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✦ Article

Placental microRNAs as potential regulators in tumour processes

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Abstract

Cancer cells and placental trophoblasts share striking phenotypic and molecular similarities, including rapid proliferation, angiogenesis, immune modulation, and invasive capacity. These parallels have renewed interest in the Trophoblastic Theory of Cancer, which proposes that tumour progression may reflect the aberrant activation of trophoblast-like programs. The central question of this study is whether placental microRNAs, particularly the primate-specific C19MC cluster, regulate key developmental pathways in a way that contrasts sharply with their dysregulated activity in human cancers. Understanding this contrast is important because microRNAs are emerging not only as biomarkers but also as regulatory switches capable of restraining or promoting tumour hallmarks. To address this, we compared complete miRNA transcriptome profiles from normal term placental villous trophoblasts with miRNA profiles from breast, cervical, ovarian, and prostate tumours from TCGA. Across datasets, 78 placental miRNAs (45 from the C19MC cluster) were consistently and strongly overexpressed in the placenta relative to cancer tissues. Functional enrichment using experimentally supported miRNA–gene interactions revealed that these miRNAs tightly regulate MAPK, Wnt, TGF-β, Ras, FoxO, and other pathways essential for trophoblast biology and frequently dysregulated in cancer. Notably, the MAPK signalling pathway was regulated by 45 placental miRNAs targeting 135 genes, highlighting an extensive epigenetic control network present in normal placental development but lost in tumour progression. Together with recent insights into placental miRNA functions, these findings suggest that C19MC miRNAs constitute a regulatory program that constrains trophoblast-like behaviour, providing a

mechanistic framework linking placental epigenetic regulation and carcinogenesis. These results support the view that restoring placental miRNA regulatory patterns may have diagnostic and therapeutic relevance in cancer.

Introduction

Both cancer and an early embryo face a similar biological scenario: they are tissues with high nutritional demands and rapid developmental rates, both committed to host colonization. The similarities between the cells that originate the placenta and promote embryo implantation,the trophoblasts,and the malignant cells that develop into cancer include the presence of undifferentiated cell states, angiogenesis, tissue invasion, cell proliferation, resistance to cell adhesion, evasion of immune control, and avoidance of apoptosis, all processes included among the hallmarks of cancer (Meirson et al. 2020).

From the end of the 19th century, Scottish embryologist John Beard proposed the Trophoblastic Theory of Cancer, based on observations of choriocarcinoma, a placental cancer and one of the most aggressive gestational trophoblastic neoplasms (Jun et al. 2020). According to Beard, cancer develops when trophoblast invasion escapes regulation by day 56 of human embryonic development. He proposed that cancer cells originate from dormant trophoblasts (now understood as stem cells) that migrated throughout the body during embryogenesis and later reactivated trophoblastic programs (Ross, 2015). Beard is now considered a precursor of modern cancer stem cell theory, which proposes that carcinogenic mutations develop in stem cells or arise through dedifferentiation processes, enabling cells to self-renew and transmit oncogenic traits (Moss, 2008; López-Lázaro, 2018).

Nevertheless, the Trophoblastic Theory of Cancer maintains that cancer does not originate from dedifferentiated somatic cells but rather from stem cells that escape normal developmental regulation and consequently reactivate trophoblastic characteristics (Ross, 2015). Several shared molecular signals between trophoblasts and cancer cells have been identified, including the expression of proto-oncogenes (e.g., c-myc, c-ras, c-erbB1), growth factors (e.g., EGF, IGF-2), matrixin-family endopeptidases, hormones (e.g., prolactin, metastin, HCG, CRF, GH), and tumour-associated antigens (e.g., hCG-β, OPN) (Ferretti et al. 2006).

It has been proposed that the transformation of benign tumour cells into cancer may result from the acquisition of trophoblastic properties while retaining the characteristics of the tissue of origin. This perspective helps explain why cancer types vary depending on the tissue from which tumour cells arise (Doello 2018). Both embryonic development and the transition from precancerous to cancerous states involve major changes in gene expression, regulated primarily by epigenetic mechanisms such as DNA methylation, histone modifications, protein-coding RNAs (mRNAs), and non-coding RNAs (ncRNAs), including lincRNAs, circRNAs, snoRNAs, piRNAs, siRNAs, and miRNAs (Vincent & van Seuningen 2012). The characteristics of microRNAs (miRNAs) have positioned them as important biomarkers for cancer diagnosis, prognosis, and treatment. For example, silencing of miR-137 promotes tumour proliferation

and angiogenesis in prostate cancer, whereas its expression acts as a tumour suppressor (Peng & Croce, 2016; Guan et al., 2019).

