REVIEW

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Expression, regulation and function of MicroRNAs in endometriosis

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Endometriosis (EMS), characterized by the presence and growth of functional endometrial-like tissues outside the uterine cavity, is a common and benign gynecological disorder with a poorly understood and somewhat enigmatic etiopathogenesis and pathophysiology. MicroRNAs (miRNAs) are single-stranded 19-25 nucleotide-long RNAs and have an important role in post-transcriptional gene silencing by base pairing with target mRNAs. Recent research has shown that miRNAs and their target mRNAs are differentially expressed in endometriosis and other disorders of the female reproductive system. In this paper, we review the recent progress in understanding the roles of miRNAs in endometriosis, and specific miRNAs as biomarkers and therapeutic targets for endometriosis.

1. Introduction

Endometriosis (EMS), characterized by the presence and growth of functional endometrial-like tissues outside the uterine cavity, is a common and benign gynecological disorder with a poorly understood and somewhat enigmatic etiopathogenesis and pathophysiology (Giudice and Kao 2004). It is a leading cause of disability in women of reproductive age, responsible for dysmenorrhea, pelvic pain and infertility (Farquhar 2000). Endometriosis is likely a polygenic multifactorial disease (Santamaria and Tayler 2014), which has a genetic predisposition with a sevenfold risk of endometriosis in women whose mother or sister has the disease (Moen et al. 1993; Simpson and Bischoff 2002). Specific genes are differentially expressed in eutopic endometrium of endometriosis patients as compared to those from normal woman controls (Kao et al. 2003; Taylor et al. 2008). The results suggest that gene dysregulation may play a role in the pathogenesis of endometriosis.

MicroRNAs (miRNAs) are single-stranded 19-25 nucleotide-long RNAs and have an important role in post-transcriptional gene silencing by base pairing with target mRNAs (Ma et al. 2014). miRNA "genes" are transcribed in the nucleus, producing primary transcripts termed "pri-miRNAs". pri-miRNAs undergo substantial processing, resulting in the generation of a 70- to 90-nucleotide (nt) stem-loop precursor miRNA (pre-miRNA) in the nucleus. After transportation into the cytoplasm, the pre-miRNAs undergo a second cleavage by Dicer, generating a double-stranded miRNA duplex containing 2-nt-long 3′ overhangs. Double-stranded miRNAs unwind to form single-strand, mature miRNAs (Bernstein et al. 2001, 2003; Paroo et al. 2007). Mature miRNAs incorporate into the RNA-induced silencing complex (RISC) and regulate target gene expression mostly, but not always through translational repression by complementary interaction with target genes (Bartel 2004; Zamore and Haley 2005). miRNA-induced translational repression is considered to involve two distinct mechanisms: the inhibition of translation initiation and/or inhibition of a "postinitiation" step in translation, which also elicits cotranslational degradation of the nascent peptide (Jackson and Standart 2007; Nilsen 2007; Pillai et al. 2007). Through this mechanism, miRNAs influence the outcome of various cellular activities under normal and disease conditions. To date, it has been estimated that 2588 unique mature human miRNAs have been identified (http://www.mirbase.org/). Usually a total of 1,309 human miRNAs are used in analysis (Cook et al. 2015). MiRNAs are essential for normal mammalian development, determining cell identity and fate and regulating diverse biological processes including cell proliferation, metabolism, differentiation and apoptosis. Recent research has shown that miRNAs and their target mRNAs are differentially expressed in endometriosis and other disorders of the female reproductive system (Teague et al. 2010). miRNAs may thus be attractive candidates for novel diagnostic markers and therapeutic interventions in endometriosis, as recently demonstrated in other miRNA regulated diseases (Elmen et al. 2008; Mitchell et al. 2008).Thus, research on the role of miRNAs in endometriosis has attracted much attention (Fig. 1). In this paper, we review the recent progress in understanding the roles of miRNAs in endometriosis, and specific miRNAs as biomarkers and therapeutic targets for endometriosis.

