the best-characterized class. MicroRNAs are thought to be important for fine-tuning of gene expression in diverse

developmental and physiological settings (Bartel, 2009; Bushati and Cohen, 2007; He and Hannon, 2004), where they repress gene expression by pairing with mRNAs of protein-coding genes and directing their degradation, or by inhibiting their translation. Although most miRNAs have a modest impact on the level of discrete proteins, miRNAs can have a marked influence on molecular pathways and, consequently, on cellular regulatory networks. Consistent with this notion, a growing number of pathological processes are associated with mis-expression of certain types of miRNA species.

The survival and growth of the eutherian fetus is entirely dependent upon intact function of placenta villi. The placental trophoblast layer actively orchestrates processes that are obligatory for fetal development, including gas exchange, supply of nutrients, removal of waste products, hormonal support, and immunological defense. The molecular machinery underlying placental development and function is complex, and comprises numerous interconnected regulatory pathways. Mutations of proteins involved in these molecular networks derail murine placental morphogenesis and commonly lead to embryonic lethality or abnormal fetal growth (Rawn and Cross, 2008; Rossant and Cross, 2001). Whereas the role of many protein-coding genes has been documented, the placental miRNA landscape remains poorly characterized. Recent studies validated that miRNAs are abundant in the placenta, with discrete miRNA types exhibiting a unique pattern of expression, suggesting a potential regulatory role (Landgraf et al., 2007; Liang et al., 2007). Nonetheless, the function of most placental miRNA remains to be determined. In this article, we review published information on miRNA expression patterns in the human placenta. Improved knowledge of miRNA function will undoubtedly enhance our understanding of the physiology and pathology of the placenta.

MicroRNA biogenesis

The detailed processes leading to formation of mature miRNAs are incompletely elucidated. Current information indicates that the canonical pathway of miRNA biogenesis begins with RNA polymerase II-dependent transcription of long primary transcripts (pri-miRNAs), which fold into distinctive stem-loop structures (Cai et al., 2004; Lee et al., 2004). In vertebrates, these pri-miRNAs are processed in the nucleus by the “microprocessor complex” that includes the RNase III enzyme Drosha, and the dsRNA-binding protein, DGCR8, forming a pre-miRNA hairpin product of nearly 70 nucleotides long (Denli et al., 2004; Gregory et al., 2004). Pre-miRNAs are subsequently transported to the cytoplasm by Exportin 5, where they are further processed by a different RNase III enzyme, Dicer, into miRNA duplexes (Hutvagner et al., 2001; Lund et al., 2004). Finally, the miRNA duplex is unwound and one strand (the mature miRNA) is incorporated into the RNA-induced silencing complex (RISC), which contains Argonaute (Ago) proteins at its core (Meister and Tuschl, 2004; Tomari and Zamore, 2005). The fate of the other strand, known as the passenger strand (or miRNA*) is not entirely clear, and may be lost through unknown mechanisms. The miRNA-RISC complex binds specific sites within the 3'UTR of its target mRNA, and disables it through deadenylation and destabilization, as well as translational repression (Filipowicz et al., 2008). Whereas translation inhibition has been considered the main miRNA mechanism to reduce protein expression, recent data strongly suggest that miRNAs largely act by destabilizing target mRNAs (Guo et al., 2010). In contrast to plant

miRNAs, which form perfect base pairing with mRNAs target sites, most animal miRNAs exhibit partial complementarity to their targets in the “seed region”, corresponding to nucleotides 2–7 of the miRNA.

In addition to the canonical pathway, additional miRNA pathways have been recently described. Some rare miRNAs, called mirtrons, are produced from short hairpin introns that are released by the splicing machinery. After splicing, mirtrons are linearized by the lariat debranching enzyme and folded into pre-miRNAs. Although mirtrons bypass Drosha cleavage, they are further processed in manner similar to the canonical miRNAs (Okamura et al., 2007; Ruby et al., 2007). Other miRNAs derived from small RNAs, including snoRNAs, shRNA and tRNAs, bypass the microprocessor complex (Babiarz et al., 2008; Cole et al., 2009; Ender et al., 2008). While structurally similar to canonical miRNAs, the function of these species, which was largely inferred from high-throughput sequencing data, remains to be established. Lastly, two recent reports have shed light on a distinct mechanism in which a pre-miRNA with an atypical structure is not cleaved by Dicer but directly by Ago2 (Cheloufi et al., 2010; Cifuentes et al., 2010). Only miR-451, which is abundant and functional in erythropoiesis (Cheloufi et al., 2010 ; Cifuentes et al., 2010; Papapetrou et al., 2010; Patrick et al., 2010; Yu et al., 2010), has been thus far identified as a product of this pathway.

Placenta-specific miRNAs

Global tissue surveys of human miRNAs revealed that they are particularly abundant in the placenta, where they exhibit a distinctive expression profile (Barad et al., 2004; Landgraf et al., 2007; Liang et al., 2007). In addition, the miRNAs biogenesis machinery is essential for placental development and function. For example, a mutation in mouse Ago2, which disables the miRNA machinery, causes abnormal development of the placenta and results in embryonic lethality (Cheloufi et al., 2010). Other miRNA biogenesis proteins are expressed in human placental trophoblasts (Donker et al., 2007) and may be germane for placenta development. However, mice deficient in these proteins exhibit early developmental defects that precede placental formation, precluding a detailed investigation into placental function of most miRNA biogenesis proteins (Bernstein et al., 2003; Mouillet et al., 2008; Wang et al., 2007). A remarkable observation regarding human placental miRNAs is the abundance of a family of miRNAs originating from a large, primate-specific genomic cluster, located on chromosomal region 19q13.41 and commonly referred to as the chromosome 19 miRNA cluster (C19MC). It contains 46 highly related miRNAs within a ~100 kb region of genomic DNA (Bentwich et al., 2005). The expression level of C19MC miRNAs is variable, with some members among the most abundant placental miRNA species. While the function of C19MC members remains unknown, C19MC constitutes a significant portion of the total pool of placental miRNAs, and therefore has the potential to markedly impact the trophoblast proteome (Luo et al., 2009). While predominant in the placenta, expression of C19MC miRNAs has also been reported in human embryonic stem cells (Bar et al., 2008; Laurent et al., 2008; Morin et al., 2008; Ren et al., 2009). C19MC is also noted for many Alu repeats, a family of mobile repetitive primate-specific short-interspersed elements (SINEs). Duplications and rearrangement mediated by these Alu repeats flanking the miRNA genes might have contributed to the evolution of C19MC (Bentwich et al., 2005;

