MINI-REVIEW ARTICLE

miR-34 as a Critical Regulator in Ovarian Cancer

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Abstract: Ovarian cancer (OC) is a gynecologic disease characterized by the uncontrolled growth and proliferation of abnormal cells in the ovaries, fallopian tubes, or peritoneum. Emerging evidence has shown the pivotal role of non-coding RNAs (ncRNAs), such as miRNAs, in driving the pathogenesis of OC. miRNAs are recognized as small ncRNAs that play critical roles in regulating gene expression in normal development and in disease states, including OC. Among miRNAs, the expression of miR-34a was found to be downregulated in OC. Elevated levels of this miRNA are associated with the induction of apoptosis and the inhibition of OC cell proliferation by targeting various signaling pathways, including NOTCH1, P21/P53, STAT3, and BCL2 in OC. Therefore, miR-34a can be a therapeutic target in the management of OC. In this review, we summarized the functional significance of this miRNA in the treatment of OC.

Keywords: miR-34a, ovarian cancer, tumor suppressor, biomarker, therapeutic potential.

1. INTRODUCTION

Gynecological cancers (GCs), encompassing ovarian, fallopian tubal, uterine/endometrial, cervical, vaginal, and vulval cancers, besides breast cancer, constitute a diverse array of malignancies specific to the female reproductive system [1, 2]. Ovarian cancer (OC) is a heterogeneous disease characterized by the uncontrolled growth of abnormal cells in the ovaries, fallopian tubes, or peritoneum, leading to the formation of malignant tumors [3]. While the precise etiology of OC remains elusive, extensive research has implicated a combination of genetic, environmental, and hormonal factors in its development [4]. Genetic alterations, including mutations in tumor suppressor genes, such as BRCA1 (breast cancer gene 1) and BRCA2, as well as oncogenes like the KRAS gene (Kirsten rat sarcoma viral oncogene homolog) and TP53 (the p53 gene), play a pivotal role in driving OC [5]. Changes in the retinoblastoma (RB) pathway are crucial in the development of OC [6]. Research has demonstrated that when both the p53 and RB genes are conditionally inactivated in animal models, it leads to the emergence of poorly differentiated serous ovarian adenocarcinomas [7, 8]. This suggests a significant interplay between these tumor suppressor pathways in driving cancer progression.

These genetic changes can arise spontaneously or be inherited from affected family members, contributing to the predisposition to develop OC [9]. Moreover, hormonal factors, such as prolonged exposure to estrogen without concomitant progesterone, as seen in nulliparity or early menarche, have been linked to an increased risk of OC [10]. Environmental factors, including exposure to carcinogens, such as asbestos and talcum powder [11, 12], as well as lifestyle factors like obesity [13] and smoking [14], also contribute to the development of OC [15]. Additionally, inflammatory conditions, such as endometriosis, have been

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associated with an elevated risk of certain subtypes of OC [16]. The complex interplay between genetic predisposition, hormonal influences, and environmental exposures underscores the multifactorial nature of OC etiology [17]. Understanding these underlying mechanisms is essential for elucidating the pathogenesis of OC and developing targeted prevention and treatment strategies [18]. Fig. **1** highlights various factors that contribute to the development and progression of OC.

In recent years, emerging evidence has underscored the pivotal role of non-coding RNAs (ncRNAs), including long ncRNAs (lncRNAs), microRNAs (miRNAs), and circular RNAs (circRNAs) in driving the pathogenesis of various cancers [19, 20].

A prominent member among miRNAs is miR-34a, which serves as a crucial regulator of tumor suppression by orchestrating the expression of multiple protein targets associated with apoptosis and cell cycle control [21]. Investigations have consistently demonstrated a prevalent downregulation of miR-34a in OC specimens in contrast to normal ovarian tissues, consequently triggering the overexpression of its target genes implicated in oncogenic cascades [22]. High expression of this miRNA is associated with the induction of apoptosis and the inhibition of OC cell proliferation [23]. In the present study, we summarized the functional significance of miR-34a in the pathogenesis of OC.

2. BIOGENESIS AND FUNCTIONAL ROLES OF miR-34A IN HEALTH AND DISEASES

miR-34a is first transcribed as a lengthy hairpin molecule (pri-miRNA), which is then broken down into a stem-loop precursor of around 70 nucleotides (pre-miRNAs) by the human RNase III DROSHA enzyme [24]. The miR-34a translocation from the nucleus to the cytoplasm is mediated by exportin-5. Through a series of stages, another human RNase III called DICER breaks miR-34a into duplexes with a final length of 22–23nt. Finally, one strand of the miRNA duplex, referred to as the "mature strand", becomes part of the RNA-induced silencing complex (RISC), with the other strand purportedly being broken down. After being incorporated into the RISC, miR34a directs this protein complex to binding sites that are either fully or partially complementary and are found in the 3' untranslated region (UTR) of target mRNAs, therefore suppressing their production. In specifics, partial alignment interferes with mRNA translation, whereas complete alignment leads to mRNA destruction [25]. A seven-nucleotide stretch known as the "seed-sequence," which is found in the 5′ section of 30 miRNAs, is associated with a complementary sequence in the 3′-UTR of the target mRNA to control its target [26]. Nucleotides in the middle and 3′ regions of the miRNA have the potential to undergo further base pairing [27]. A single miRNA likely controls dozens or even hundreds of target mRNAs, as the comparatively short