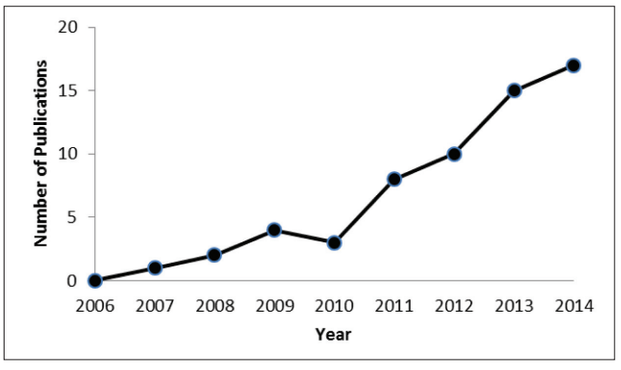

Fig. 1: Estimated number of publications about studies on miRNAs in endometriosis yearly from 2006 to 2014. Based on the retrieved papers from the PUBMED database after searching related references by means of miRNA, endometriosis key words, the number of publications about the studies on miRNAs in endometriosis were calculated.

2. Expression of microRNAs in endometriosis

In recent years, there has been a significant focus on understanding the pathogenesis of endometriosis and the role of miRNAs in the pathogenesis of the disease. It has been considered that the aberrantly expressed miRNAs in endometriosis may be responsible for and may stimulate the development of endometriosis (Burney et al. 2009). Previous studies have profiled miRNA expression in

endometriotic implants and in the eutopic endometrium of women with or without endometriosis (Burney 2009; Hawkins et al. 2011; Ohlsson Teague et al. 2009; Pan et al. 2008). Pan et al. (2007) identified 48 aberrantly expressed miRNAs in endometriosis, which affected a variety of target genes involved in the development of endometriosis, such as estrogen receptor a (ERa), ERb, progesterone receptor and transforming growth factor-β. Toloubeydokhti et al. (2008) demonstrated an aberrant miRNA expression pattern in endometriotic tissues. They observed repressed expression of miR-23b and miR-542-3p and increased expression of miR-17-5p in paired endometriotic tissues when compared with normal endometrium. Filigheddu et al. (2010) investigated the differential expression of miRNAs in endometriosis by direct comparison between paired ectopic and eutopic endometrium samples. About 50 microRNAs were identified to be differentially expressed and the differential expression of five microRNAs (including miR-200a, miR-200b, miR-200c, -miR-182 and miR-202) was validated by real-time RT-PCR in other 13 patients. Indeed, these reports demonstrated that there were significant differential expressions of specific miRNAs in eutopic versus ectopic tissue. miR-200a, miR-200b, miR-200c and miR-182 levels in ectopic endometrium were reduced up to 95%, while miR-202 expression in ectopic endometrium was increased up to 60 folds as compared to that in eutopic endometrium.

It has been reported that 10 miRNAs were upregulated (miR-202, 193a-3p, 29c, 708, 509-3-5p, 574-3p, 193a-5p, 485-3p, 100 and 720) and 12 miRNAs were downregulated (miR-504, 141, 429, 203, 10a, 200b, 873, 200c, 200a, 449b, 375 and 34c-5p) in ovarian endometriotic cysts when compared with endometrium (Hawkins 2011). Similarly, Ohlsson et al. (2009) investigated miRNA expression profiles in paired ectopic and eutopic endometrial tissues and identified 14 upregulated (miR-145, miR-143, miR-99a, miR-99b, miR-126, miR-100, miR-125b, miR-150, miR-125a, miR-223, miR-194, miR-365, miR-29c and miR-1) and 8 downregulated (miR-200a, miR-141, miR-200b, miR-142-3p, miR-424, miR-34c, miR-20a and miR-196b) miRNAs.