Borchert et al., 2006; Bortolin-Cavaille et al., 2009; Lehnert et al., 2009; Zhang et al., 2008). The conserved C19MC miRNAs secondary structure as well as the low density of SNPs within the pre-miRNA regions compared to the flanking regions suggest an evolutionary selective pressure, and therefore a functional requirement (Zhang et al., 2008). Originally thought to be transcribed by the RNA pol-III (Borchert et al., 2006), recent data suggest that the C19MC is processed by the RNA pol-II, producing a large non-coding transcript from which mature miRNAs are generated (Bortolin-Cavaille et al., 2009). The regulation of expression of C19MC miRNAs is poorly understood. In cell lines, the C19MC seem to be exclusively expressed trophoblast-derived lines, including JEG3, JAR, and BeWo (with the notable exception of HTR8/SVneo). Expression of these miRNAs can be reactivated in certain cells by treatment with 5-aza-2'-deoxycytidine (5-Aza-CdR), a DNA methylation inhibitor (Saito et al., 2009; Tsai et al., 2009), suggesting an epigenetic control. In addition, a CpG-rich region located ~17 kb upstream of the first gene within C19MC was found to be hypermethylated in cells that do not express these miRNAs (Tsai et al., 2009). Recent data indicate that C19MC is imprinted in the placenta, with expression from the paternally inherited chromosome (Noguer-Dance et al., 2010). Interestingly, a large cluster of 80 miRNAs of unknown function, located within intron 10 of the imprinted *Sfmbt2* gene, is predominantly expressed in the mouse placenta (Noguer-Dance et al., 2010). Ectopic expression of C19MC members (miR-520g or 517c) promote cell proliferation and self-renewal (Li et al., 2009a). Consistent with this notion, aberrant expression of miRNAs from this locus has been observed in several types of aggressive cancers (Foekens et al., 2008; Huang et al., 2008; Li et al., 2009a; Pfister et al., 2009; Rippe et al., 2010). Finally, in human embryonic stem cells expression of C19MC miRNAs is strongly reduced in more differentiated states such as embryoid bodies, supporting a role in differentiation or the maintenance of pluripotency (Ren et al., 2009). Although these data do not explicate the function of C19MC in the placenta, the unique abundance and regulation of placental C19MC suggest a role in the biology of placental trophoblasts.

MicroRNA expression in placental injury

The altered miRNA landscape in the placenta may have important implications for a number of pathologies, including placentas of women experiencing complications in pregnancy, such as preeclampsia. To date, a limited number of microarray-based placental miRNA profiles have been performed (Hu et al., 2009; Pineles et al., 2007; Zhu et al., 2009). The paucity of data and the use of different experimental settings and array platforms resulted in inconsistent information regarding differential expression of miRNA species in placentas of preeclamptic women (Table 1). Curiously, the level of hypoxia-regulated miR-210 was found in two studies to be significantly elevated in preeclampsia (Pineles et al., 2007; Zhu et al., 2009). Oxygen tension is a known crucial regulator of placental development, and may influence the differentiation of trophoblasts throughout pregnancy (Adelman et al., 2000; Caniggia et al., 2000; Genbacev et al., 1996; Genbacev et al., 1997; Nelson et al., 1999). Both preeclampsia and fetal growth restriction are associated with trophoblast hypoxia and defective placental development or function. (Baschat and Hecher, 2004; Pardi et al., 2002; Wang et al., 2009). MiR-210 is consistently upregulated during hypoxic stress in both physiological and malignant conditions (review in Huang et al., 2009). Whereas the precise

mechanism of miR-210 regulation remains to be elucidated, proposed pathways include hypoxia inducible factor -1 α (HIF1 α , (Camps et al., 2008; Crosby et al., 2009; Huang et al., 2009; Kim et al., 2009) and HIF2 α (Zhang et al., 2009). Interestingly, HIF1 α is also a critical regulator of placental development, predominantly during the first trimester when oxygen levels are low (review in Dunwoodie, 2009). It remains to be determined whether miR-210 levels are higher during early placental development and whether it participates in the molecular mechanisms underlying placental development. Another miRNA, miR-155, has been identified in a screen for differentially expressed species in preeclampsia (Pineles et al., 2007; Zhang et al., 2010). An inverse correlation exists between the expression of miR-155 and the angiogenic factor CYR61 (CCN1) (Zhang et al., 2010), which is downregulated in preeclamptic placentas (Gellhaus et al., 2006; Gellhaus et al., 2007). CYR61 promotes cell proliferation, adhesion, differentiation, and plays a role in angiogenesis (Chen and Du, 2007), and mouse embryos harboring a targeted disruption of *Cyr61* die in part due to a defective placenta (Mo et al., 2002). MiR-155 also has a well-documented role in hematopoietic lineage differentiation, immune response, and tumorigenesis (review in O'Connell et al., 2010). While miR-155 is expressed in most immune cells, the cell type expressing miR-155 in the placenta is unknown. In our miRNA profiling of primary term human trophoblasts, we observed low expression of miR-155 (Mouillet et al, unpublished), supporting the possibility that miR-155 might be produced by other placental cells, such as NK cells of Hofbauer cells.

Altered miRNA expression has been interrogated in placentas of pregnant women experiencing preterm labor (Montenegro et al., 2009). A microarray-based profile of miRNA expression identified 39 miRNAs species that are differentially regulated in the placenta and associated membranes, obtained from term or preterm pregnancies (Table 1). Among these miRNAs, 31 were significantly reduced in term tissues compared to the preterm group. Interestingly, the expression of the miRNA biogenesis enzyme Dicer was markedly decreased at term compared to preterm tissues. These data suggest that large-scale de-repression of a gene network might be involved in the initiation of labor. In contrast, using a miRNA-based screen, we recently found that the population of placental miRNAs was unchanged between women with term versus preterm birth (Mouillet et al, unpublished). Lastly, exposure to xenobiotics can also influence miRNA expression in the human placenta. In particular, maternal cigarette smoking is associated with a decrease in the placental expression of several miRNAs, including miR-16, miR-21, and miR-146a (Maccani et al., 2010). Exposure of trophoblasts to nicotine and benzo[a]pyrene, which are active components of cigarette smoke, downregulates miR-146a. The endocrine disruptor bisphenol A also influences the expression of miR-146a in trophoblast cell lines (Avissar-Whiting et al., 2010). Whereas miR-146a is known to regulate the immune suppression function of Foxp3(+) in regulatory T cells (Treg cells) (Lu et al., 2010), these data seem insufficient to draw meaningful conclusions regarding the role of placental miR-146a.