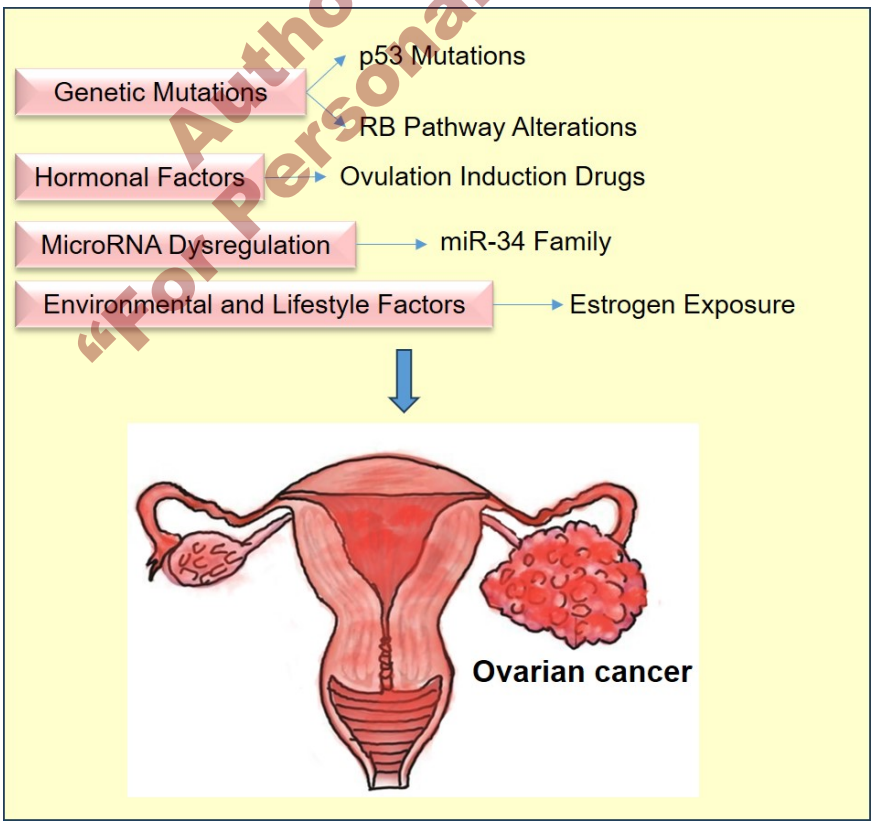

Fig. (1). The significant factors associated with the onset and advancement of ovarian cancer. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

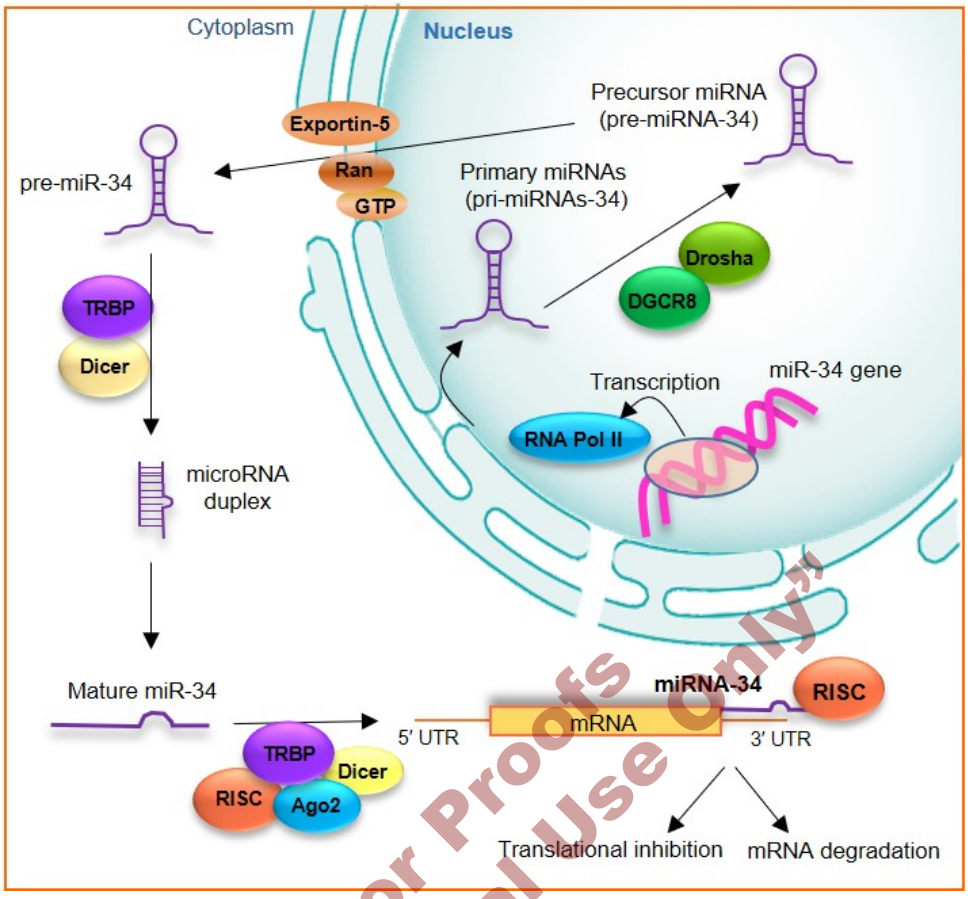

Fig. (2). The mechanisms involved in the biogenesis of miR-34. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

seed region is the main factor influencing target identification. According to bioinformatics predictions, the miR-34a seed sequence is matched by several hundred mRNAs [28]. Fig. **2** showcases how miR-34a is generated.