Interestingly, the perturbed gene expression in eutopic secretory endometrium of affected patients coincides with differential expression of several miRNA species (Burney 2009). Eutopic secretory endometrium from women with endometriosis is characterized by a miRNA expression profile that differs from that of healthy eutopic secretory endometrium. In particular, members of the miR-9 and miR-34 families (i.e. miR-9, miR-34b and miR-34c-5p) are downregulated in the endometrium from women with endometriosis compared with healthy individuals. The predicted targets of the miR-9 and miR-34 families include the cell-cycle regulator genes cyclin E1, cyclin E2, CDK4, CDK6 and CDC25A and the anti-apoptotic gene, BCL-2, which are also differently expressed in endometrium from women with and without endometriosis (Hawkins 2011). Specifically, several miRNA families including miR-9, miR-34, let-7, miR-15, miR16, and miR-125 were found to be downregulated in eutopic secretory endometrium from women with endometriosis. Other miRNAs such as miR-199a and miR-122 are upregulated in endometriotic patients compared to non-endometriotic women (Pan et al. 2008; Pan 2008). Total RNA extracted from serum and quantitative reverse-transcription polymerase chain reaction to determine levels of miRNA let-7a-f and miR-135a,b. The levels of circulating let-7b and miR-135a were statistically significantly decreased in women with endometriosis compared with controls, and let-7d and 7f showed a trend toward downregulation. When the patients were analyzed according to phase of the menstrual cycle, the expression of let-7b, 7c, 7d, and 7e was statistically significantly lower in the women with endometriosis during the proliferative phase. These results indicated that the combination of serum let-7b, 7d, and 7f levels during the proliferative phase may serve as a diagnostic marker for endometriosis (Cho et al. 2015).

Taken together, these findings suggest that endometriotic tissues have aberrant miRNA expression patterns and these aberrantly expressed miRNAs may be responsible for the pathogenesis of endometriosis. Upregulated and downregulated miRNAs in different samples from the patients with endometriosis were shown in Table 1 and Table 2, respectively.

Table 1: Upregulated miRNAs expressed in different samples from endometriosis patients

miRNA	Sample	Reference
miR-145	Ectopic endometrial tissues	(Hawkins 2011)
miR-143		(Hawkins 2011)
miR-99a		(Hawkins 2011)
miR-99b		(Hawkins 2011)
miR-126		(Hawkins 2011)
miR-100		(Hawkins 2011)
miR-125b		(Hawkins 2011)
miR-150		(Hawkins 2011)
miR-125a		(Hawkins 2011)
miR-223		(Hawkins 2011)
miR-194		(Hawkins 2011)
miR-365		(Hawkins 2011)
miR-29c		(Hawkins 2011)
miR-1		(Filigheddu 2010)
miR-17-5p	Endometriotic tissues	(Filigheddu 2010)
miR-202	Ovarian endometriotic cysts	(Filigheddu 2010)
miR-193a-3p		(Hawkins 2011)
miR-29c		(Hawkins 2011)
miR-708		(Hawkins 2011)
miR-509-3-5p		(Hawkins 2011)
miR-574-3p		(Hawkins 2011)
miR-193a-5p		(Hawkins 2011)
miR-485-3p		(Hawkins 2011)
miR -720		(Hawkins 2011)

Table 2: Downregulated miRNAs expressed in different samples from endometriosis patients

miRNA	Sample	Reference
miR-200a	Ectopic endometrial tissues	(Filigheddu 2010)
miR-141		(Hawkins 2011)
miR-200b		(Filigheddu 2010)
miR-142-3p		(Hawkins 2011)
miR-424		(Hawkins 2011)
miR-34c		(Hawkins 2011)
miR-20a		(Hawkins 2011)
miR-196b		(Hawkins 2011)
miR-23b	Endometriotic tissues	(Toloubeydokhti 2008)
miR-542-3p		(Toloubeydokhti 2008)
miR -504	Ovarian endometriotic cysts	(Hawkins 2011)
miR -141		(Hawkins 2011)
miR- 429		(Hawkins 2011)
miR -203		(Hawkins 2011)
miR -10a		(Hawkins 2011)
miR -873		(Hawkins 2011)
miR -200c		(Filigheddu 2010)
miR -449b		(Hawkins 2011)
miR -375		(Hawkins 2011)
miR -34c-5p		(Hawkins 2011)