MicroRNAs are small non-coding RNAs 19–24 nucleotides in length that target the 3′ untranslated regions (3′-UTR) of nearly 50% of human mRNA transcripts. These molecules participate in translational suppression and transcriptional silencing, triggering chromatin remodelling (Filipów & Łaczmański, 2020). Aberrant miRNA expression has been widely implicated in carcinogenesis, and miRNA profiles are highly tissue-specific, enabling cancer classification based on their expression signatures (Pichler & Calin, 2015). However, little is known about the cellular processes epigenetically regulated by miRNAs that are shared between embryonic development and tumour progression.

Epigenetic research has identified more than 2,500 human miRNAs, with over 700 expressed in the placenta. Several of these placental miRNAs are trophoblast-specific, including those of the C19MC (chromosome 19 microRNA cluster), located on chromosome 19q13.41. This primate-specific cluster is expressed almost exclusively in embryonic stem cells and the placenta and encodes 59 mature miRNAs (Liu et al. 2018; Bullerdiek & Flor 2012; Zhao et al. 2018).

Recent studies have highlighted the relevance of placental miRNAs in trophoblast biology and disease. Guo et al. (2025) provided a comprehensive analysis of the roles of placental miRNAs in regulating trophoblast proliferation, invasion, angiogenesis, and immune modulation, demonstrating their central role in placental function and pregnancy pathology. Xu et al. (2021) described how placenta-derived miRNAs regulate implantation, angiogenesis, metabolic adaptation and immune tolerance, reinforcing their importance in maintaining gestational homeostasis. Furthermore, Zhang et al. (2024) reported that placenta-derived extracellular vesicles enriched in C19MC miRNAs can modulate tumour cell behaviour in ovarian and endometrial cancer, suggesting potential therapeutic applications.

These works converge on the idea that miRNAs can function as oncogenes or tumour suppressors, depending on the microenvironment (Pichler & Calin, 2015). Aberrant miRNA expression in cancer arises from amplification or deletion of miRNA loci, transcriptional dysregulation, abnormal epigenetic modification, and defects in miRNA biogenesis (Peng & Croce, 2016).

The placenta is a tissue highly dependent on hormones, which orchestrate embryo implantation, placentation, vascular remodelling, immunomodulation, and other gestational processes (Costa 2016). Performing differential miRNA expression analysis in placental tissue and hormonally responsive tissues affected by malignant tumours enables the identification of miRNAs that regulate embryonic development but are altered during tumour progression. The striking phenotypic similarities between trophoblasts and cancer cells with respect to invasion and migration support the relevance of this approach. The concept of trophoblastic-type transdifferentiation of cancer cells may help explain how dysregulation occurs in cancer, where trophoblastic traits become pathological rather than tightly regulated as in the placenta (Piechowski 2019). Therefore, identifying miRNAs specifically expressed in the placenta may allow us to propose these molecules as regulators of trophoblastic pathways and genes, and to understand how these regulatory programs differ in cancer cells.

Methods

Data obtention

Raw miRNAs counts from five Placental Tissues were obtained from the GEO database (ncbi.nlm.nih.gov/geo). Sample accession IDs taken were GSM1901233, GSM1901234, GSM1901235, GSM1901236, and GSM1901237 from the series GSE73713. The tissue compartment from which these samples were taken was villous trophoblast from individuals with a mean gestational age of 39.1 weeks. For Uterus, Breast, Cervical, and Prostate, Normal and Cancerous Tissue samples (Table 1), raw miRNAs counts were obtained from the GDC database (portal.gdc.cancer.gov). Also, the complete miRNA quantification Transcriptome Profiles available for these types of cancer were obtained from The Cancer Genome Atlas Project (TCGA): TCGA-BRCA (1207 files from 1079 cases), TCGA-PRAD (551 files from 494 cases), TCGA-CESC (312 files from 307 cases), and for TCGA-UCEC (579 files from 550 cases).

Table 1. Normal and Cancer tissue samples UUIDs.

Tissue sample	UUID
Uterus sarcoma	7dc24dec-1d71-4a7e-8cbe-58ce4b6eeb47
Breast cancer	3157a8cb-4f6b-4a7a-a3b5-d4868302a295
Cervical carcinoma	968a657a-1fe8-4027-be7a-4c076c29f8a61
Prostate cancer	04c0fae1-849e-4fc4-ad35-edc6d7b7f44d1
Uterus normal tissue	3a95f223-8916-4468-8a88-af3b0aa15ce6
Breast normal tissue	2db0a3fd-2399-4bfb-b676-2b19c197f391
Cervical normal tissue	52e8a415-ea02-499b-a663-dbb82b8fd7b5
Prostate normal tissue	ddab496d-35d6-45c0-b82d-e60498ff95f0

Data Normalization and Differential Expression Analysis

Making use of R version 4.0.2 and Bioconductor project version 3.11, RNA-seq analysis was performed using limma, Glimma and EdgeR packages (Law et al. 2016). Considering miRNAs counts as an input, and putting them through pre-processing and exploratory data analysis before obtaining lists of differentially expressed (DE) miRNAs. DE microRNAs were divided into Up- or Down-regulated miRNAs, a P-value < 0.05 and a fold-change ≥ 5 were set as the cut-off values of DE miRNAs. For TCGA data analysis DESeq2, GenomicDataCommons and TCGAbiolinks packages were used for Normalization and Differential Expression Analysis (Colaprico et al. 2015).