MicroRNAs in primary human trophoblasts

Studies using cultured trophoblasts complement analyses performed in intact human placentas, yet enable a more in depth, mechanistic analysis of miRNA function in trophoblasts. Using primary human trophoblasts exposed to hypoxia as a model of placental

injury we observed a subset of miRNA species that was consistently altered in hypoxia (Donker et al., 2007; Mouillet et al., 2010b). Importantly, hypoxia does not alter the expression level of several miRNA biogenesis proteins, including Drosha, Exportin 5, Dicer, Ago2, and DP103 (Donker et al., 2007). The epithelium-specific miR-205 was among the differentially expressed miRNAs, and expressed at a higher level in hypoxic trophoblasts (Mouillet et al., 2010b). Notably, miR-205 is implicated in the epithelial to mesenchymal transition and in the maintenance of the epithelial phenotype (Gregory et al., 2008; Yu et al., 2008). Aberrant miR-205 expression is also linked to cancer (Dijckmeester et al., 2009; Feber et al., 2008; Gandellini et al., 2009; Gottardo et al., 2007; Gregory et al., 2008; Iorio et al., 2009; Iorio et al., 2007; Lebanony et al., 2009; Sempere et al., 2007; Song and Bu, 2009; Wiklund et al., 2010; Wu et al., 2009). We showed that increased expression of trophoblastic miR-205 decreased the levels of MED1, a known regulator of placental development (Landles et al., 2003; Zhu et al., 2000). Similarly, siRNA-based silencing of MED1 in primary trophoblasts perturbs the expression of several markers of trophoblast differentiation, supporting a role for miR-205 in placental adaptation to hypoxia. We also found that hypoxic primary human trophoblasts express a higher level of miR-93. Consistent with this finding, VEGF was recently identified as a target of miR-93 in an experimental model of diabetes (Long et al., 2010). Although the interaction between miR-93 and VEGF was studied in the context of diabetic liver, this functional interaction is likely relevant to placental development. Interestingly, among differentially regulated miRNAs in hypoxic trophoblasts, miR-424 was significantly down-regulated. MiR-424 is a mammal-specific miRNA (Finnerty et al., 2010) and likely plays a prominent role in the differentiation of the monocyte-macrophage lineage (Forrest et al., 2009; Rosa et al., 2007). MiR-424 is highly expressed in the placenta (Landgraf et al., 2007; Liang et al., 2007) (Mouillet, in preparation), yet its role in trophoblast biology remains to be established.

Placenta-derived circulating miRNAs as biomarkers of placental dysfunction

It is now clear that miRNAs are released into the circulation at levels that may reflect tissue physiological or pathological states (review in Wittmann and Jack, 2010). Although the precise origin of circulating miRNAs is not entirely clear, they are encased in cell-derived microparticles, including microvesicles, exosomes, and apoptotic bodies, likely sheltering them from plasma ribonucleases (Thery et al., 2009; Valadi et al., 2007; Zernecke et al., 2009). Notably, a substantial fraction of circulating miRNAs is not associated with cellular microparticles, but rather with the RNA-binding protein nucleophosmin 1 (NPM1) (Wang et al., 2010). Placental miRNAs are readily detectable in the circulation of pregnant women (Chim et al., 2008; Gilad et al., 2008; Luo et al., 2009; Miura et al., 2010). Consistent with their placental origin, the level of most of these pregnancy-associated miRNAs return to their basal, pre-pregnancy levels within 24 h after delivery. Despite a lack of standardized methodology to accurately measure circulating miRNAs, miRNAs from the C19MC region are consistently expressed in the plasma of pregnant women, where they contribute to a significant fraction of all circulating miRNAs during pregnancy (Miura et al., 2010). As trophoblasts are known to produce exosomes, which may have a role in the establishment of maternal immune tolerance (Frangsmyr et al., 2005; Mincheva-Nilsson and Baranov, 2010;

Taylor et al., 2006), miRNAs in circulating exosomes may have a role in immunologic adaptation of pregnancy. Even though systemic targets to circulating placental miRNAs remain to be defined, plasma miRNAs of placental origin may serve as biomarkers for diseases associated with placental dysfunction. We recently assessed plasma levels of a series of miRNAs in pregnant women with fetal growth restriction, compared to uncomplicated pregnancies. Focusing on a set of miRNAs whose expression was altered in hypoxic trophoblasts, we did not detect a significant difference in the level of individual species (Mouillet et al., 2010a). In contrast, we detected a significant increase in the total level of all interrogated miRNA species. The expression level of some of these miRNAs was not changed in trophoblasts exposed to hypoxia, suggesting an increased release of these miRNAs in pregnancies complicated by fetal growth restriction (Mouillet et al., 2010a). Interestingly, there was a corresponding decline in the level of these miRNAs in the placenta from the same pregnancies. Lastly, we note that information is lacking regarding the miRNA landscape in fetal blood. In a preliminary analysis using microRNA arrays, we recently detected miRNA species in the fetal circulation, with altered miRNA expression between samples from preterm versus term pregnancy (unpublished data).

Challenges in normalization of high-throughput data

Review of high-throughput studies in the area of placental biology uncovered a recurring hurdle that stems from the need to use adequate normalization procedures in order to obtain reliable results. Whereas RT-qPCR, miRNA microarrays, and high throughput sequencing are generally highly reproducible (Pradervand et al., 2010), each of these methods has its own limitations, contributing to signal variability. RT-qPCR is commonly considered the “gold standard” of miRNA measurement, and used to validate the results of microarray analysis. Yet, there is no consensus on universal endogenous normalization controls. SnoRNAs and snRNAs, including RNU48 and RNU6B, have been suggested as reference RNAs, but exhibit high variability (Wong et al., 2007). Efforts to systematically define tissue specific reference RNAs (Chang et al., 2010; Davoren et al., 2008) did not include the placenta, rendering un-normalized RT-qPCR as an acceptable alternative (Sato et al., 2009). A similar concern adds to noise and variability in miRNA microarrays and high throughput sequencing assays, where the assumption of uniformity of total mRNA amount per cell is likely false (Lu et al., 2005), thus preventing the application of normalization procedures, and resulting in increased coefficient of variation and poor concordance with RT-qPCR measurements (Sato et al., 2009). When the total amount of miRNA can be assumed to be constant across samples, microarray data may be normalized using quantile normalization without background correction, which was shown to reduce variability among biological replicates (Lopez-Romero et al., 2010; Sah et al., 2010). Similarly, high throughput sequencing measurement of miRNA expression can also be normalized using either quantile normalization, or the library size. Taken together, caution is recommended when results based on high-throughput miRNA analyses are used to inform placental dysfunction.

Concluding remarks

Because of their abundance and diversity, miRNAs likely play a central role in regulatory pathways controlling lineage determination, cell differentiation and function of placental

trophoblasts. Yet, the impact of miRNA-mediated repression on the placental cell transcriptome remains largely unknown. Further studies are required to unravel the functional significance of miRNAs in placental development and function. It is also becoming clear that the role of miRNAs likely involves complex modulation of gene expression, including co-regulation of genetic networks, noise control and regulatory switches (Herranz and Cohen, 2010). These functions serve to buffer changes in gene expression in response to genetic and environmental perturbations, thereby stabilizing the transcriptome and conferring system robustness (Hilgers et al., 2010; Hornstein and Shomron, 2006; Li et al., 2009b; Stark et al., 2005; Wu et al., 2009). Such robustness is particularly germane in the placenta, where miRNAs likely play a central role in regulatory pathways controlling lineage determination, differentiation and function of placental trophoblasts.

Acknowledgments

Grants: The project was supported by NIH R01HD065893 (to YS), and Pennsylvania Department of Health Research Formula Funds (to JFM).

