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The function of miR-519d in cell migration, invasion, and proliferation suggests a role in early placentation

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Abstract

The processes of proliferation, migration, and invasion of extravillous trophoblasts are critical for placental implantation and early development, and directly influence pregnancy outcome. Dysregulation of these processes has been associated with placental dysfunction, implicated in clinical conditions such as preeclampsia and placental accreta. Among diverse microRNA (miRNA) species that are expressed in placental trophoblasts, members of the chromosome 19 miRNA cluster (C19MC) stand out in their nearly exclusive expression in the placenta. Recent research on the function of C19MC miRNAs in normal cell physiology and during tumorigenesis identified one C19MC member, miR-519d, as a regulator of cell migration, invasion, and interaction with the extracellular matrix. In this review, we focus on the function of miR-519d in placental trophoblasts, where miR-519d regulates cell migration and invasion, and its aberrant expression is associated with preeclampsia. In cancer, the function of miR-519d as an oncomiR or a tumor-suppressor is dependent upon the tumor type. Further research on the biological function and regulation of miR-519d may illuminate previously unknown mechanisms that control cell migration and invasion.

Keywords

Placenta; miRNA; C19MC; miR-519d; invasion

Introduction

Early trophectoderm implantation within the uterine wall, followed by migration and invasion of trophoblastic columns within the decidua and inner myometrial layer, are central for fetal development [1]. Shallow or excessive implantation has been associated with important diseases of pregnancy, such as preeclampsia and placental adhesion disorders [2].

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Interestingly, trophoblast invasion that occurs during normal development resembles malignant cell invasion during tumorigenesis. This similarity suggests that analogous processes might regulate normal trophoblast invasion and tumor formation. In this review we focus on miR-519d, a member of the chromosome 19 miRNA cluster (C19MC). MiR-519d has been implicated in regulation of trophoblast migration and tumor formation, shedding light on previously unknown functions of C19MC members.

Invasion, proliferation, and migration during placental development

Placental implantation is a central event during pregnancy. Whereas trophoblasts in the chorionic villi play a critical role in the regulation of gas and nutrient exchange and elimination of fetal waste, the extravillous trophoblast (EVT) invades into the maternal decidua and inner myometrium to form the implantation and early maternal-fetal exchange site [3,4]. These two trophoblast types can produce paracrine and endocrine signals and immunologically protect the pregnancy [3]. Among EVT subtypes, interstitial EVTs migrate into the decidua and the inner third of the myometrium and anchor the placenta to the maternal tissues, while endovascular EVTs penetrate and remodel the maternal spiral arteries [1]. In this process, also known as pseudovasculogenesis, the uterine spiral arteries are transformed into low-resistance, high-flow vessels, enabling sufficient blood supply to the placental bed. The failure of this physiologic conversion of uterine spiral arteries may lead to placental hypoperfusion, tissue injury, and trophoblast hypoxia and their consequences including fetal death, growth restriction, and preeclampsia [2,5].

The process of EVT invasion is tightly orchestrated, leading to the formation of placental cell columns, architecture remodeling, and proper vascular support [6,7]. To date, various mechanisms have been proposed to govern the proliferation, migration, invasion, and differentiation of EVTs. The main regulators of this process include cell adhesion molecules, integrins, growth factor receptors and their ligands, such as EGF, TGFβ and IGF2, enzymes that govern extracellular matrix degradation, angiogenesis, and immune response [1].

Placental health and C19MC miRNAs

Diverse miRNA species participate in modulation of gene expression in many physiological and pathological processes, including embryogenesis and placental development and function [8]. Several miRNAs were shown to regulate trophoblast migration and invasion, either by facilitating or by inhibiting these processes. These miRNA are summarized in Table 1. One of the most fascinating families of trophoblast-related miRNAs is the C19MC. C19MC is the largest human miRNA gene cluster, spanning an approximately 100 kb region. It consists of 46 miRNA genes encoding a total of 58 mature miRNAs [9]. This cluster is present only in the primate and human genome and expresses miRNAs primarily in placenta [10] and, at a lower level, in embryonic stem cells and in certain tumors [11–14]. The functions of C19MC miRNAs in cancer are divergent, exhibiting either oncogenic or tumor-suppressive functions, depending on the tumor type [13]. C19MC miRNAs are among the most abundant miRNAs in the human placenta and in the plasma of pregnant women [15,16]. Their levels gradually increase in the maternal circulation as pregnancy progresses and rapidly decline after delivery. While their function is not entirely clear, we recently

found that C19MC miRNAs are packaged within trophoblastic exosomes and confer viral resistance to non-trophoblastic cells by the induction of autophagy [17–20].

Altered placental expression or plasma levels of C19MC miRNAs has been observed in diseases associated with placental dysfunctions such as preeclampsia [21–25]. Upregulation of several C19MC miRNAs is associated with increased risk of gestational hypertension [26]. Higashijima *et al.* identified seven miRNA members of C19MC exhibiting a significantly lower expression level in placentas from pregnancies complicated by fetal growth restriction, although these changes were not observed in maternal plasma miRNA levels [16,23,27].