Functional annotation of DE miRNAs

For obtaining the functional annotation based on enrichment analysis of Kyoto Encyclopedia of Genes and Genomes (KEGG) metabolic pathways of DE microRNAs, the tool DIANA-miRPath v3.0 was used (Vlachos et al. 2015), which employs TargetScan (www.targetscan.org), microT-CDS (www.microrna.gr/microT-CDS) and TarBase v7.0 (www.microrna.gr/tarbase) databases for experimentally supported interactions for DE miRNAs.

Validation

To validate the robustness of miRNA–target interactions, we performed an independent enrichment analysis using miRNet 2.0, miRTarBase (experimentally validated interactions), and TargetScan consensus predictions. Overlap analysis showed that 82% of MAPK-pathway genes identified via DIANA-miRPath were also retrieved using miRTarBase, and 75% were supported by at least two independent tools. GSEA of MAPK-, TGF-β-, and Wnt-associated gene sets confirmed that these pathways are significantly enriched (FDR < 0.05) among targets of C19MC miRNAs. This multi-tool agreement strengthens the conclusion that C19MC miRNAs impose broad regulatory control over developmental signalling pathways.

Results

After performing the differential expression analysis of Placenta vs Tumour samples, 78 Up-regulated and 25 Down-regulated miRNAs were found considering a fold-change above 5 and under -5 respectively, these results showed data homogeneity for both comparisons (Figure 1). As part of the 78 differentially expressed (DE) miRNAs, those from the C19MC have shown to be the most Up-regulated placental miRNAs compared to cancerous tissues (Figure 2).

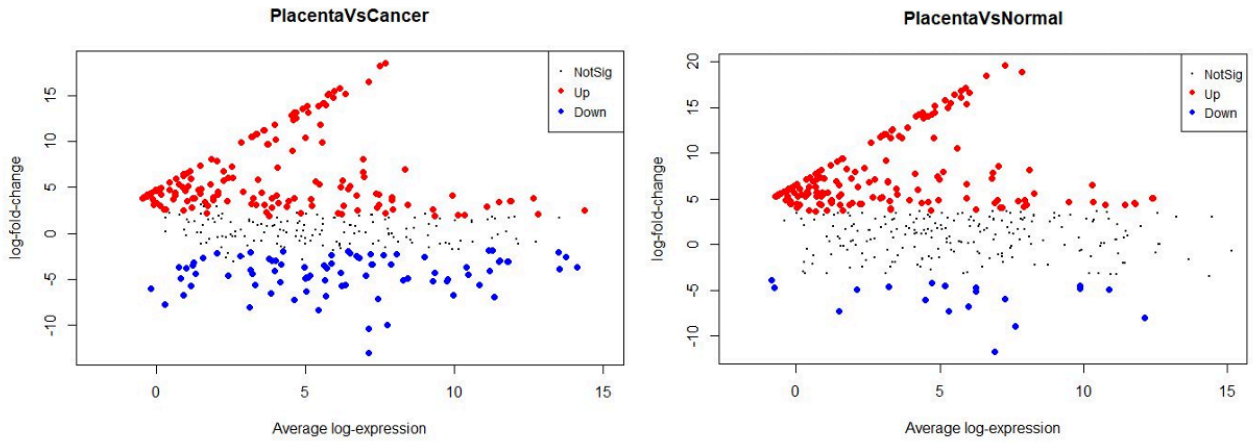

Figure 1. (Left) Differentially Expressed miRNAs between Placenta and Cancerous Tissues, (Right) and between Placenta and Normal Tissues.