3. Regulation and function of microRNAs in endometriosis

The presence of distinct miRNA profiles between endometriotic and nonendometriotic tissues indirectly indicates that miRNA may have a function in the pathophysiology of endometriosis. Several pathological processes such as inflammation, local estrogen biosynthesis, progesterone resistance, cell invasion, extracellular matrix remodelation, angiogenesis, and epigenetic regulation are crucial in the pathophysiology of endometriosis, miRNAs seem to have an essential role in regulating these processes (Santamaria and Taylor 2014). In particular, miRNAs target the expression of genes involved in cell-cycle progression, differentiation, apoptosis, inflammatory and immune response, and angiogenesis (Carleton et al. 2007; Harfe et al. 2005; Jovanovic et al. 2006; Kuehbacher et al. 2008; Li et al. 2007; Linsley et al. 2007). These cellular processes are integrated in parts of the endometrial regeneration throughout the menstrual cycle and a vast number of gene products whose expression may be the target of miRNA regulatory functions (Pan 2008) (Fig. 2).

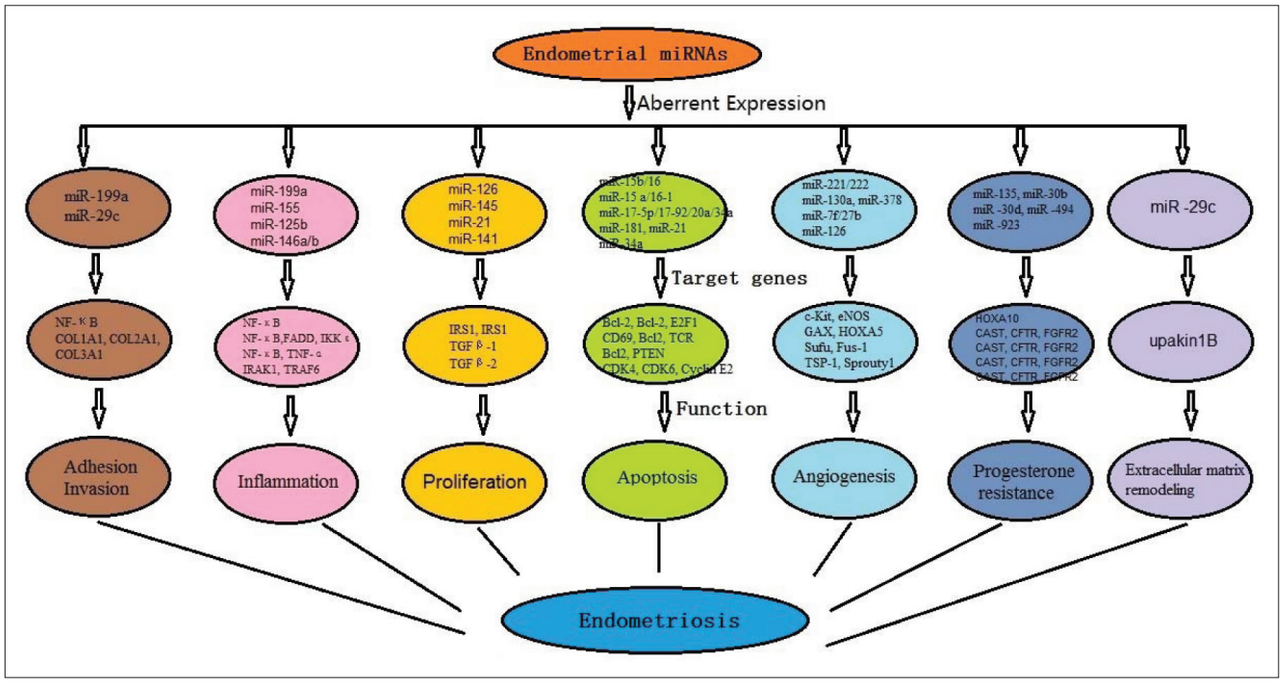

Fig. 2: miRNA regulatory functions in the processes of endometriosis. miRNA expression may play a role in these processes, regulating transcripts involved in cell adhesion and invasion, inflammation, cellular proliferation, apoptosis, angiogenesis, progesterone resistance and extracellular matrix remodelling.