We thank Lori Rideout for editing the manuscript.

References

- Avisar-Whiting M, Veiga KR, Uhl KM, Maccani MA, Gagne LA, Moen EL, Marsit CJ. Bisphenol A exposure leads to specific microRNA alterations in placental cells. *Reprod Toxicol*. 2010; 29:401–406. [PubMed: 20417706]
- Babiarz JE, Ruby JG, Wang Y, Bartel DP, Blelloch R. Mouse ES cells express endogenous shRNAs, siRNAs, and other Microprocessor-independent, Dicer-dependent small RNAs. *Genes Dev*. 2008; 22:2773–2785. [PubMed: 18923076]
- Bar M, Wyman SK, Fritz BR, Qi J, Garg KS, Parkin RK, Kroh EM, Bendoraite A, Mitchell PS, Nelson AM, Ruzzo WL, Ware C, Radich JP, Gentleman R, Ruohola-Baker H, Tewari M. MicroRNA discovery and profiling in human embryonic stem cells by deep sequencing of small RNA libraries. *Stem Cells*. 2008; 26:2496–2505. [PubMed: 18583537]
- Barad O, Meiri E, Avniel A, Aharonov R, Barzilai A, Bentwich I, Einav U, Gilad S, Hurban P, Karov Y, Lobenhofer EK, Sharon E, Shibolet Y, Shtutman M, Bentwich Z, Einat P. MicroRNA expression detected by oligonucleotide microarrays: system establishment and expression profiling in human tissues. *Genome Res*. 2004; 14:2486–2494. [PubMed: 15574827]
- Bartel DP. MicroRNAs: target recognition and regulatory functions. *Cell*. 2009; 136:215–233. [PubMed: 19167326]
- Bentwich I, Avniel A, Karov Y, Aharonov R, Gilad S, Barad O, Barzilai A, Einat P, Einav U, Meiri E, Sharon E, Spector Y, Bentwich Z. Identification of hundreds of conserved and nonconserved human microRNAs. *Nat Genet*. 2005; 37:766–770. [PubMed: 15965474]
- Bernstein E, Kim SY, Carmell MA, Murchison EP, Alcorn H, Li MZ, Mills AA, Elledge SJ, Anderson KV, Hannon GJ. Dicer is essential for mouse development. *Nat Genet*. 2003; 35:215–217. [PubMed: 14528307]
- Borchert GM, Lanier W, Davidson BL. RNA polymerase III transcribes human microRNAs. *Nat Struct Mol Biol*. 2006; 13:1097–1101. [PubMed: 17099701]
- Bortolin-Cavaille ML, Dance M, Weber M, Cavaille J. C19MC microRNAs are processed from introns of large Pol-II, non-protein-coding transcripts. *Nucleic Acids Res*. 2009; 37:3464–3473. [PubMed: 19339516]
- Bushati N, Cohen SM. microRNA functions. *Annu Rev Cell Dev Biol*. 2007; 23:175–205. [PubMed: 17506695]

- Cai X, Hagedorn CH, Cullen BR. Human microRNAs are processed from capped, polyadenylated transcripts that can also function as mRNAs. *RNA*. 2004; 10:1957–1966. [PubMed: 15525708]
- Camps C, Buffa FM, Colella S, Moore J, Sotiriou C, Sheldon H, Harris AL, Gleadle JM, Ragoussis J. hsa-miR-210 Is induced by hypoxia and is an independent prognostic factor in breast cancer. *Clin Cancer Res*. 2008; 14:1340–1348. [PubMed: 18316553]
- Chang KH, Mestdagh P, Vandesompele J, Kerin MJ, Miller N. MicroRNA expression profiling to identify and validate reference genes for relative quantification in colorectal cancer. *BMC Cancer*. 2010; 10:173. [PubMed: 20429937]
- Cheloufi S, Dos Santos CO, Chong MM, Hannon GJ. A dicer-independent miRNA biogenesis pathway that requires Ago catalysis. *Nature*. 2010; 465:584–589. [PubMed: 20424607]
- Chen Y, Du XY. Functional properties and intracellular signaling of CCN1/Cyr61. *J Cell Biochem*. 2007; 100:1337–1345. [PubMed: 17171641]
- Chim SS, Shing TK, Hung EC, Leung TY, Lau TK, Chiu RW, Lo YM. Detection and characterization of placental microRNAs in maternal plasma. *Clin Chem*. 2008; 54:482–490. [PubMed: 18218722]
- Cifuentes D, Xue H, Taylor DW, Patnode H, Mishima Y, Cheloufi S, Ma E, Mane S, Hannon GJ, Lawson ND, Wolfe SA, Giraldez AJ. A novel miRNA processing pathway independent of Dicer requires Argonaute2 catalytic activity. *Science*. 2010; 328:1694–1698. [PubMed: 20448148]
- Cole C, Sobala A, Lu C, Thatcher SR, Bowman A, Brown JW, Green PJ, Barton GJ, Hutvagner G. Filtering of deep sequencing data reveals the existence of abundant Dicer-dependent small RNAs derived from tRNAs. *RNA*. 2009; 15:2147–2160. [PubMed: 19850906]
- Crosby ME, Kulshreshtha R, Ivan M, Glazer PM. MicroRNA regulation of DNA repair gene expression in hypoxic stress. *Cancer Res*. 2009; 69:1221–1229. [PubMed: 19141645]
- Davoren PA, McNeill RE, Lowery AJ, Kerin MJ, Miller N. Identification of suitable endogenous control genes for microRNA gene expression analysis in human breast cancer. *BMC Mol Biol*. 2008; 9:76. [PubMed: 18718003]
- Denli AM, Tops BB, Plasterk RH, Ketting RF, Hannon GJ. Processing of primary microRNAs by the Microprocessor complex. *Nature*. 2004; 432:231–235. [PubMed: 15531879]
- Dijkmeester WA, Wijnhoven BP, Watson DI, Leong MP, Michael MZ, Mayne GC, Bright T, Astill D, Hussey DJ. MicroRNA-143 and -205 expression in neosquamous esophageal epithelium following Argon plasma ablation of Barrett's esophagus. *J Gastrointest Surg*. 2009; 13:846–853. [PubMed: 19190970]
- Donker RB, Mouillet JF, Nelson DM, Sadovsky Y. The expression of Argonaute2 and related microRNA biogenesis proteins in normal and hypoxic trophoblasts. *Mol Hum Reprod*. 2007; 13:273–279. [PubMed: 17327266]
- Dunwoodie SL. The role of hypoxia in development of the Mammalian embryo. *Dev Cell*. 2009; 17:755–773. [PubMed: 20059947]
- Ender C, Krek A, Friedlander MR, Beitzinger M, Weinmann L, Chen W, Pfeffer S, Rajewsky N, Meister G. A human snoRNA with microRNA-like functions. *Mol Cell*. 2008; 32:519–528. [PubMed: 19026782]
- Feber A, Xi L, Luketich JD, Pennathur A, Landreneau RJ, Wu M, Swanson SJ, Godfrey TE, Little VR. MicroRNA expression profiles of esophageal cancer. *J Thorac Cardiovasc Surg*. 2008; 135:255–260. [PubMed: 18242245]
- Filipowicz W, Bhattacharyya SN, Sonenberg N. Mechanisms of post-transcriptional regulation by microRNAs: are the answers in sight? *Nat Rev Genet*. 2008; 9:102–114. [PubMed: 18197166]
- Finnerty JR, Wang WX, Hebert SS, Wilfred BR, Mao G, Nelson PT. The miR-15/107 group of microRNA genes: Evolutionary biology, cellular functions, and roles in human diseases. *J Mol Biol*. 2010; 402:491–509. [PubMed: 20678503]
- Foekens JA, Sieuwerts AM, Smid M, Look MP, de Weerd V, Boersma AW, Klijn JG, Wiemer EA, Martens JW. Four miRNAs associated with aggressiveness of lymph node-negative, estrogen receptor-positive human breast cancer. *Proc Natl Acad Sci USA*. 2008; 105:13021–13026. [PubMed: 18755890]
- Forrest AR, Kanamori-Katayama M, Tomaru Y, Lassmann T, Ninomiya N, Takahashi Y, de Hoon MJ, Kubosaki A, Kaiho A, Suzuki M, Yasuda J, Kawai J, Hayashizaki Y, Hume DA, Suzuki H. Induction of microRNAs, mir-155, mir-222, mir-424 and mir-503, promotes monocytic