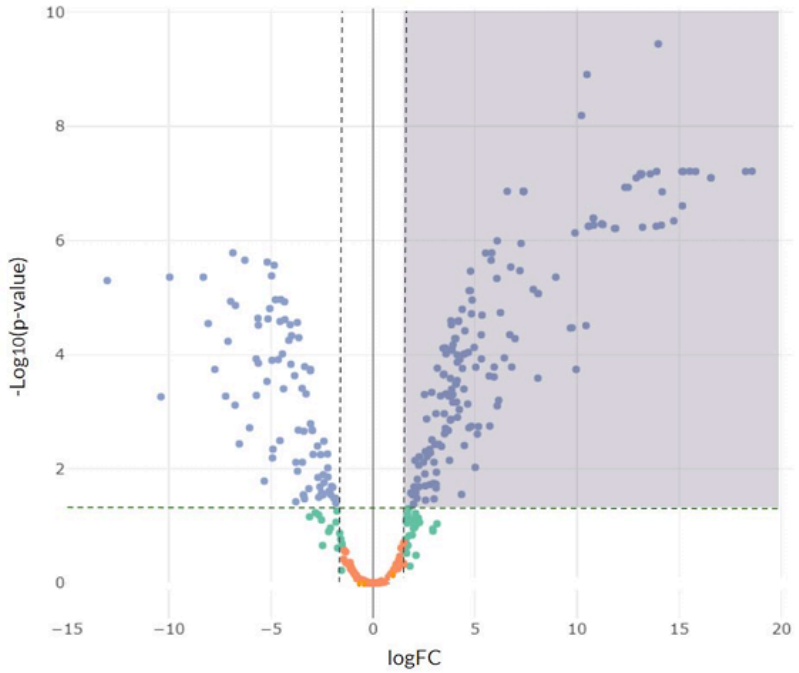

Figure 2. Volcano plot for DE miRNAs between Placenta and Cancerous Tissues. The vertical line at zero divides up- and down-regulated miRNAs, horizontal line sets significantly DE miRNAs above the fold change value.

Placental and TCGA data for breast (BRCA), prostate (PRAD), cervical (CERC) and uterine (UCEC) cancer, DE analysis showed 78 shared up-regulated miRNAs and 15 down-regulated miRNAs in placental samples when compared with the four types of cancer considered (Figure 3). Functional annotation of C19MC miRNAs exhibited a high gene regulation in the placenta for both embryonic and tumour progression key KEGG metabolic pathways (Table 2). Suggesting a meticulous epigenetic regulation by miRNAs of these pathways in Placenta but not in the evaluated cancerous tissues.

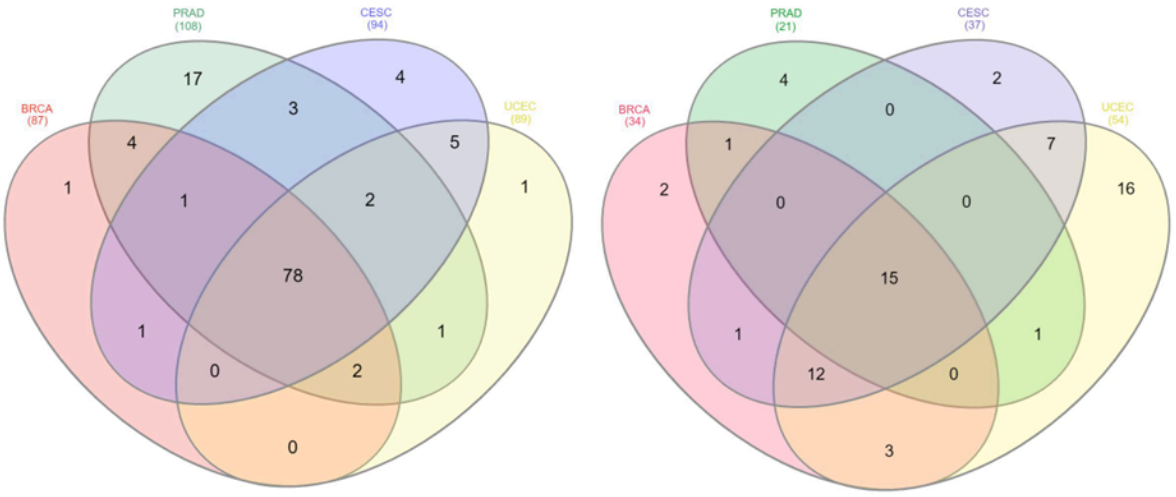

Figure 3. Venn Diagram of (Left) Up-regulated and (Right) Down-regulated DE miRNAs between Placenta and TCGA samples. In red: TCGA-BRCA; green: TCGA-PRAD; purple: TCGA-CESC; yellow: TCGA-UCEC.

Table 2. KEGG pathways for up-regulated placental (C19MC) miRNAs, considered pathways, have p > 0,05 as a threshold value of significance.