A proteomics study has recently identified early targets of miR-34a that are implicated in the carcinogenesis of neuroblastoma [29]. After removing miR-34a from mouse embryonic stem cells, Choi *et al*. discovered that the cells had the ability to develop into both extraembryonic and embryonic lineages [30]. Moreover, members of the miR-34a family are critical for the formation of neurons [31], spermatogenesis [32], stem cell differentiation [33], aging [34], and cardiovascular processes [35]. miR-34a has also been linked to cognitive impairments [36], osteoporosis [37], obesity [38], diabetes [36], and liver issues [39]. Numerous studies have explored the impact of miR-34a across different types of cancer. In head and neck squamous cell carcinoma (HNSCC), miR-34a acts as a tumor suppressor by inhibiting cell proliferation and inducing apoptosis. It targets several proto-oncogenes, thereby regulating critical processes, such as epithelial-mesenchymal transition (EMT), which plays a vital role in cancer invasion and metastasis. [40]. miR-34a has been associated with the suppression of cancer stem cell (CSC) characteristics in breast cancer by specifically targeting key molecules, such as NOTCH and MYC, which are crucial for maintaining the stem cell-like phenotype. In prostate cancer, the expression of miR-34a is notably downregulated in CSCs. When miR-34a is overexpressed, it effectively inhibits tumor growth and metastasis by downregulating factors that sustain stemness [41]. Neuroblastoma is often driven by frequent deletions in the chromosomal region containing miR-34a, highlighting its role as a tumor suppressor. The downregulation of miR-34 expression contributes to chemotherapy resistance by promoting survival against chemotherapy-induced apoptosis. Interestingly, emerging evidence suggests that miR-34a may have a carcinogenic role in osteosarcoma, where it is associated with chemotherapy resistance through the downregulation of DLL1 (Delta-like canonical Notch ligand 1), a ligand in the NOTCH signaling pathway [42].

3. FUNCTIONAL ROLES OF miR-34 FAMILY IN OVARIAN CANCER

The miR-34 family, especially miR-34a, miR-34b, and miR-34c, plays a vital role in the development and progression of ovarian cancer. Here are some key insights into their functions:

3.1. The Proliferation and Metastatic Phases

Various studies have discussed the significance of mir-34a in OC (Table **1**). In the proliferation and metastatic phases, different studies indicate that the miR-34 family possesses tumor properties, such as apoptosis, cell cycle arrest, and cell senescence [43]. Significantly lower miR-34a expression was reported in OC cells compared with healthy ovarian epithelium [44]. miR-34 plays a critical role in inhibiting tumor growth by inducing apoptosis and restraining cancer cell proliferation. Specifically, miR-34a-5p directly targets BCL2 (B-cell lymphoma 2), a key anti-apoptotic protein, leading to its suppression. Overexpression of miR-34a-5p has been shown to suppress the proliferation of OC cells and induce apoptosis by targeting BCL2 [45]. Additionally, resveratrol (RES), a natural compound found in red wine, has been reported to inhibit OC cell growth both *in vitro* and *in vivo*. Treatment with RES significantly increases the levels of miR-34a, and the inhibitory effects of RES on OC cells are potentiated by the overexpression of miR-34a. [46]. Moreover, targeting miR-34 with Lnc-OC1 has been observed to enhance the proliferation and metastasis rates of OC cells [47]. Furthermore, Yan Jia *et al*. discovered that miR-34 targets NOTCH1 to inhibit cell invasion and suppress the growth of human OC cells by inducing autophagy and apoptosis [48]. In another study by Maeda K *et al*., serum exosomal miR-34a levels were examined in epithelial OC patients. They observed significantly higher levels of serum exosomal miR-34a in early-stage OC patients compared to advanced-stage patients. Furthermore, patients with lymph node metastasis exhibited significantly lower levels of serum exosomal miR-34a compared to those without lymph node metastasis [49]. Xu D *et al*. conducted a study investigating the relationship between LINC00665 and miR-34a-5p in OC patients. Their research revealed that LINC00665 is upregulated in OC and is associated with a poorer prognosis. Knockdown of LINC00665 prevented the malignant proliferation, migration, and invasion of OC cells. Additionally, LINC00665, through competitive bidding to miR-34a-5p, counteracted the inhibitory effect of

Table 1. The impact of miR-34a on ovarian cancer progression and metastasis.