3.1. Regulation and function of microRNAs in inflammation of endometriosis

The onset of menstruation is associated with the expression of a network of highly active substances with inflammatory and immune-related activities (Chegini et al. 2002; Jabbour et al. 2006). Abdominal local microenvironment inflammation plays an important role in breeding and planting of ectopic endometrial cells. MicroRNA involved in regulation of inflammatory cells to raise and the release of inflammatory cytokines, may play an important role in the formation of the local microenvironment of ectopic lesions. Anyhow, MicroRNA may participate in raising the inflammatory cells, and the formation of the inflammatory microenvironment, be beneficial to the occurrence and development of endometriosis. NF-κB pathway is a critical path of the inflammatory cytokine release of ectopic lesions. The study of Chen et al. showed that miR-199a negatively regulates the NF – κB pathway to inhibit the expression of protein kinase B whereas the expression of miR-199a is reduced in endometriosis which may be related to the abnormal activation of NF – κB in ectopic endometrial cells (Dai and Di 2011).

A recent study revealed that stromal cells from endometriosis lesions have higher miR20a levels. MiR200a expression results in decreased expression of dual-specificity phosphatase-2 that subsequently results in prolonged extracellular-signal-regulated kinases activation through hypoxia-inducible factor. Moreover, fibroblast growth factor-9 is induced by prostaglandin E2 through extracellular-signal-regulated kinases activation in endometriotic stromal cells contributing to inflammation in the pathogenesis of endometriosis (Lin et al. 2012; Santamaria and Taylor 2014).

3.2. Regulation and function of microRNAs in cell survival and cell invasion of endometriosis

Adhesion and invasion are the key steps in the formation of endometriosis which has similar transfer and erosion characteristics than a malignant tumor. Degradation and reshaping of extra cellular matrix (ECM) are essential conditions of the adhesion and invasion of ectopic endometrial cells, miRNA participates in regulating the degradation and reshaping of ECM and may have an important regulatory role in adhesion and invasion of ectopic endometrial cells. Matrix metalloproteinase (MMP) 9 is an important protein kinase which is closely related to the degradation of ECM and the formation of endometriosis. The expression of MMP-9 in the eutopic and ectopic endometrium of endometriosis patients increased to promote the degradation of the ECM and increase the aggressivity of endometrial cells. MMP-9 is the target gene of NF – κB whereas the activation of NF – κB is negatively regulated by miRNA-199a which is down-expressed in endometriosis. So miRNA-199a may indirectly regulate the synthesis and release of MMP-9 through the NF – κB pathway (Dai and Di 2011).

There is increasing evidence that incomplete transition of the endometrium from proliferative to secretory phase enhances the survival capacity and implantation of the refluxed endometrium. Certain miRNAs such as miR-183 that are downregulated in endometriosis seem to be involved in this process through regulation of cell growth, cell differentiation, cell invasion, cell adhesion, and apoptosis. Local inflammation and tissue remodeling are crucial during endometrial role development. The downregulation of miR-17-5p induces lower expression of transforming growth factor-b and interleukin-8 and higher expression of hypoxia inducible transcription factor-1a and vascular endothelial growth factor (VEGF)-A enhancing cell survival and cell proliferation in endometriosis (Flores et al. 2007; Santamaria and Taylor 2014; Shi et al. 2014; Volinia et al. 2006; Yu et al. 2010). Dai and Di (2011) found miR-199a can inhibit the adhesion, migration and invasion of the human eutopic endometrial stromal cells (ESC), Ikappa B kinase beta (IKKβ) is the target gene of miR-199a in ESC, which means one of the mechanisms of the inhibition effect is probably that miR-199a inhibits the activation of nuclear factor-kappa B (NF-κB) signaling pathway by targeting IKKβ gene.