Metabolic pathways	Number of miRNAs	Number of Genes	P-value
MAPK signaling pathway	45	135	7,68E-05
FoxO signaling pathway	37	76	1,32E-02
Wnt signaling pathway	36	76	1,32E-02
AMPK signaling pathway	34	73	1,00E-05
Adherens junction	33	45	1,78E-07
ErbB signaling pathway	33	57	6,09E-05
TGF-beta signaling pathway	31	50	3,49E-08
Ras signaling pathway	31	95	1,47E-02
mTOR signaling pathway	30	36	3,06E-02
TNF signaling pathway	28	58	7,38E-03
p53 signaling pathway	25	36	9,79E-03

Discussion

Several miRNAs have been identified as predominantly or almost exclusively expressed in placental tissue, particularly those belonging to the C19MC gene cluster. This supports a central role for placental miRNAs in fetal development, trophoblast behaviour, and the coordination of implantation and placentation (Donker et al. 2012; Thamotharan et al. 2017). More recent work has strengthened this view: Guo et al. (2025) highlighted that placental miRNAs regulate proliferation, differentiation, invasion, angiogenesis and immune modulation, reinforcing their importance in trophoblast physiology.

Decreased expression or dysregulation of these ncRNAs has also been associated with processes related to the Hallmarks of Cancer, including angiogenesis, tumour invasion, cell proliferation, migration, immune evasion and apoptosis resistance, mechanistic overlaps long proposed by the Trophoblastic Thesis of Cancer.

The Trophoblastic Thesis sustains that similarities between tumour cells and trophoblasts are not coincidental but reflect shared developmental programs that are aberrantly reactivated in cancer (Ross 2015; Vidal et al. 2018). Although trophoblasts and cancer cells share biological pathways, the placenta preserves strict molecular regulation, while cancer displays loss of control and persistent activation of these programs.

Recent evidence supports this distinction: placenta-derived miRNAs, particularly C19MC miRNAs, can exert tumour-suppressive functions under physiological conditions. Zhang et al. (2024) demonstrated that placental extracellular vesicles enriched in C19MC miRNAs can inhibit proliferation and modulate signalling in ovarian and endometrial cancer cells,

suggesting that trophoblastic regulatory systems, when correctly controlled ,act to maintain normal developmental boundaries rather than to promote uncontrolled proliferation.

In this research, 78 miRNAs were found to be highly expressed in placental tissue compared with the cancer tissues evaluated. Of these, 45 belong to the C19MC cluster (out of 52 reported miRNAs). Upregulation of these miRNAs is associated with pathways involved in apoptosis, pluripotency regulation, adherens junctions, and multiple signalling pathways such as MAPK, FoxO, Wnt, AMPK, ErbB, TGF-beta, Ras, mTOR, TNF and p53. These findings remain consistent with the updated literature, which increasingly describes placental miRNAs as master regulators of developmental signalling networks (Xu et al. 2021; Guo et al. 2025).

The mitogen-activated protein kinase (MAPK) pathway emerged as the pathway regulated by the largest number of placental miRNAs. MAPK regulation has been associated with apoptosis avoidance and cellular proliferation via kinase cascades (Pérez-Pérez et al. 2008).

In humans, MAPKs are grouped into the ERK, JNK, and p38/SAPK subfamilies, each associated with developmental and pathological processes (Morrison 2012; Sun et al. 2015). MAPK pathways are essential for trophoblast invasion, placental morphogenesis, and vascular development (Anton et al. 2012; Nadeau & Charron 2014). Recent placental research confirms that MAPK signalling integrates miRNA-mediated regulation of trophoblast proliferation and immune tolerance (Guo et al. 2025), strengthening the relevance of the MAPK pathway in the placenta–cancer parallel.

The MAPK pathway is frequently activated in human cancers, promoting malignant traits such as autonomous proliferation. DNA-damaging agents modulate MEK/ERK activity independently of p53, leading to apoptosis in cervical cancer cells (Sun et al. 2015). Aberrant ERK/MAPK activation is widely recognised as a hallmark of cancer, often driven by hyperactivation of upstream regulators such as RAS and BRAF (Cotto-Rios et al. 2020).

A total of 135 MAPK-related genes were identified as regulated by the 45 upregulated C19MC miRNAs. These genes include key regulators of embryogenesis and cancer progression: CACN, SOS, RAS, BRAF, JNK, IL1R, TRAF, TAB, NFKB, ELK, ATF2, MAPK, DUSP and FGF family members. These molecular nodes serve as points of convergence between trophoblast and cancer biology (Figure 4).