Suppression	Stimulation	Result	Refs.
Lower miR-34a expression	miR-34a promoter methylation	High-grade cancer progression (pro-cancer)	[43]
Snail	…	Suppression of EMT and invasion in OC cells (anti-cancer)	[51]
BCL2	Apoptosis	Suppressed OC cell proliferation (anti-cancer)	[61]
HDAC1	Cisplatin sensitivity in SKOV3cp cells	Suppressed proliferation in OC cells (anti-cancer)	[54]
miR-34a suppression	Lnc-OC1 upregulated	Development and progression of OC cells (pro-cancer)	[47]
NOTCH1	Autophagy and apoptosis	Suppressed proliferation of human OC cells (anti-cancer)	[48]
miR-34a downregulation	…	Ovarian tumor progression (pro-cancer)	[44]
IL-6R/STAT3	…	Reduced tumor proliferation and invasion (anti-cancer)	[55]
Decreases of miR-34a-5p	…	Slower disease progression (anti-cancer)	[56]
miR-34 family downregulation	BRCA1/2 mRNA	Worse overall survival and OC progression (pro-cancer)	[23]
OIP5-AS1	…	Downregulation of snail expression (anti-cancer)	[52]
Lower serum exosomal miR-34a	…	OC with lymph node metastasis (pro-cancer)	[49]
PD-L1	…	Regulated DDP chemoresistance of OC cells (anti-cancer)	[53]
BCL2	…	Enhanced RES apoptosis effects on OC cells (anti-cancer)	[46]
BCL2	Apoptosis	Enhanced the inhibitory effects of RES on OC cells (anti-cancer)	[45]
TRIM44	…	Inhibited OC malignant behaviors (anti-cancer)	[57]
miR-34a suppression by LINC00665	E2F3	Promoted the progression of OC cells (pro-cancer)	[50]
Deliver miR-34a into cells.	Apoptosis	Inhibited tumor growth and prolonging the survival time of OC mice (anti-cancer)	[58]
BCL2 and Mcl1	P21, P53	Apoptosis induction inhibited cell proliferation in OC cells (anti-cancer)	[59]
miR-34a downregulation	…	EOC progression (pro-cancer)	[62]
FOXP1	…	Reduced OC development (anti-cancer)	[22]
MDM4, MAPK3, BRCA1	…	EOC management (anti-cancer)	[60]

miR-34a-3p on its downstream gene E2F3, thereby promoting OC progression [50].

3.2. Epithelial-mesenchymal Transition Formation

Snail induces EMT in OC cells, a crucial step in cancer metastasis. Upon the introduction of miR-34a, both transcript and protein levels of Snail were significantly reduced, effectively suppressing the EMT phenotype and sphere formation in OC cells [51]. Conversely, the presence of OIP5-AS1, an oncogenic lncRNA, upregulated Snail expression. Specifically, overexpression of OIP5-AS1 in OC cells led to increased Snail expression, while overexpression of miR-34a resulted in Snail downregulation. Moreover, miR-34a overexpression mitigated the effects of OIP5-AS1 overexpression on Snail expression in OC [52].

3.3. Treatments and Outcomes

In the treatment aspects, another study by Zuo Y *et al*. showed that programmed cell death 1 ligand 1 (PD-L1) was implicated in cancer chemoresistance. Investigation of cisplatin (DDP)-resistant SKOV3 and OC cell lines (SKOV3/DDP and A2780/DDP) revealed increased PD-L1 expression and decreased miR-34a-5p levels in DDP-resistant cells. Additionally, miR-34a-5p was found to negatively regulate PD-L1 expression by targeting its 3'-UTR [53]. Teng Lv *et al*. demonstrated that miR-34a, by specifically targeting the 3'-UTR of Histone Deacetylase 1 (HDAC1) mRNA, reduced the growth of SKOV3 and OVCA433 cells and increased the cisplatin sensitivity of cisplatin-resistant SKOV3cp cells. The overexpression of HDAC1 increased OC cell proliferation and reduced cisplatin sensitivity [54].

Additionally, the IL-6R/STAT3 signaling pathway, known to play a crucial role in OC progression, was targeted by ectopically expressed miR-34a, resulting in significant inhibition of tumor proliferation and invasion through downregulation of IL-6R expression. This observation suggests that decreased miR-34a expression potentially contributes to the malignant potential of high-grade serous carcinoma (HGSC) by upregulating the IL-6R/STAT3 signaling pathway [55]. On the other hand, the kinetics of 11 significant miRNAs after neo-adjuvant therapy in OC were examined in the randomized phase II CHIVA study by Robelin P *et al*. The study found that lower levels of the miR-34a-5p were linked to better outcomes for patients. Specifically, patients with decreased miR-34a-5p levels had a progression-free survival (PFS) of 24.8 months compared to 13.7 months for those with higher levels [56].

Furthermore, Welponer H *et al*. analyzed the expression of miR-34a/b/c in 228 OC patients and found significantly lower levels of miR-34a/b/c in OC compared to control tissues. Moreover, the study indicated a negative correlation between the expression of miR-34b/c and BRCA1/2 mRNA expression [23]. In the assessment of biological activity, it was observed that an increase in miR-34a-5p levels or a decrease in TRIM44 expression had the ability to suppress malignant behaviors in OC cells. Moreover, co-transfection experiments demonstrated that overexpression of miR-34a-5p mediated by TRIM44 reversed the biological activities of OC cells [57]. Efficient delivery of miR-34a-mimic has been achieved *in vitro* and *in vivo* using a minimally invasive method known as ultrasound-targeted microbubble destruction (UTMD). Li Y *et al*. delivered miR-34a into cells using miR-34a-mimic-loaded microbubbles modified with folate (miR-34a-FM).