differentiation through combinatorial regulation. *Leukemia*. 2009; 24:460–466. [PubMed: 19956200]

- Frangsmyr L, Baranov V, Nagaeva O, Stendahl U, Kjellberg L, Mincheva-Nilsson L. Cytoplasmic microvesicular form of Fas ligand in human early placenta: switching the tissue immune privilege hypothesis from cellular to vesicular level. *Mol Hum Reprod*. 2005; 11:35–41. [PubMed: 15579659]
- Gandellini P, Folini M, Longoni N, Pennati M, Binda M, Colecchia M, Salvioni R, Supino R, Moretti R, Limonta P, Valdagni R, Daidone MG, Zaffaroni N. miR-205 Exerts tumor-suppressive functions in human prostate through down-regulation of protein kinase Cepsilon. *Cancer Res*. 2009; 69:2287–2295. [PubMed: 19244118]
- Gellhaus A, Schmidt M, Dunk C, Lye SJ, Kimmig R, Winterhager E. Decreased expression of the angiogenic regulators CYR61 (CCN1) and NOV (CCN3) in human placenta is associated with pre-eclampsia. *Mol Hum Reprod*. 2006; 12:389–399. [PubMed: 16675545]
- Gellhaus A, Schmidt M, Dunk C, Lye SJ, Winterhager E. The circulating proangiogenic factors CYR61 (CCN1) and NOV (CCN3) are significantly decreased in placenta and sera of preeclamptic patients. *Reprod Sci*. 2007; 14:46–52. [PubMed: 18089610]
- Gilad S, Meiri E, Yogev Y, Benjamin S, Lebanony D, Yerushalmi N, Benjamin H, Kushnir M, Cholakh H, Melamed N, Bentwich Z, Hod M, Goren Y, Chajut A. Serum microRNAs are promising novel biomarkers. *PLoS ONE*. 2008; 3:e3148. [PubMed: 18773077]
- Gottardo F, Liu CG, Ferracin M, Calin GA, Fassan M, Bassi P, Sevignani C, Byrne D, Negrini M, Pagano F, Gomella LG, Croce CM, Baffa R. Micro-RNA profiling in kidney and bladder cancers. *Urol Oncol*. 2007; 25:387–392. [PubMed: 17826655]
- Gregory PA, Bert AG, Paterson EL, Barry SC, Tsykin A, Farshid G, Vadas MA, Khew-Goodall Y, Goodall GJ. The miR-200 family and miR-205 regulate epithelial to mesenchymal transition by targeting ZEB1 and SIP1. *Nat Cell Biol*. 2008; 10:593–601. [PubMed: 18376396]
- Gregory RI, Yan KP, Amuthan G, Chendrimada T, Doratotaj B, Cooch N, Shiekhattar R. The microprocessor complex mediates the genesis of microRNAs. *Nature*. 2004; 432:235–240. [PubMed: 15531877]
- Guo H, Ingolia NT, Weissman JS, Bartel DP. Mammalian microRNAs predominantly act to decrease target mRNA levels. *Nature*. 2010; 466:835–840. [PubMed: 20703300]
- He L, Hannon GJ. MicroRNAs: small RNAs with a big role in gene regulation. *Nat Rev Genet*. 2004; 5:522–531. [PubMed: 15211354]
- Herranz H, Cohen SM. MicroRNAs and gene regulatory networks: managing the impact of noise in biological systems. *Genes Dev*. 2010; 24:1339–1344. [PubMed: 20595229]
- Hilgers V, Bushati N, Cohen SM. Drosophila microRNAs 263a/b confer robustness during development by protecting nascent sense organs from apoptosis. *PLoS Biol*. 2010; 8:e1000396. [PubMed: 20563308]
- Hornstein E, Shomron N. Canalization of development by microRNAs. *Nat Genet*. 2006; 38(Suppl):S20–24. [PubMed: 16736020]
- Hu Y, Li P, Hao S, Liu L, Zhao J, Hou Y. Differential expression of microRNAs in the placenta of Chinese patients with severe pre-eclampsia. *Clin Chem Lab Med*. 2009; 47:923–929. [PubMed: 19642860]
- Huang Q, Gumireddy K, Schrier M, le Sage C, Nagel R, Nair S, Egan DA, Li A, Huang G, Klein-Szanto AJ, Gimotty PA, Katsaros D, Coukos G, Zhang L, Pure E, Agami R. The microRNAs miR-373 and miR-520c promote tumour invasion and metastasis. *Nat Cell Biol*. 2008; 10:202–210. [PubMed: 18193036]
- Huang X, Ding L, Bennewith KL, Tong RT, Welford SM, Ang KK, Story M, Le QT, Giaccia AJ. Hypoxia-inducible mir-210 regulates normoxic gene expression involved in tumor initiation. *Mol Cell*. 2009; 35:856–867. [PubMed: 19782034]
- Hutvagner G, McLachlan J, Pasquinelli AE, Balint E, Tuschl T, Zamore PD. A cellular function for the RNA-interference enzyme Dicer in the maturation of the let-7 small temporal RNA. *Science*. 2001; 293:834–838. [PubMed: 11452083]