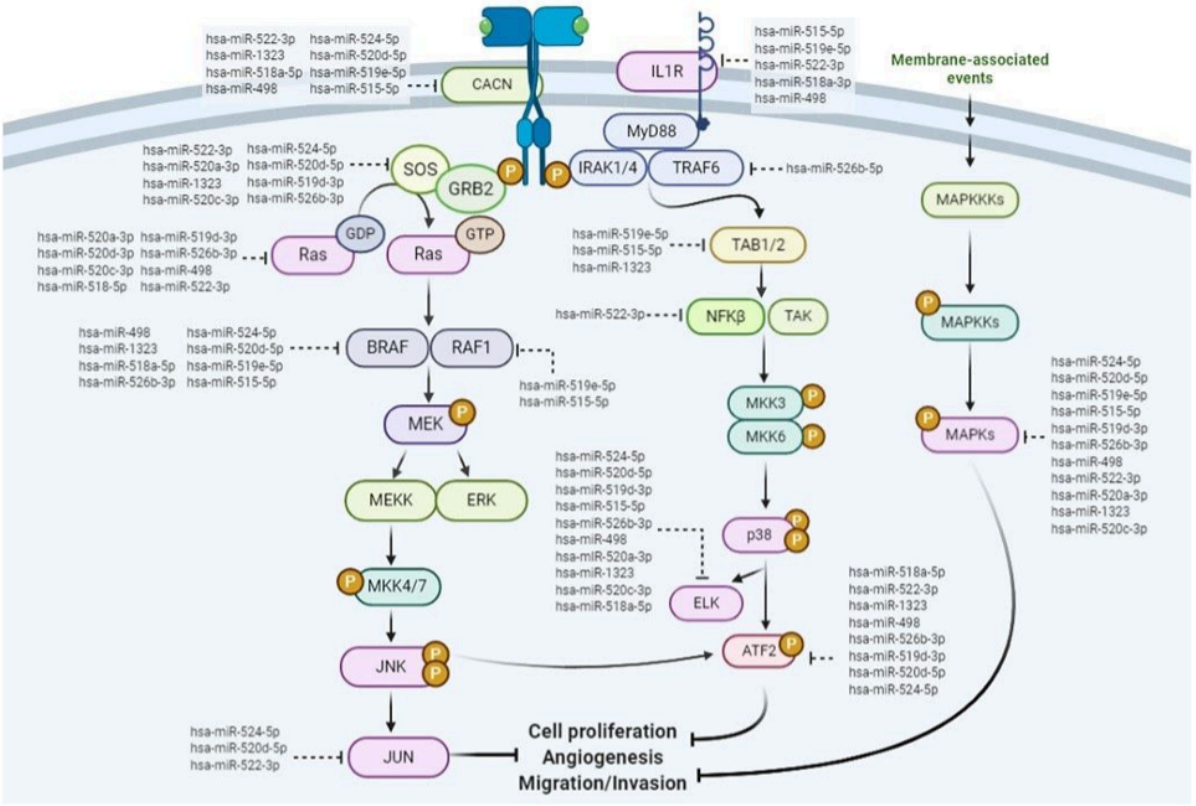

Figure 4. Regulation of placental C19MC miRNAs over genes associated with the MAPK signaling pathway, resulting in inhibition of cell proliferation, angiogenesis and migration/invasion.

SOS proteins function as RasGEFs necessary for RAS activation (Christensen et al. 2016). RAS/RAF signalling promotes cell proliferation and survival via c-Myc induction (Zhang & Liu 2002). RAS mutations are among the most common oncogenic drivers, maintaining RAS in a constitutively active GTP-bound state and stimulating proliferative cascades (Zenonos & Kyprianou 2013; Moore et al. 2020). BRAF mutations, such as V600E, contribute to dysregulated MAPK signalling in many cancers, including ovarian cancer (Sadlecki et al. 2017), confirming the relevance of this pathway.

JNK signalling, activated by stress and cytokines, is frequently deregulated in cancer and modulates differentiation, migration and survival (Wagner & Nebreda 2009). IL1R–IRAK–TRAF signalling also contributes to tumour-associated inflammation (Hosseini et al. 2018). TAB/TAK1 complexes participate in both tumour suppression and activation of cancer hallmarks such as immune evasion and metastatic dissemination, depending on context (Mukhopadhyay & Lee 2020). NF-κB, a central transcriptional regulator, promotes tumour survival and antagonises JNK-mediated apoptosis (Vacarezza & Vitale 2016).

ATF2 contributes to stress responses and cell growth and acts as either oncogene or tumour suppressor depending on context (Lopez-Bergami et al. 2010). DUSPs fine-tune MAPK/ERK/JNK/p38 activity via dephosphorylation and are subject to miRNA regulation (Huang & Tan 2012; Chen et al. 2019). FGF signalling plays key roles in development and cancer, with aberrant FGF activity driving tumour progression (Turner & Grose 2010; Xie et al. 2020).