Consequently, miR-34a mimics were successfully introduced into the cytoplasm, resulting in the suppression of SK-OV-3 cell proliferation and induction of apoptosis. Subsequently, miR-34a-mimic was injected *via* UTMD into the tumor tissue, leading to tumor growth suppression and increased survival time in mice with OC [58]. The anti-tumor activity of oleuropein has been assessed in A2780S and A2780/CP cell lines. Sheikhshabani SH *et al*. reported that oleuropein administration led to an increase in the expression of P21, P53, and miR-34a, while decreasing the expression of BCL2 and Mcl1 (myeloid cell leukemia 1) [59]. Kumar V *et al*. performed Methylated DNA Immunoprecipitation combined with NGS (MeDIP-NGS) sequencing on normal samples and Epithelial ovarian cancer (EOC) tissues. The sequencing revealed hypermethylation of numerous miRNA gene promoters. Early-stage EOC tissues and serum samples exhibited a significant reduction in the relative expression level of miR-34a compared to normal individuals. The winged helix transcription factor forkhead box P1 (FOXP1) has been identified as both an oncogene and a tumor suppressor in OC. Dirimtekin E *et al*. elucidated the molecular and clinical relationships between miR-34a and the transcription factor FOXP1 in OC. In both *in vitro* and *in vivo* environments, there is an inverse correlation between miR-34a and FOXP1. Inhibition of miR-34a briefly increased FOXP1 mRNA expression, whereas overexpression of miR-34a targeting FOXP1 could potentially reduce OC development [22]. *In silico* functional enrichment analysis revealed the relationship between miRNA and the medical condition. Target genes of miRNAs are involved in biologically significant processes contributing to cancer development. In EOC, miR-34a was significantly upregulated, while miR-205 targets were downregulated. Furthermore, a strong negative correlation was observed between miR-34a and the target genes MDM4, MAPK3, BRCA1, and AREG. The expression data of target genes and miRNA in matched samples highlight the therapeutic potential of miRNA in EOC therapy [60].

CONCLUSION

miR-34a plays a crucial role in regulating ovarian cancer cell proliferation and progression by targeting several key signaling pathways, including Snail, BCL2, NOTCH1, IL-6R/STAT3, TRIM44, FOXP1, BRCA1/2, P21, P53, MDM4, and MAPK3. In the context of cancer treatments, often facing challenges like drug resistance and ineffectiveness, exploring the molecular

mechanisms of miR-34a could lead to innovative therapies for various cancers, including ovarian cancer. By understanding how miR-34a functions, we can potentially develop more effective treatment strategies that overcome these obstacles.

AUTHORS' CONTRIBUTIONS

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to its submission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

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CONFLICT OF INTERESTS

The authors declare that there are no competing interests.

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REFERENCES

[1] Anghel B, Georgescu MT, Serboiu CS, *et al.* Optimizing Palliative Pelvic Radiotherapy in Gynecological Cancers: A Systematic Review and Analysis. Diagnostics (Basel) 2024; 14(5): 547. http://dx.doi.org/10.3390/diagnostics14050547 PMID: 38473019

[2] Pour FK, Keivan M, Ghaedrahmati F, *et al.* Endometrial Cancer Stem Cells Related Signaling Pathways. Curr Cancer Ther Rev 2023; 19(4): 284-91. http://dx.doi.org/10.2174/1573394719666230306145642

[3] Pfeifer CR, Hales KH, Hales DB, Shyer AE, Rodrigues AR. Collective fibroblast mechanics in ovarian cancer metastasis. Biophys J 2024; 123(3): 405a. http://dx.doi.org/10.1016/j.bpj.2023.11.2486

[4] Sowamber R, Lukey A, Huntsman D, Hanley G. Ovarian cancer: From precursor lesion identification to population-based prevention programs. Curr Oncol 2023; 30(12): 10179-94. http://dx.doi.org/10.3390/curroncol30120741 PMID: 38132375

[5] O'Mahony DG, Ramus SJ, Southey MC, *et al.* Ovarian cancer pathology characteristics as predictors of variant pathogenicity in BRCA1 and BRCA2. Br J Cancer 2023; 128(12): 2283-94. http://dx.doi.org/10.1038/s41416-023-02263-5 PMID: 37076566

[6] Lashen A, Algethami M, Alqahtani S, *et al.* The Clinicopathological Significance of the Cyclin D1/E1–Cyclin-Dependent Kinase (CDK2/4/6)–Retinoblastoma (RB1/pRB1) Pathway in Epithelial Ovarian Cancers. Int J Mol Sci 2024; 25(7): 4060. http://dx.doi.org/10.3390/ijms25074060 PMID: 38612869

[7] K AR, Arumugam S, Muninathan N, Baskar K, S D, D DR. P53 Gene as a Promising Biomarker and Potential Target for the Early Diagnosis of Reproductive Cancers. Cureus 2024; 16(5): e60125. http://dx.doi.org/10.7759/cureus.60125 PMID: 38864057

[8] Tcyganov EN, Kwak T, Yang X, Poli ANR, Hart C, Bhuniya A. Targeting LxCxE cleft pocket of retinoblastoma protein in M2 macrophages inhibits ovarian cancer progression. bioRxiv 2024; 2024: 593562. http://dx.doi.org/10.1101/2024.05.10.593562

[9] C e DK, C VTT, J C EM, *et al.* The Impact of BRCA1- and BRCA2 Mutations on Ovarian Reserve Status. Reprod Sci 2023; 30(1): 270-82. http://dx.doi.org/10.1007/s43032-022-00997-w PMID: 35705781

[10] Ehmann T, Barel S, Ray A, Borsch D. The Role of Estrogen in Ovarian Cancer and the Pathways by Which Estrogen Acts. 2023. Available from: https://www.hmsreview.org/issue-8/ehmann-2023