- Iorio MV, Casalini P, Piovan C, Di Leva G, Merlo A, Triulzi T, Menard S, Croce CM, Tagliabue E. microRNA-205 Regulates HER3 in human breast cancer. *Cancer Res.* 2009; 69:2195–2200. [PubMed: 19276373]
- Iorio MV, Visone R, Di Leva G, Donati V, Petrocca F, Casalini P, Taccioli C, Volinia S, Liu CG, Alder H, Calin GA, Menard S, Croce CM. MicroRNA signatures in human ovarian cancer. *Cancer Res.* 2007; 67:8699–8707. [PubMed: 17875710]
- Kim HW, Haider HK, Jiang S, Ashraf M. Ischemic preconditioning augments survival of stem cells via miR-210 expression by targeting caspase-8-associated protein 2. *J Biol Chem.* 2009; 284:33161–33168. [PubMed: 19721136]
- Landgraf P, Rusu M, Sheridan R, Sewer A, Iovino N, Aravin A, Pfeffer S, Rice A, Kamphorst AO, Landthaler M, Lin C, Socci ND, Hermida L, Fulci V, Chiaretti S, Foa R, Schliwka J, Fuchs U, Novosel A, Muller RU, Schermer B, Bissels U, Inman J, Phan Q, Chien M, Weir DB, Choksi R, De Vita G, Frezzetti D, Trompeter HI, Hornung V, Teng G, Hartmann G, Palkovits M, Di Lauro R, Wernet P, Macino G, Rogler CE, Nagle JW, Ju J, Papavasiliou FN, Benzing T, Lichter P, Tam W, Brownstein MJ, Bosio A, Borkhardt A, Russo JJ, Sander C, Zavolan M, Tuschl T. A mammalian microRNA expression atlas based on small RNA library sequencing. *Cell.* 2007; 129:1401–1414. [PubMed: 17604727]
- Landles C, Chalk S, Steel JH, Rosewell I, Spencer-Dene B, Lalani el N, Parker MG. The thyroid hormone receptor-associated protein TRAP220 is required at distinct embryonic stages in placental, cardiac, and hepatic development. *Mol Endocrinol.* 2003; 17:2418–2435. [PubMed: 14500757]
- Laurent LC, Chen J, Ulitsky I, Mueller FJ, Lu C, Shamir R, Fan JB, Loring JF. Comprehensive microRNA profiling reveals a unique human embryonic stem cell signature dominated by a single seed sequence. *Stem Cells.* 2008; 26:1506–1516. [PubMed: 18403753]
- Lebanony D, Benjamin H, Gilad S, Ezagouri M, Dov A, Ashkenazi K, Gefen N, Izraeli S, Rechavi G, Pass H, Nonaka D, Li J, Spector Y, Rosenfeld N, Chajut A, Cohen D, Aharonov R, Mansukhani M. Diagnostic assay based on hsa-miR-205 expression distinguishes squamous from nonsquamous non-small-cell lung carcinoma. *J Clin Oncol.* 2009; 27:2030–2037. [PubMed: 19273703]
- Lee Y, Kim M, Han J, Yeom KH, Lee S, Baek SH, Kim VN. MicroRNA genes are transcribed by RNA polymerase II. *Embo J.* 2004; 23:4051–4060. [PubMed: 15372072]
- Lehnert S, Van Loo P, Thilakarathne PJ, Marynen P, Verbeke G, Schuit FC. Evidence for co-evolution between human microRNAs and Alu-repeats. *PLoS One.* 2009; 4:e4456. [PubMed: 19209240]
- Li M, Lee KF, Lu Y, Clarke I, Shih D, Eberhart C, Collins VP, Van Meter T, Picard D, Zhou L, Boutros PC, Modena P, Liang ML, Scherer SW, Bouffet E, Rutka JT, Pomeroy SL, Lau CC, Taylor MD, Gajjar A, Dirks PB, Hawkins CE, Huang A. Frequent amplification of a chr19q13.41 microRNA polycistron in aggressive primitive neuroectodermal brain tumors. *Cancer Cell.* 2009a; 16:533–546. [PubMed: 19962671]
- Li X, Cassidy JJ, Reinke CA, Fischboeck S, Carthew RW. A microRNA imparts robustness against environmental fluctuation during development. *Cell.* 2009b; 137:273–282. [PubMed: 19379693]
- Liang Y, Ridzon D, Wong L, Chen C. Characterization of microRNA expression profiles in normal human tissues. *BMC Genomics.* 2007; 8:166. [PubMed: 17565689]
- Long J, Wang Y, Wang W, Chang BH, Danesh FR. Identification of microRNA-93 as a novel regulator of vascular endothelial growth factor in hyperglycemic conditions. *J Biol Chem.* 2010; 285:23457–23465. [PubMed: 20501654]
- Lopez-Romero P, Gonzalez MA, Callejas S, Dopazo A, Irizarry RA. Processing of Agilent microRNA array data. *BMC Res Notes.* 2010; 3:18. [PubMed: 20205787]
- Lu J, Getz G, Miska EA, Alvarez-Saavedra E, Lamb J, Peck D, Sweet-Cordero A, Ebert BL, Mak RH, Ferrando AA, Downing JR, Jacks T, Horvitz HR, Golub TR. MicroRNA expression profiles classify human cancers. *Nature.* 2005; 435:834–838. [PubMed: 15944708]
- Lu LF, Boldin MP, Chaudhry A, Lin LL, Taganov KD, Hanada T, Yoshimura A, Baltimore D, Rudensky AY. Function of miR-146a in Controlling Treg Cell-Mediated Regulation of Th1 Responses. *Cell.* 2010; 142:914–929. [PubMed: 20850013]
- Lund E, Guttinger S, Calado A, Dahlberg JE, Kutay U. Nuclear export of microRNA precursors. *Science.* 2004; 303:95–98. [PubMed: 14631048]