3.3. Regulation and function of microRNAs in angiogenesis of endometriosis

Vascularization degree around the endometriosis lesions is the important factor of affecting the growth and invasion of ectopic endometrium. Ectopic lesions stimulate the proliferation and migration of vascular endothelial cells by release of a variety of angiogenic factors to form new capillaries. MiRNA participates in the regulation of various angiogenesis factors, and may play an important role in the formation of blood vessels in endometriosis.

Studies showed that miR-126 participates in regulating angiogenesis during development as well as the vascular remodeling. This shows that miR-126 plays a crucial role during angiogenesis while it is up-expressed in endometriosis which means it may be involved in the blood vessel formation in endometriosis (Dai and Di 2011). Meanwhile, VEGF-A and the angiogenesis inhibitor thrombospondin-1 (TSP-1) play an important role in the pathogenesis of endometriosis. Women with endometriosis showed a significant increase in TSP-1 protein levels and a decrease in VEGF-A expression in ovarian endometriomas compared to the eutopic endometrium in a recent study. While miR-125a, miR-222, and miR-17-5p showed a significant inverse correlation with VEGF-A and TSP-1 protein levels, suggesting that the expression of TSP-1 and VEGF-A may be regulated by these miRNAs (Santamaria and Taylor 2014). Additionally, some miRNAs have demonstrated anti-angiogenic properties (miRNA-15b, -16, -221, and -222), whereas others are proangiogenic (miRNA-17-92 cluster) (Santamaria and Taylor 2014; Urbich et al. 2008; Wu et al. 2009).

In an another recent study (Braza-Boils et al. 2014), endometrial tissue showed significantly lower levels of miR-202-3p, miR-424-5p, miR-449b-3p and miR-556-3p, and higher levels of VEGF-A and uPA than healthy (control) endometrium. However, tissue affected by ovarian endometrioma showed significantly lower expression of miR-449b-3p than endometrium from both controls and patients, and higher levels of PAI-1 and the angiogenic inhibitor TSP-1. A significant inverse correlation between miR-424-5p and VEGF-A protein levels was observed in patient endometrium, and an inverse correlation between miR-449b-3p and TSP-1 protein levels was observed in ovarian endometrioma. Peritoneal implants had significantly higher levels of VEGF-A than ovarian endometrioma. These results suggest that differences in miRNA levels could modulate the expression of VEGF-A and TSP-1, which may play an important role in the pathogenesis of endometriosis. The higher angiogenic and proteolytic activities observed in eutopic endometrium from patients might facilitate the implantation of endometrial cells at ectopic sites.

3.4. Regulation and function of microRNAs in proliferation and apoptosis of endometriosis

Proliferation and apoptosis are the basic processes of sustaining the growth and stability of ectopic endometrial cells and are regulated by multiple genes whose expression may be regulated by miRNA. Insulin receptor substrate1 (IRSI) is a gene related to cell growth which is closely associated with insulin biological regulation and can promote cell proliferation. IRSI is the target gene of miR-126 and miR-145. A study showed that both of these miRNA are up-expressed in endometriosis suggesting that they play an important role in suppressing ectopic endometrial cell growth. In addition, transforming growth factor (TGF) B is also regulated by miRNA. miR-21 and miR-141 respectively inhibit the transcription of TGFβ-1 and TGFβ-2 whereas the expression of miR-21 and miR-141 decreases in endometriosis. Thus it can be seen that miR-21 and miR-141 are involved in promoting the transcription of TGFβ and participate in regulating the ectopic endometrium cell growth (Dai and Di 2011).

Bcl-2 is an important apoptosis suppressor gene. It is high expressed in ectopic endometrial cells and negatively correlated with the incidence of apoptosis. Xia et al. showed that bcl-2 is the target gene of miR-15b/16 while miR-15b/16 is down-expressed in endometriosis which means miR-15b/16 may be related with the increase of antiapoptotic proteins in ectopic endometrial cells (Dai and Di 2011).