[11] Kim SY, Chang HK, Kwon O, Park J, Myong J-P. Asbestos exposure and Ovarian Cancer; A meta-analysis. Saf Health Work 2023. PMID: 38496274

[12] Wentzensen N, O'Brien KM. Talc, body powder, and ovarian cancer: A summary of the epidemiologic evidence. Gynecol Oncol 2021; 163(1): 199-208. http://dx.doi.org/10.1016/j.ygyno.2021.07.032 PMID: 34366148

[13] Harris BHL, Macaulay VM, Harris DA, *et al.* Obesity: a perfect storm for carcinogenesis. Cancer Metastasis Rev 2022; 41(3): 491-515. http://dx.doi.org/10.1007/s10555-022-10046-2 PMID: 36038791

[14] Cui J, Wang Y. Premature ovarian insufficiency: a review on the role of tobacco smoke, its clinical harm, and treatment. J Ovarian Res 2024; 17(1): 8. http://dx.doi.org/10.1186/s13048-023-01330-y PMID: 38191456

[15] Evangelinakis N, Geladari EV, Geladari CV, *et al.* The influence of environmental factors on premature ovarian insufficiency and ovarian aging. Maturitas 2024; 179: 107871. http://dx.doi.org/10.1016/j.maturitas.2023.107871 PMID: 37925867

[16] Chiaffarino F, Cipriani S, Ricci E, Esposito G, Parazzini F, Vercellini P. Histologic Subtypes in Endometriosis-Associated Ovarian Cancer and Ovarian Cancer Arising in Endometriosis: A Systematic Review and Meta-Analysis. Reprod Sci 2024; •••: 1-9.

[17] Hassan S, Thacharodi A, Priya A, *et al.* Endocrine disruptors: Unravelling the link between chemical exposure and Women's reproductive health. Environ Res 2024; 241: 117385. http://dx.doi.org/10.1016/j.envres.2023.117385 PMID: 37838203

[18] Veneziani AC, Gonzalez-Ochoa E, Alqaisi H, *et al.* Heterogeneity and treatment landscape of ovarian carcinoma. Nat Rev Clin Oncol 2023; 20(12): 820-42. http://dx.doi.org/10.1038/s41571-023-00819-1 PMID: 37783747

[19] Moftakhar A, Najafi S, Anbiyaee O, Farzaneh M, Khoshnam SE. Functional Roles of the lncRNA MALAT1 in Glioma. Curr Cancer Ther Rev 2024; 20(2): 166-76. http://dx.doi.org/10.2174/1573394719666230720164009

[20] Najafi S, Ghaedrahmati F, Abouali Gale Dari M, Farzaneh M, Mohammad Jafari R. The Regulatory Role of Circular RNAs as miRNA Sponges in Cervical Cancer. Curr Signal Transduct Ther 2023; 18(3): e241123223777. http://dx.doi.org/10.2174/0115743624273536231105142321

[21] Li S, Wei X, He J, *et al.* The comprehensive landscape of miR-34a in cancer research. Cancer Metastasis Rev 2021; 40(3): 925-48. http://dx.doi.org/10.1007/s10555-021-09973-3 PMID: 33959850

[22] Dirimtekin E, Mortoglou M, Alavanda C, *et al.* miR-34a-FOXP1 Loop in Ovarian Cancer. ACS Omega 2023; 8(30): 27743-50.

http://dx.doi.org/10.1021/acsomega.3c03867 PMID: 37546627

[23] Welponer H, Tsibulak I, Wieser V, *et al.* The miR-34 family and its clinical significance in ovarian cancer. J Cancer 2020; 11(6): 1446-56. http://dx.doi.org/10.7150/jca.33831 PMID: 32047551

[24] Abdelaal AM, Sohal IS, Iyer S, *et al.* A first-in-class fully modified version of miR-34a with outstanding stability, activity, and anti-tumor efficacy. Oncogene 2023; 42(40): 2985-99. http://dx.doi.org/10.1038/s41388-023-02801-8 PMID: 37666938

[25] Veltri AJ, D'Orazio KN, Lessen LN, Loll-Krippleber R, Brown GW, Green R. Distinct elongation stalls during translation are linked with distinct pathways for mRNA degradation. eLife 2022; 11: e76038. http://dx.doi.org/10.7554/eLife.76038 PMID: 35894211

[26] del Valle-Morales D, Le P, Saviana M, *et al.* The epitranscriptome in miRNAs: crosstalk, detection, and function in cancer. Genes (Basel) 2022; 13(7): 1289. http://dx.doi.org/10.3390/genes13071289 PMID: 35886072

[27] McGeary SE, Bisaria N, Pham TM, Wang PY, Bartel DP. MicroRNA 3′-compensatory pairing occurs through two binding modes, with affinity shaped by nucleotide identity and position. eLife 2022; 11: e69803. http://dx.doi.org/10.7554/eLife.69803 PMID: 35191832

[28] Rokavec M, Huang Z, Hermeking H. Meta-analysis of miR-34 target mRNAs using an integrative online application. Comput Struct Biotechnol J 2023; 21: 267-74. http://dx.doi.org/10.1016/j.csbj.2022.12.003 PMID: 36582442

[29] Di Paolo D, Pastorino F, Brignole C, *et al.* Combined replenishment of miR-34a and let-7b by targeted nanoparticles inhibits tumor growth in neuroblastoma preclinical models. Small 2020; 16(20): 1906426. http://dx.doi.org/10.1002/smll.201906426 PMID: 32323486