- Luo SS, Ishibashi O, Ishikawa G, Ishikawa T, Katayama A, Mishima T, Takizawa T, Shigihara T, Goto T, Izumi A, Ohkuchi A, Matsubara S, Takeshita T. Human villous trophoblasts express and secrete placenta-specific microRNAs into maternal circulation via exosomes. *Biol Reprod*. 2009; 81:717–729. [PubMed: 19494253]
- Maccani MA, Avissar-Whiting M, Banister CE, McGonnigal B, Padbury JF, Marsit CJ. Maternal cigarette smoking during pregnancy is associated with downregulation of miR-16, miR-21 and miR-146a in the placenta. *Epigenetics*. 2010; 5 Epub ahead of print.
- Meister G, Tuschl T. Mechanisms of gene silencing by double-stranded RNA. *Nature*. 2004; 431:343–349. [PubMed: 15372041]
- Mincheva-Nilsson L, Baranov V. The role of placental exosomes in reproduction. *Am J Reprod Immunol*. 2010; 63:520–533. [PubMed: 20331583]
- Miura K, Miura S, Yamasaki K, Higashijima A, Kinoshita A, Yoshiura KI, Masuzaki H. Identification of pregnancy-associated MicroRNAs in maternal plasma. *Clin Chem*. 2010 Epub ahead of print.
- Mo FE, Muntean AG, Chen CC, Stolz DB, Watkins SC, Lau LF. CYR61 (CCN1) is essential for placental development and vascular integrity. *Mol Cell Biol*. 2002; 22:8709–8720. [PubMed: 12446788]
- Montenegro D, Romero R, Kim SS, Tarca AL, Draghici S, Kusanovic JP, Kim JS, Lee DC, Erez O, Gotsch F, Hassan SS, Kim CJ. Expression patterns of microRNAs in the chorioamniotic membranes: a role for microRNAs in human pregnancy and parturition. *J Pathol*. 2009; 217:113–121. [PubMed: 18991333]
- Morin RD, O'Connor MD, Griffith M, Kuchenbauer F, Delaney A, Prabhu AL, Zhao Y, McDonald H, Zeng T, Hirst M, Eaves CJ, Marra MA. Application of massively parallel sequencing to microRNA profiling and discovery in human embryonic stem cells. *Genome Res*. 2008; 18:610–621. [PubMed: 18285502]
- Mouillet JF, Chu T, Hubel CA, Nelson DM, Parks WT, Sadovsky Y. The levels of hypoxia-regulated microRNAs in plasma of pregnant women with fetal growth restriction. *Placenta*. 2010a; 31:781–784. [PubMed: 20667590]
- Mouillet JF, Chu T, Nelson DM, Mishima T, Sadovsky Y. MiR-205 silences MED1 in hypoxic primary human trophoblasts. *FASEB J*. 2010b; 24:2030–2039. [PubMed: 20065103]
- Mouillet JF, Yan X, Ou Q, Jin L, Muglia LJ, Crawford PA, Sadovsky Y. DEAD-box protein-103 (DP103, Ddx20) is essential for early embryonic development and modulates ovarian morphology and function. *Endocrinology*. 2008; 149:2168–2175. [PubMed: 18258677]
- Noguer-Dance M, Abu-Amero S, Al-Khtib M, Lefevre A, Coullin P, Moore GE, Cavaillie J. The primate-specific microRNA gene cluster (C19MC) is imprinted in the placenta. *Hum Mol Genet*. 2010; 19:3566–3582. [PubMed: 20610438]
- O'Connell RM, Rao DS, Chaudhuri AA, Baltimore D. Physiological and pathological roles for microRNAs in the immune system. *Nat Rev Immunol*. 2010; 10:111–122. [PubMed: 20098459]
- Okamura K, Hagen JW, Duan H, Tyler DM, Lai EC. The mirtron pathway generates microRNA-class regulatory RNAs in *Drosophila*. *Cell*. 2007; 130:89–100. [PubMed: 17599402]
- Papapetrou EP, Korkola JE, Sadelain M. A genetic strategy for single and combinatorial analysis of miRNA function in mammalian hematopoietic stem cells. *Stem Cells*. 2010; 28:287–296. [PubMed: 19911427]
- Patrick DM, Zhang CC, Tao Y, Yao H, Qi X, Schwartz RJ, Jun-Shen Huang L, Olson EN. Defective erythroid differentiation in miR-451 mutant mice mediated by 14-3-3zeta. *Genes Dev*. 2010; 24:1614–1619. [PubMed: 20679397]
- Pfister S, Remke M, Castoldi M, Bai AH, Muckenthaler MU, Kulozik A, von Deimling A, Pscherer A, Lichter P, Korshunov A. Novel genomic amplification targeting the microRNA cluster at 19q13.42 in a pediatric embryonal tumor with abundant neuropil and true rosettes. *Acta Neuropathol*. 2009; 117:457–464. [PubMed: 19057917]
- Pineles BL, Romero R, Montenegro D, Tarca AL, Han YM, Kim YM, Draghici S, Espinoza J, Kusanovic JP, Mittal P, Hassan SS, Kim CJ. Distinct subsets of microRNAs are expressed differentially in the human placentas of patients with preeclampsia. *Am J Obstet Gynecol*. 2007; 196:261, e261–266. [PubMed: 17346547]

- Pradervand S, Weber J, Lemoine F, Consales F, Paillusson A, Dupasquier M, Thomas J, Richter H, Kaessmann H, Beaudoin E, Hagenbuchle O, Harshman K. Concordance among digital gene expression, microarrays, and qPCR when measuring differential expression of microRNAs. *Biotechniques*. 2010; 48:219–222. [PubMed: 20359303]
- Rawn SM, Cross JC. The evolution, regulation, and function of placenta-specific genes. *Annu Rev Cell Dev Biol*. 2008; 24:159–181. [PubMed: 18616428]
- Ren J, Jin P, Wang E, Marincola FM, Stroncek DF. MicroRNA and gene expression patterns in the differentiation of human embryonic stem cells. *J Transl Med*. 2009; 7:20. [PubMed: 19309508]
- Rippe V, Dittberner L, Lorenz VN, Drieschner N, Nimzyk R, Sendt W, Junker K, Belge G, Bullerdiek J. The two stem cell microRNA gene clusters C19MC and miR-371-3 are activated by specific chromosomal rearrangements in a subgroup of thyroid adenomas. *PLoS One*. 2010; 5:e9485. [PubMed: 20209130]
- Rosa A, Ballarino M, Sorrentino A, Sthandier O, De Angelis FG, Marchioni M, Masella B, Guarini A, Fatica A, Peschle C, Bozzoni I. The interplay between the master transcription factor PU.1 and miR-424 regulates human monocyte/macrophage differentiation. *Proc Natl Acad Sci USA*. 2007; 104:19849–19854. [PubMed: 18056638]
- Rossant J, Cross JC. Placental development: lessons from mouse mutants. *Nat Rev Genet*. 2001; 2:538–548. [PubMed: 11433360]
- Ruby JG, Jan CH, Bartel DP. Intronic microRNA precursors that bypass Drosha processing. *Nature*. 2007; 448:83–86. [PubMed: 17589500]
- Sah S, McCall MN, Eveleigh D, Wilson M, Irizarry RA. Performance evaluation of commercial miRNA expression array platforms. *BMC Res Notes*. 2010; 3:80. [PubMed: 20298588]
- Saito Y, Suzuki H, Tsugawa H, Nakagawa I, Matsuzaki J, Kanai Y, Hibi T. Chromatin remodeling at Alu repeats by epigenetic treatment activates silenced microRNA-512-5p with downregulation of Mcl-1 in human gastric cancer cells. *Oncogene*. 2009; 28:2738–2744. [PubMed: 19503096]
- Sato F, Tsuchiya S, Terasawa K, Tsujimoto G. Intra-platform repeatability and inter-platform comparability of microRNA microarray technology. *PLoS One*. 2009; 4:e5540. [PubMed: 19436744]
- Sempere LF, Christensen M, Silahtaroglu A, Bak M, Heath CV, Schwartz G, Wells W, Kauppinen S, Cole CN. Altered MicroRNA expression confined to specific epithelial cell subpopulations in breast cancer. *Cancer Res*. 2007; 67:11612–11620. [PubMed: 18089790]
- Song H, Bu G. MicroRNA-205 inhibits tumor cell migration through down-regulating the expression of the LDL receptor-related protein 1. *Biochem Biophys Res Commun*. 2009; 388:400–405. [PubMed: 19665999]
- Stark A, Brennecke J, Bushati N, Russell RB, Cohen SM. Animal MicroRNAs confer robustness to gene expression and have a significant impact on 3'UTR evolution. *Cell*. 2005; 123:1133–1146. [PubMed: 16337999]
- Taylor DD, Akyol S, Gercel-Taylor C. Pregnancy-associated exosomes and their modulation of T cell signaling. *J Immunol*. 2006; 176:1534–1542. [PubMed: 16424182]
- Thery C, Ostrowski M, Segura E. Membrane vesicles as conveyors of immune responses. *Nat Rev Immunol*. 2009; 9:581–593. [PubMed: 19498381]
- Tomari Y, Zamore PD. Perspective: machines for RNAi. *Genes Dev*. 2005; 19:517–529. [PubMed: 15741316]
- Tsai KW, Kao HW, Chen HC, Chen SJ, Lin WC. Epigenetic control of the expression of a primate-specific microRNA cluster in human cancer cells. *Epigenetics*. 2009; 4:587–592. [PubMed: 19923923]
- Valadi H, Ekstrom K, Bossios A, Sjostrand M, Lee JJ, Lotvall JO. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. *Nat Cell Biol*. 2007; 9:654–659. [PubMed: 17486113]
- Wang K, Zhang S, Weber J, Baxter D, Galas DJ. Export of microRNAs and microRNA-protective protein by mammalian cells. *Nucleic Acids Res*. 2010 Epub ahead of print.
- Wang Y, Medvid R, Melton C, Jaenisch R, Blueloch R. DGCR8 is essential for microRNA biogenesis and silencing of embryonic stem cell self-renewal. *Nat Genet*. 2007; 39:380–385. [PubMed: 17259983]