Several miRNAs are aberrantly expressed in endometriotic cyst stromal cells (ECSCs), including miR-196b whose expression is repressed in endometriotic stromal cells. The anti-apoptotic and excessive proliferative properties of endometriotic cells are considered to be involved in the development and progression of endometriosis. Abe et al. (2013) identified eight downregulated miRNAs (including miR-196b) and four upregulated miRNAs in ECSCs by miRNA microarray analysis. Compulsory expression of miR-196b directed the inhibition of proliferation and the induction of apoptosis in ECSCs. MiR-196b was found to suppress c-myc and Bcl-2 mRNA expression in ECSCs, and there was a significant correlation between miR-196b and HOXA10 expression in ECSCs and NESCs. The miR-196b gene was hypermethylated in ECSCs when compared with NESCs, and the treatment with a DNA demethylating agent restored the expression of miR-196b in ECSCs. These findings suggest that aberrant miRNA expression plays an important role in the pathogenesis of endometriosis as a part of epigenetic mechanisms, that expression of miR-196b in ECSCs is repressed by DNA hypermethylation of the miR-196b gene and this repression may be involved in the development of proliferative and anti-apoptotic characteristics of endometriosis (Abe et al. 2013).

4. microRNAs as endometriosis diagnostic markers

Endometriosis is generally diagnosed by visualization of the endometriotic lesions and the current gold standard technique for diagnosis of endometriosis is surgical assessment by laparoscopy. For this reason, diagnosis and intervention in this disease are often delayed. This delay is further compounded by the absence of symptoms in some patients and lack of sensitive biomarkers for detecting early stage disease (Guo 2009; Santamaria and Taylor 2014). Therefore, newer and less invasive diagnostic and therapeutic tools for disease diagnosis and therapy in the early stages are required.

Results have demonstrated that miR-17-5p, miR-20a, and miR22 were downregulated in women with endometriosis compared to non-endometriotic women (Jia et al. 2013). Several miRNAs have been assessed not only as potential diagnostic markers, but also as markers associated with the distinct clinical features of the disease (Resnick et al. 2009). Among six dysregulated miRNAs analyzed in this study, miR-199a and miR-122 were upregulated in patient serum and could be used to differentiate between severe and mild endometriosis. Further analysis also indicated that the relative concentration of miR-122 might be correlated with that of miR-199a. Among them, miR-199a and miR-542-3p were found to be particularly useful, when combined reaching a sensitivity and a specificity in diagnosing endometriosis of up to 96.61% and 79.66%, respectively (Yu et al. 2012). In addition, miR-199a is correlated with pelvic adhesion and lesion distribution as well as with hormone-mediated signaling pathways, demonstrating that it may play an important role in the progression of the disease (Hull and Nisenblat 2013).

Women with endometriosis have characteristic differences in eutopic endometrial transcript and protein profiles when compared with women without endometriosis. Several researchers have tried to develop a semi-invasive test for endometriosis by analyzing eutopic endometrial biopsies obtained at an outpatient clinic visit. It seems reasonable to postulate that the eutopic endometrial miRNA profile can be used to distinguish eutopic endometrium from women with and without endometriosis in a simple, reliable way with good sensitivity and specificity (Teague 2010). A recent study identified three distinct miRNA signatures with reliable differential expression between healthy individuals, patients with endometriosis, and patients with endometriosis-associated ovarian cancer (EAOC). When profiled against the control serous ovarian cancer (SOC) category, the results revealed different miRNAs, suggesting that the identified signatures are reflective of disease-specific pathogenic mechanisms. This study reports that distinct plasma miRNA expression patterns may serve as highly specific and sensitive diagnostic biomarkers to discriminate between healthy, endometriosis, and endometriosis-associated ovarian cancer (EAOC) cases (Suryawanshi et al. 2013).

A strong correlation was demonstrated between the miRNA profiles of serum and cancer tissue in patients with ovarian cancer (Resnick 2009; Taylor 2008), suggesting that miRNAs may be secreted from tissues into the bloodstream. If endometriosis associated miRNAs can be identified in serum, a non-invasive blood test could be developed to diagnose this chronic condition (Teague 2010). Therefore, studies on the expression, regulation and function of miRNAs in patients with endometriosis will provide the unique insights for the development of specific miRNAs as diagnostic markers and therapeutic targets for endometriosis in the future.

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