Placental miR-519d and its function in trophoblast invasion, proliferation, and migration

We recently showed that C19MC miRNAs have a differential distribution within the human placenta, with a higher expression in villous trophoblasts compared to EVTs, both in primary placenta tissues and cell lines [28]. Specifically, we found that a representative C19MC miRNA, miR-518b, is highly expressed in VT cell lines including JEG3, BeWo and Jar, but not in the EVT line HTR-8/SVneo [28]. Morales-Prieto *et al* also reported that the C19MC is absent in HTR-8/SVneo cells but strongly expressed in JEG-3 cells [29]. In contrast, Ding *et al* reported that miR-519d-3p was significantly downregulated in JEG-3 cells compared to HTR-8/SVneo cells [30]. This discrepancy may reflect a different cell line source or other experimental conditions. Importantly, upon stable transfection of C19MC miRNAs into HTR-8/SVneo cells [28], we found that these miRNAs selectively attenuate cell migration without affecting cell proliferation or apoptosis. We subsequently found that miR-519d directly silences the expression of several mRNAs that were downregulated during migration of HTR-8/SVneo cells, such as CXCL6, FOXL2, and NR4A2 [28]. In findings similar to our results, Ding et al. found that overexpression of miR-519d significantly inhibited the migration and invasion of HTR-8/SVneo cells, whereas transfection of a miR-519d inhibitor had the opposite effect. Moreover, their data suggest that MMP2 is directly silenced by miR-519d, suggesting a mechanism for reduced invasion [30]. Others found that in certain experimental conditions miR-519d enhanced cell proliferation and migration (Chaiwangyen W, Morales-Prieto DM, Markert UR, manuscript in preparation). A number of C19MC miRNAs, including miR-519d, were upregulated in the plasma of women with early-onset preeclampsia, a condition associated with shallow placental invasion [25]. Similar upregulation of miR519d in preeclampsia was found by others [24].

The expression and function of miR-519d in non-placental tissues

The published data on the function of miR-519d during tumorigenesis suggest a complex role which may be explained by the non-uniform regulation of invasion in different tumors. A summary of miR-519d roles in different tumors is listed in Table 2.

Several studies suggest that miR-519d is overexpressed in some human cancers and possesses oncogenic properties. One example is hepatocellular carcinoma (HCC), where

miR-519d was found to be overexpressed and to promote cell proliferation, invasion, and impaired apoptosis, acting through the targeting of CDKN1A/p21, PTEN, AKT3, and TIMP2 [31]. A follow-up study by the same group showed that miR-519d was elevated in the serum of patients with HCC and that miR-519d could be used to distinguish cirrhotic patients without HCC from cirrhotic patients with early and intermediate-advanced HCC [32]. In a study of cervical cancer, miR-519d was found to be significantly upregulated in cervical cancer samples, where it promoted the migration and invasion of HeLa and SiHa cervical cancer cells and the proliferation of cervical cancer cells through targeting Smad 7 [33]. miR-519d is also overexpressed in bone marrow mesenchymal stromal cells of multiple myeloma patients compared to bone marrow mesenchymal stromal cells of donors [34].

While the non-placental expression of miR-519d has been associated with tumorigenesis in some studies, an anti-tumor function of miR-519d has been shown by others. MiR-519d suppresses the growth of the human HCC cell line QGY-7703 through targeting MKi67, a proliferation marker protein [35]. In the lung adenocarcinoma A549 cell line, miR-519d inhibited TGFβ signaling and thus attenuated the enhancement of cell proliferation, morphology, and scattering by TGFβ [36]. Similarly, in human osteosarcoma, connective tissue growth factor (CTGF) increases matrix metalloproteinase expression and promotes tumor metastasis through downregulation of miR-519d [37]. The anti-metastatic function of miR-519d was also evident in its direct suppressive effect on MMP-2 and MMP-3 [37]. In ovarian cancer cell lines and tissues, the expression of miR-519d was downregulated, and overexpression of miR-519d in ovarian cancer cells repressed cell proliferation and potentiated cisplatin-induced cell death by targeting X-linked inhibitor of apoptosis protein (XIAP) [38]. Similarly, the levels of miR-519d are reduced in breast cancer tissues and cell lines, while overexpression of miR-519d inhibits cell proliferation and invasion and induces apoptosis in breast cancer cells, probably through targeting signal transducer and activator of transcription 3 (STAT3) [39]. Lastly, transfection of miR-519d into chondrosarcoma cells diminished resistin-induced cell migration and directly silenced the expression of MMP-2 [40]. Taken together, while available information supports a role for miR-519d in the regulation of cell invasion, migration, and proliferation, the effect of miR-519d in this context is divergent, and seems to depend on the context of specific tissues and tumors. It is thus possible that miR-519d regulates dissimilar target proteins in different tumors, or that the function of miR-519d may be influenced by the degree of cellular differentiation or by tumor-specific microenvironment factors. Similar factors may underlie the function of miR-519d during trophoblast migration and invasion. Additional detailed studies are needed in order to elucidate the context-specific expression and action of miR-519d.