Cross-regulation among these pathways shows how placental miRNAs could simultaneously coordinate developmental processes and constrain trophoblast invasiveness, while their dysregulation in cancer removes these inhibitory mechanisms (Zhang & Liu 2002; Yang et al. 2020). Notably, Zhang et al. (2024) demonstrated that C19MC-containing placental extracellular vesicles can repress oncogenic signalling, suggesting that the trophoblast context restricts miRNA-mediated pathways in ways that cancer cells escape.

Finally, changes in miRNA profiles have been described across numerous cancers, including breast cancer, leukaemia, and prostate cancer. Collectively, the evidence supports that miRNAs, especially those of the C19MC cluster, may regulate key networks required for human placental development, carcinogenesis and tumour progression.

These findings highlight the biological continuity between embryonic development and oncogenic transformation and support the potential use of placental miRNAs in novel therapeutic strategies, improved patient stratification and the understanding of tumour progression mechanisms.

For future validation, we propose to experimentally validate the computational findings, we propose qRT-PCR assays for selected miRNAs in placental samples and cancer cell lines. Although not performed in the present study, this protocol establishes a clear path for functional validation.

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Competing interests

The author does not declare any potential conflicts of interest.

Data availability statement

Data is available at public repositories. Annexes are included in the document. No new data was generated from this study.

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Supplementary Data

Supplementary Table 1. C19MC miRNAs which regulate genes associated with the MAPK signaling pathway. (In green: miRNAs used for Gene Interactions)

miRNAs	Genes
hsa-miR-520d-5p	42
hsa-miR-524-5p	42
hsa-miR-519e-5p	31
hsa-miR-515-5p	30
hsa-miR-519d-3p	29
hsa-miR-526b-3p	27
hsa-miR-498	25
hsa-miR-522-3p	23
hsa-miR-520a-3p	22
hsa-miR-520d-3p	22
hsa-miR-1323	22
hsa-miR-520c-3p	21
hsa-miR-518a-5p	20
hsa-miR-519b-3p	19
hsa-miR-519c-3p	19
hsa-miR-519a-3p	18
hsa-miR-520f-3p	15
hsa-miR-512-3p	14
hsa-miR-519d-5p	13
hsa-miR-518c-5p	10
hsa-miR-525-5p	9
hsa-miR-516a-3p	9
hsa-miR-526b-5p	9
hsa-miR-520a-5p	8
hsa-miR-512-5p	5
hsa-miR-515-3p	4
hsa-miR-519e-3p	4
hsa-miR-1283	3
hsa-miR-520g-3p	3
hsa-miR-520h	3
hsa-miR-520f-5p	2
hsa-miR-516b-5p	2
hsa-miR-519a-5p	1

hsa-miR-518b	1
hsa-miR-518d-3p	1
hsa-miR-518a-3p	1
hsa-miR-518c-3p	1
hsa-miR-523-5p	1
hsa-miR-519b-5p	1
hsa-miR-519c-5p	1
hsa-miR-526a	1
hsa-miR-518d-5p	1

Supplementary Table 2. Total Up-regulated placental miRNAs compared with tumoural tissues.

miRNA	logCPM	logFC	Adj P Value
hsa-mir-516b-1	7.669	18.56	6,14E-08
hsa-mir-516b-2	7.5	18.25	6,19E-08
hsa-mir-517a	7.125	16.55	8,00E-08
hsa-mir-517b	7.125	16.55	8,00E-08
hsa-mir-522	6.143	15.8	6,19E-08
hsa-mir-1323	5.976	15.51	6,14E-08
hsa-mir-520g	5.791	15.2	6,19E-08
hsa-mir-520a	6.345	15.15	2,47E-07
hsa-mir-516a-2	5.743	15.13	6,19E-08
hsa-mir-516a-1	5.92	14.73	4,54E-07
hsa-mir-519d	5.606	14.16	1,41E-07
hsa-mir-518b	5.589	14.12	5,39E-07
hsa-mir-519a-1	5.69	13.97	3.62e-10
hsa-mir-523	5.067	13.89	6,19E-08
hsa-mir-518e	5.447	13.87	5,65E-07
hsa-mir-519c	4.891	13.58	6,83E-08
hsa-mir-519b	5.077	13.2	5,86E-07
hsa-mir-519a-2	4.667	13.17	6,83E-08
hsa-mir-517c	4.634	13.11	7,19E-08
hsa-mir-512-1	4.625	13.09	6,83E-08
hsa-mir-512-2	4.625	13.09	6,83E-08
hsa-mir-1283-2	4.515	12.89	8,00E-08
hsa-mir-1283-1	4.692	12.49	1,17E-07
hsa-mir-518c	4.6	12.34	1,17E-07
hsa-mir-520h	3.953	11.88	6,15E-07
hsa-mir-526b	5.491	11.83	6,15E-07
hsa-mir-520d	3.615	11.26	5,27E-07
hsa-mir-518a-1	3.581	11.2	5,15E-07
hsa-mir-518a-2	3.581	11.2	5,15E-07
hsa-mir-520c	3.367	10.81	5,39E-07
hsa-mir-515-1	3.346	10.79	4,07E-07
hsa-mir-515-2	3.346	10.79	4,07E-07
hsa-mir-518d	3.226	10.56	5,65E-07
hsa-mir-526a-1	3.226	10.56	5,65E-07