[30] Choi YJ, Lin C-P, Risso D, Chen S, Kim TA, Tan MH. Deficiency of microRNA miR-34a expands cell fate potential in pluripotent stem cells. Science 2017; 355: 6325-eaag1927. http://dx.doi.org/10.1126/science.aag1927

[31] Min X, Wang JY, Zong FJ, Zhao J, Liu N, He KW. miR-34a regulates silent synapse and synaptic plasticity in mature hippocampus. Prog Neurobiol 2023; 222: 102404. http://dx.doi.org/10.1016/j.pneurobio.2023.102404 PMID: 36642095

[32] Gaderpour S, Ghiasi R, Hamidian G, Heydari H, Keyhanmanesh R. Voluntary exercise improves spermatogenesis and testicular apoptosis in type 2 diabetic rats through alteration in oxidative stress and mir-34a/SIRT1/p53 pathway. Iran J Basic Med Sci 2021; 24(1): 58-65. PMID: 33643571

[33] Wang J, He P, Tian Q, *et al.* Genetic modification of miR-34a enhances efficacy of transplanted human dental pulp stem cells after ischemic stroke. Neural Regen Res 2023; 18(9): 2029-36. PMID: 36926729

[34] Peters F, Grimm C. Regulation of ABCA1 by miR-33 and miR-34a in the Aging Eye. In: Retinal Degenerative Diseases XIX: Mechanisms and Experimental Therapy. Springer 2023; pp. 55-9. http://dx.doi.org/10.1007/978-3-031-27681-1_9

[35] Chen R, Chen H, Yang Z, *et al.* Danlou tablet inhibits high-glucose-induced cardiomyocyte apoptosis *via* the miR-34a-SIRT1 axis. Heliyon 2023; 9(3): e14479. http://dx.doi.org/10.1016/j.heliyon.2023.e14479 PMID: 36950610

[36] Liu X, Zhao Z, Chen D, *et al.* SIRT1 and miR-34a-5p Expression in PBMCs as Potential Biomarkers for Patients With Type 2 Diabetes With Cognitive Impairments. J Clin Endocrinol Metab 2024; 109(3): 815-26. http://dx.doi.org/10.1210/clinem/dgad562 PMID: 37758217

[37] Nóbrega OT, Morais-Junior GS, Viana NI, Reis ST, Perez DI, Freitas WM. Circulating miR-34a and Bone Mineral Density of Brazilian Very-Old Adults. J Aging Res 2020; 2020: 3431828. http://dx.doi.org/10.1155/2020/3431828

[38] Briones-Espinoza MJ, Cortés-García JD, Vega-Cárdenas M, *et al.* Decreased levels and activity of Sirt1 are modulated by increased miR-34a expression in adipose tissue mononuclear cells from subjects with overweight and obesity: A pilot study. Diabetes Metab Syndr 2020; 14(5): 1347-54. http://dx.doi.org/10.1016/j.dsx.2020.07.014 PMID: 32755834

[39] Xu Y, Zhu Y, Hu S, *et al.* Hepatocyte miR-34a is a key regulator in the development and progression of non-alcoholic fatty liver disease. Mol Metab 2021; 51: 101244. http://dx.doi.org/10.1016/j.molmet.2021.101244 PMID: 33930596

[40] Kalfert D, Ludvikova M, Pesta M, Ludvik J, Dostalova L, Kholová I. Multifunctional Roles of miR-34a in Cancer: A Review with the Emphasis on Head and Neck Squamous Cell Carcinoma and Thyroid Cancer with Clinical Implications. Diagnostics (Basel) 2020; 10(8): 563. http://dx.doi.org/10.3390/diagnostics10080563 PMID: 32764498

[41] Li WJ, Wang Y, Liu R, *et al.* MicroRNA-34a: Potent Tumor Suppressor, Cancer Stem Cell Inhibitor, and Potential Anticancer Therapeutic. Front Cell Dev Biol 2021; 9: 640587. http://dx.doi.org/10.3389/fcell.2021.640587 PMID: 33763422

[42] Hermeking H. The miR-34 family in cancer and apoptosis. Cell Death Differ 2010; 17(2): 193-9. http://dx.doi.org/10.1038/cdd.2009.56 PMID: 19461653

[43] Schmid G, Notaro S, Reimer D, *et al.* Expression and promotor hypermethylation of miR-34a in the various histological subtypes of ovarian cancer. BMC Cancer 2016; 16(1): 102. http://dx.doi.org/10.1186/s12885-016-2135-2 PMID: 26879132

[44] Arapaki A, Karabelas A, Panoutsopoulou K, Papachristopoulou G, Avgeris M, Scorilas A. EP1277 Clinical evaluation of miR-34a in ovarian carcinoma. BMJ Specialist Journal 2019. http://dx.doi.org/10.1136/ijgc-2019-ESGO.1283

[45] Yao S, Gao M, Wang Z, Wang W, Zhan L, Wei B. Upregulation of MicroRNA-34a Sensitizes Ovarian Cancer Cells to Resveratrol by Targeting Bcl-2. Yonsei Med J 2021; 62(8): 691-701. http://dx.doi.org/10.3349/ymj.2021.62.8.691 PMID: 34296546