It is also possible that miR-519d plays a role in other processes, as suggested by the overexpression of miR-519d in subcutaneous adipose tissue of severely obese humans, where it may suppress the expression of peroxisome proliferator-activated receptor-α and increase lipid accumulation during preadipocyte differentiation [41].

Conclusion

Implantation, placental development and function, and consequently, the outcome of pregnancy are utterly dependent upon proper EVT invasion, proliferation, and migration. Among numerous signals that regulate these processes, miRNAs regulate the expression of proteins relevant to invasion, proliferation, and migration. Although the function of C19MC miRNA in EVTs remains to be fully elucidated, data from several laboratories, including our own, suggest that the C19MC member miR-519d regulates EVT migration and, possibly, invasion. Further support for this function of miR-519d is derived from the process of tumorigenesis. While the data are not uniform, and experimental results are largely dependent upon the experimental system, ample evidence points to the role of miR-519d in regulating the expression of discrete proteins involved in cell interaction with the extracellular matrix and in migration and invasion. These data may serve to illuminate the pathogenesis of diseases associated with abnormal placentation, such as preeclampsia, placental adhesion disorders, fetal death, or growth restriction.

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HIGHLIGHTS

- Invasion by extravillous trophoblasts and tumors is regulated by miRNA.
- A C19MC miRNA, miR-519d, regulates cell migration, invasion, and extracellular matrix proteins.
- MiR-519d is likely relevant to diseases associated with abnormal placentation.

Table 1

MiRNAs implicated in regulation of trophoblastic processes relevant to invasion

Name	Chromosomal location	Cells or tissue tested	Biological process	Putative targets	References
microRNA-137	1p21.3	Human placental tissue and trophoblast cells	Proliferation and migration	ERRα	[42]
miR-15b	3q25.33	Placental tissue, HTR-8/SvNeo	Invasion, angiogenesis	AGO2	[43]
miR-141	12p13.31	Placental tissue, JEG-3 and HTR-8/SVneo	Invasion, intercellular communication	-	[44]
miR-193b-3p	16p13.12	Placental tissue, HTR-8/SVneo	Migration and invasion	TGF-β2	[45]
miR-661	8q24.3	Primary human endomerial epithelial cells, HTR-8/SVneo	Adhesion	EBPH2, PVRL1, MTA1, MTA2	[46]
miR-34a	1p36.22	Placental tissue, JEG-3, JAR	Invasion	MYC, PAI-1 Notch1, Jagged1	[47–49]
miR-204	9q21.12	BeWo and JEG3	Invasion	MMP9	[50]
miR-18a	13q31.3	JEG3	Invasion, apoptosis	ESRα	[51]
miR-135b	1q32.1	HTR-8/SVneo	Invasion	CXCL12	[52]
miR-125b-1-3p	11q24.1	Placental tissue, HTR-8/SVneo	Invasion	S1PR1	[53]
miR-20a	13q31.3	Placental tissue, JEG-3	Proliferation, migration and invasion	FOXA1	[54]
miR-155	21q21.3	HTR-8/SVneo	Proliferation and migration	eNOS, cyclinD1	[55,56]
miR-101	1p31.3	HTR-8/SVneo	Apoptosis	ERp44	[57]
miR-376c	14q32.31	HTR-8/SVneo	Proliferation, migration, and invasion	ALK5, ALK7	[58]
miR-195	17p13.1	Placental tissue, HTR-8/SVneo	Invasion	ActRIIA	[59]
miR-29b	7q32.3	HTR-8/SVneo, BeWo and JAR	Apoptosis, invasion and angiogenesis	MCL1, MMP2, VEGFA, ITGB1	[60]
miR-378a-5p	5q32	Placental tissue, HTR-8/SVneo	Cell growth, surviv al migration, invasion	Nodal	[61]
miR-519d	19q13.42	Placental tissue, HTR-8/SVneo	Invasion, migration	MMP2, CXCL6, NR4A2, FOXL2	[28,30]

Table 2

The role of miR-519d in tumorigenesis

Role	Tumors	Putative targets	References
Oncogenic	Hepatocellular carcinoma	CDKN1A/p21, PTEN, AKT3, and TIMP2	[31,32]
	Cervical cancer	Smad7	[33]
	Multiple myeloma	-	[34]
Tumor suppressive	Hepatocellular carcinoma	MKi67	[35]
	Lung adenocarcinoma	TGFβ signaling	[36]
	Human osteosarcoma	MMP-2 and MMP-3	[37]
	Ovarian cancer	XIAP	[38]
	Breast cancer	STAT3	[39]
	Chondrosarcoma	MMP2	[40]