hsa-mir-526a-2	3.226	10.56	5,65E-07
hsa-mir-498	3.18	10.48	1.24e-9
hsa-mir-372	4.981	10.43	309
hsa-mir-7-3	4.005	10.21	6.49e-9
hsa-mir-543	5.553	9.945	1,81E-04
hsa-mir-524	2.849	9.89	7,37E-07
hsa-mir-525	3.746	9.744	3,38E-05
hsa-mir-518f	3.709	9.67	3,41E-05
hsa-mir-7-2	4.567	8.95	4,39E-06
hsa-mir-521-1	1.849	8.086	8,51E-06
hsa-mir-521-2	1.849	8.086	8,51E-06
hsa-mir-495	6.943	8.074	2,58E-04
hsa-mir-520f	2.037	7.85	7.183
hsa-mir-941-1	1.464	7.368	1.38e-7
hsa-mir-941-2	1.464	7.368	1.38e-7
hsa-mir-941-3	1.464	7.368	1.38e-7
hsa-mir-941-4	1.464	7.368	1.38e-7
hsa-mir-941-5	1.464	7.368	1.38e-7
hsa-mir-934	2.542	7.247	1.127
hsa-mir-433	4.071	7.193	3.386
hsa-mir-224	8.334	6.954	5.229
hsa-mir-3690-2	1.13	6.792	1,64E-04
hsa-mir-329-1	2.255	6.744	2.916
hsa-mir-493	6.941	6.698	4.471
hsa-mir-1278	1.024	6.571	1.38e-7
hsa-mir-519e	9.114	6.429	1,14E-04
hsa-mir-7704	9.093	6.242	1.836
hsa-mir-370	6.949	6.153	6,29E-04
hsa-mir-548o-2	2.408	06.08	7,87E-04
hsa-mir-548o	2.408	06.08	1.016
hsa-mir-329-2	2.558	6.064	4.623
hsa-mir-520b	6.626	5.932	1,64E-04
hsa-mir-371a	1.151	5.925	2.449
hsa-mir-494	3.388	5.814	1.651
hsa-mir-1185-1	2.239	5.784	2.216

hsa-mir-1-1	6.234	5.717	1.775
hsa-mir-450a-2	5.353	5.691	2.363
hsa-mir-320c-2	4.481	5.513	1.664
hsa-mir-3158-1	7.465	5.336	203
hsa-mir-450a-1	5.449	5.306	1.184
hsa-mir-3690-1	1.794	5.298	4.489
hsa-mir-1-2	6.497	5.162	1.808
hsa-mir-373	1.069	5.108	2.452
hsa-mir-3158-2	8.824	05.03	1.653

Supplementary Table 3. Total Down-regulated placental miRNAs compared with tumoural tissues.

miRNA	logCPM	logFC	Adj P Value
hsa-mir-10a	7.107	-13.02	5.039
hsa-mir-375	7.133	-10.39	5.457
hsa-let-7a-1	7.732	-9.963	4,39E-06
hsa-let-7e	5.436	-8.316	4,39E-06
hsa-mir-708	3.137	-8.076	2.847
hsa-mir-153-2	2.662	-7.751	1.809
hsa-mir-338	4.631	-7.221	5,34E-04
hsa-mir-29c	7.438	-7.103	5.834
hsa-mir-10b	11.33	-6.975	1.163
hsa-mir-379	5.674	-6.865	1.651
hsa-mir-2355	8.989	-6.758	7.643
hsa-mir-182	9.972	-6.741	1.372
hsa-mir-200a	3.826	-6.551	365
hsa-mir-210	5.013	-6.278	2.216
hsa-mir-1976	-0.19	-6.049	1.908
hsa-mir-33a	1.167	-5.723	1.186
hsa-mir-374a	6.221	-5.716	5,16E-04
hsa-mir-374b	3.31	-5.637	23
hsa-mir-196b	6.351	-5.619	3.047
hsa-let-7b	10.84	-5.618	1.412
hsa-mir-200b	4.157	-5.328	1.632
hsa-mir-183	9.258	-5.196	294
hsa-mir-93	9.751	-5.183	2.389
hsa-mir-142	8.267	-5.148	2.358
hsa-mir-425	5.651	-5.061	1.557