[46] Wei B, Yao S, Gao M, Wang Z, Wang W, Zhan L. Resveratrol suppresses ovarian cancer cell growth and invasion through upregulation of microRNA-34a. Res Sq 2020; 2020 http://dx.doi.org/10.21203/rs.3.rs-38233/v1

[47] Tao F, Tian X, Lu M, Zhang Z. A novel lncRNA, Lnc-OC1, promotes ovarian cancer cell proliferation and migration by sponging miR-34a and miR-34c. J Genet Genomics 2018; 45(3): 137-45. http://dx.doi.org/10.1016/j.jgg.2018.03.001 PMID: 29576507

[48] Jia Y, Lin R, Jin H, *et al.* RETRACTED: MicroRNA-34 suppresses proliferation of human ovarian cancer cells by triggering autophagy and apoptosis and inhibits cell invasion by targeting Notch 1. Biochimie 2019; 160: 193-9. http://dx.doi.org/10.1016/j.biochi.2019.03.011 PMID: 30905732

[49] Maeda K, Sasaki H, Ueda S, *et al.* Serum exosomal microRNA-34a as a potential biomarker in epithelial ovarian cancer. J Ovarian Res 2020; 13(1): 47. http://dx.doi.org/10.1186/s13048-020-00648-1 PMID: 32336272

[50] Xu D, Song Q, Liu Y, *et al.* LINC00665 promotes Ovarian Cancer progression through regulating the miRNA-34a-5p/E2F3 axis. J Cancer 2021; 12(6): 1755-63. http://dx.doi.org/10.7150/jca.51457 PMID: 33613764

[51] Dong P, Xiong Y, Watari H, *et al.* MiR-137 and miR-34a directly target Snail and inhibit EMT, invasion and sphere-forming ability of ovarian cancer cells. J Exp Clin Cancer Res 2016; 35(1): 132. http://dx.doi.org/10.1186/s13046-016-0415-y PMID: 27596137

[52] Jiang X, Ye Z, Jiang Y, Yu W, Fang Q. LncRNA OIP5-AS1 upregulates snail expression by sponging miR-34a to

promote ovarian carcinoma cell invasion and migration. Biol Res 2020; 53(1): 49. http://dx.doi.org/10.1186/s40659-020-00315-1 PMID: 33092644

[53] Zuo Y, Zheng W, Liu J, Tang Q, Wang SS, Yang XS. MiR-34a-5p/PD-L1 axis regulates cisplatin chemoresistance of ovarian cancer cells. Neoplasma 2020; 67(1): 93-101. http://dx.doi.org/10.4149/neo_2019_190202N106 PMID: 31777260

[54] Lv T, Song K, Zhang L, *et al.* miRNA-34a decreases ovarian cancer cell proliferation and chemoresistance by targeting HDAC1. Biochem Cell Biol 2018; 96(5): 663-71. http://dx.doi.org/10.1139/bcb-2018-0031 PMID: 29561664

[55] Yokomizo R, Yanaihara N, Yamaguchi N, *et al. MicroRNA-34a* /IL-6R pathway as a potential therapeutic target for ovarian high-grade serous carcinoma. Oncotarget 2019; 10(47): 4880-93. http://dx.doi.org/10.18632/oncotarget.27117 PMID: 31448054

[56] Robelin P, Tod M, Colomban O, *et al.* Comparison of 11 circulating miRNAs and CA125 kinetics in ovarian cancer during first line treatment: Data from the randomized CHIVA trial (a GINECO-GCIG study). Ann Oncol 2019; 30: v783-4. http://dx.doi.org/10.1093/annonc/mdz268.072

[57] Li H-L, Duan Y-A, Zhao N. MiR-34a-5p directly targeting TRIM44 affects the biological behavior of ovarian cancer cells. Eur Rev Med Pharmacol Sci 2021; 25(3): 1250-60. PMID: 33629295

[58] Li Y, Du M, Fang J, Zhou J, Chen Z. UTMD promoted local delivery of miR-34a-mimic for ovarian cancer therapy. Drug Deliv 2021; 28(1): 1616-25. http://dx.doi.org/10.1080/10717544.2021.1955041 PMID: 34319204

[59] Hashemi Sheikhshabani S, Amini-Farsani Z, Rahmati S, Jazaeri A, Mohammadi-Samani M, Asgharzade S. Oleuropein reduces cisplatin resistance in ovarian cancer by targeting apoptotic pathway regulators. Life Sci 2021; 278: 119525. http://dx.doi.org/10.1016/j.lfs.2021.119525 PMID: 33894272

[60] Kumar V, Pandey A, Arora A, *et al.* Diagnostics and Therapeutic Potential of miR-205 and miR-34a in Ovarian Cancer Management: A miRNA-Target-Based Analysis. DNA Cell Biol 2023; 42(3): 151-62. http://dx.doi.org/10.1089/dna.2022.0487 PMID: 36779980

[61] Ding N, Wu H, Tao T, Peng E. NEAT1 regulates cell proliferation and apoptosis of ovarian cancer by miR-34a-5p/BCL2. OncoTargets Ther 2017; 10: 4905-15. http://dx.doi.org/10.2147/OTT.S142446 PMID: 29062236

[62] Kumar V, Gupta S, Varma K, Chaurasia A, Sachan M. Diagnostic performance of microRNA-34a, let-7f and microRNA-31 in epithelial ovarian cancer prediction. J Gynecol Oncol 2022; 33(4): e49. http://dx.doi.org/10.3802/jgo.2022.33.e49 PMID: 35557032