- Wiklund ED, Bramsen JB, Hulf T, Dyrskjot L, Ramanathan R, Hansen TB, Villadsen SB, Gao S, Ostenfeld MS, Borre M, Peter ME, Orntoft TF, Kjems J, Clark SJ. Coordinated epigenetic repression of the miR-200 family and miR-205 in invasive bladder cancer. *Int J Cancer*. 2010 Epub ahead of print.
- Wittmann J, Jack HM. Serum microRNAs as powerful cancer biomarkers. *Biochim Biophys Acta*. 2010 Epub ahead of print.
- Wong L, Lee K, Russell I, Chen C. Endogenous controls for real-time quantitation of miRNA using TaqMan microRNA assays. *Applied Biosystems*. 2007 Application Note 127AP11-01.
- Wu H, Zhu S, Mo YY. Suppression of cell growth and invasion by miR-205 in breast cancer. *Cell Res*. 2009; 19:439–448. [PubMed: 19238171]
- Yu D, dos Santos CO, Zhao G, Jiang J, Amigo JD, Khandros E, Dore LC, Yao Y, D'Souza J, Zhang Z, Ghaffari S, Choi J, Friend S, Tong W, Orange JS, Paw BH, Weiss MJ. miR-451 protects against erythroid oxidant stress by repressing 14-3-3zeta. *Genes Dev*. 2010; 24:1620–1633. [PubMed: 20679398]
- Yu J, Ryan DG, Getsios S, Oliveira-Fernandes M, Fatima A, Lavker RM. MicroRNA-184 antagonizes microRNA-205 to maintain SHIP2 levels in epithelia. *Proc Natl Acad Sci USA*. 2008; 105:19300–19305. [PubMed: 19033458]
- Zernecke A, Bidzhekov K, Noels H, Shagdarsuren E, Gan L, Denecke B, Hristov M, Koppel T, Jahantigh MN, Lutgens E, Wang S, Olson EN, Schober A, Weber C. Delivery of microRNA-126 by apoptotic bodies induces CXCL12-dependent vascular protection. *Sci Signal*. 2009; 2:ra81. [PubMed: 19996457]
- Zhang R, Wang YQ, Su B. Molecular evolution of a primate-specific microRNA family. *Mol Biol Evol*. 2008; 25:1493–1502. [PubMed: 18417486]
- Zhang Y, Diao Z, Su L, Sun H, Li R, Cui H, Hu Y. MicroRNA-155 contributes to preeclampsia by down-regulating CYR61. *Am J Obstet Gynecol*. 2010; 202:466, e461–467. [PubMed: 20452491]
- Zhang Z, Sun H, Dai H, Walsh RM, Imakura M, Schelter J, Burchard J, Dai X, Chang AN, Diaz RL, Marszalek JR, Bartz SR, Carleton M, Cleary MA, Linsley PS, Grandori C. MicroRNA miR-210 modulates cellular response to hypoxia through the MYC antagonist MNT. *Cell Cycle*. 2009; 8:2756–2768. [PubMed: 19652553]
- Zhu XM, Han T, Sargent IL, Yin GW, Yao YQ. Differential expression profile of microRNAs in human placentas from preeclamptic pregnancies vs normal pregnancies. *Am J Obstet Gynecol*. 2009; 200:661, e661–667. [PubMed: 19285651]
- Zhu Y, Qi C, Jia Y, Nye JS, Rao MS, Reddy JK. Deletion of PBP/PPARBP, the gene for nuclear receptor coactivator peroxisome proliferator-activated receptor-binding protein, results in embryonic lethality. *J Biol Chem*. 2000; 275:14779–14782. [PubMed: 10747854]

Table 1

MicroRNAs associated with placental injury

Condition tested vs normal control	Differentially regulated miRNAs	Technique	Reference
Preeclampsia	miR-210, miR-155, miR-181b, miR-182*, miR-200b, miR-154*, miR-183	RT-PCR	(Pineles et al., 2007)
	miR-16, miR-29b, miR-195, miR-26b, miR-181a, miR-335, miR-222	Microarray	(Hu et al., 2009)
	miR-181a, miR-584, miR-30-3p, miR-210, miR-152, miR-517*, miR-518b, miR-519e*, miR-638, miR-296, miR-362	Microarray	(Zhu et al., 2009)
	miR-155	RT-PCR	(Zhang et al., 2010)
Preterm labor	miR-202*, miR-135a, miR-136, miR-302c, miR-135b, miR-449, miR-142-3p, miR181c, miR-154, miR-642, miR-101, miR-484, miR-204, miR-508, miR-502, miR-25, miR-369-3p, miR-518b, miR-573, miR-554, miR-627, miR-483, miR-370, miR-652, miR-196a, miR-128a, miR-148a, miR-634, miR-488, miR-338, miR-601, miR-628, miR-494, miR-513, miR-519c, miR-423, miR-50g, miR-520h, miR-489	Microarray	(Montenegro et al., 2009)
Exposure to toxicants	Bisphenol A: miR-146a	RT-PCR	(Avissar-Whiting et al., 2010)
	Cigarette smoking: miR-16, miR-21, miR-146a	RT-PCR	(Maccani et al., 2010)