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Review Article

MicroRNAs regulate several functions of normal tissues and malignancies

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Abstract

MicroRNAs (miRNAs, *miRs*) are a cluster of naturally occurring small non-coding RNA molecules of 19–24 nucleotides in length. *miRs* control gene expression post-transcriptionally by binding to a specific site at the 3′-UTR of target mRNA, which results in mRNA cleavage and translation repression. Nearly 1000 *miRs* in the human genome have been identified, and it is believed that these *miRs* contribute to at least 60% of the human transcriptome. Recent research has shown that *miRs* are emerging as important regulators of cellular differentiation and dedifferentiation. In addition, dysregulation of *miR* expression may play a fundamental role in the onset, progression and dissemination of cancers. In this review, we focus on some paradigms of *miR* involvement in tumorigenesis, such as ovarian cancer, and also discuss the relationship between *miRs* and cancer stem cells.

Keywords: cancer stem cell; microRNA; ovarian cancer

Introduction

MicroRNAs (miRNAs, *miRs*) are a cluster of naturally occurring small non-coding RNA molecules of 19–24 nucleotides in length (single-stranded RNAs, ssRNAs), that post-transcriptionally control gene expression by binding to a specific site at the 3′-untranslated region (3′-UTR) of target mRNA, inducing mRNA cleavage and translation repression [1]. *miR* biogenesis involves the maturation of miR precursors, assembly of the mature *miR* into microprocessor complexes and the regulation of gene expression of protein-coding genes by degrading and/or blocking translation of mRNA targets [2]. Bioinformatic analyses have predicted the existence of nearly 1000 *miRs* in the human genome [3]. *miRs* are involved in virtually all biological processes, including gene regulation, cell developmental control, for example, cell proliferation, differentiation and apoptosis, and stemness. In addition, because gene expression mediated by *miRs* is accomplished by imperfect base pairing together with protein translational repression of the target gene, and the specificity of *miR* targeting is mediated by only six to 11 nucleotides, a single miR can target hundreds of mRNAs [2], aberrant miR expression may be involved in the initiation of various types of diseases, including cancer [4,5]. Furthermore, because dysregulation of *miR* expression may play a fundamental role in the onset, progression, and dissemination of cancer, measuring circulating *miR* levels may be useful in early cancer detection, which can significantly contribute to treatment success.

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Moreover, replacement of downregulated *miRs* in tumor cells via recent biotechnology might provide a potential therapeutic role [2]. In this review, we focus on some paradigms of *miR* involvement in tumorigenesis, for example, ovarian cancer, and we also discuss the relationship between *miRs* and cancer stem cells (CSCs).

Altered *miRs* are always found in all cancers

Growing evidence has demonstrated that *miRs* can act as either oncogenes or tumor-suppressor genes [2]. However, the categorization of miRs as oncogenes or tumor-suppressor genes based on their levels of expression in tumors versus normal tissues has proven to be inaccurate, because experiments have shown that many function dually as both oncogenes and tumor-suppressor genes depending on the cancer type, stage and cellular context [2]. Regarding the relationship between miRNAs and cancer, B cell chronic lymphocytic leukemia might be the first human malignancy known to be associated with *miR* dysregulation [*miR-15* and *miR-16* are deleted or downregulated in the majority (68%) of patients with chronic lymphocytic leukemia] [5,6]. With regard to solid tumors, colon cancer might be one of the first studies of *miRs* in solid tumors, where, in a study, 28 *miRs* differentially expressed between colonic cancer and normal mucosa were identified, and it was concluded that levels of *miR-143a* and *miR-145a* were significantly lower in tumors than in normal tissue [7]. Later, genome-wide *miR* expression profiling studies using high-throughput technologies demonstrated that almost all cancer types present a specific profile of upregulated and downregulated *miRs* [2,8]. Among these *miRs*, more and more evidence has supported the prominent role of *miR-21*. *miR-21* is upregulated in various solid tumors, such as glioblastoma and astrocytoma, as well as hematological malignancies [2,9], and overexpression of *miR-21* has been shown to promote cancer cell proliferation and migration, and affect survival of patients; therefore, *miR-21* can be considered an oncomir. By contrast, members of the tumor-suppressor *miR let-7* family are downregulated in many cancers and inhibit tumor growth by targeting various oncogenes and main regulators of mitogenic pathways, including *c-myc*, *RAS* and $HMGA_2$ [10]. *miR-34* is another well-known tumor suppressor, which is the effector of *TP53* activation [11].

The role of *miR-21* in ovarian cancer

miR-21 is a cancer-associated *miR* (onco-*miR*) that is overexpressed in most human tumors, especially in highly aggressive tumors. *miR-21* promotes malignant growth and progression by acting on multiple targets, including an inhibition of *PTEN* [phosphatase and tensin homolog − an upstream negative regulator of mammalian target of rapamycin (mTOR)], activation of nuclear factor (NF)-κB activity, enhanced formation of reactive oxygen species (ROS), inducing tumor angiogenesis and through it activation of the AKT and ERK1/2 signaling pathways, thereby enhancing hypoxia-inducible factor 1, alpha subunit (HIF-1α) and vascular endothelial growth factor (VEGF) expression, reduction of the expression of potent human anti-inflammatory molecules, such as interleukin(IL)-10, and transforming growth factor(TGF)-β [12]. In ovarian cancer, the role of *miR-21* on biological behavior and function is uncertain, although one study showed that downregulation of *miR-21* by short hairpin (sh)RNA could significantly increase the percentage of cell apoptosis and necrosis compared with that in the control group, and by transwell migration assay and scratch wound assay, the ability of migration of OVCAR3 significantly decreased in the group with downregulation of *miR-21* [13]. The potential target gene of *miR-21* in ovarian cancer might be programmed cell death 4 (*PDCD4*), ribosomal protein (RPS) 7, non-structural maintenance of chromosome (SMC) condensin I complex, subunit G (*NCAPG*), tropomyosins (*TPM1*) and *PTEN* [1]. In addition, by contrast, Nam et al found that the majority of ovarian cancer samples (85%) showed upregulation of *miR-21* from their identification of 23 aberrantly expressed *miRs* in at least 60% of ovarian cancer samples [14]. However, in a study by Iorio et al, upregulation of *miR-21* was only found in endometrioid carcinomas of the ovary [15]. Therefore, in a later study in 2011 [16], The Cancer Genome Atlas (TCGA) provided the first comprehensive molecular classification of a large cohort of high-grade serous ovarian carcinomas by integrated analyses of multidimensional data, including *miR* expression profiles, to identify molecular abnormalities that influence ovarian cancer pathophysiology, affect outcome and constitute therapeutic targets [16], based on worst outcome of the ovarian cancer, including Taiwan [17,18]. However, in 2003, Yang et al used an integrated genomic analyses to reveal a *miR*-regulatory network that further defined a robust integrated mesenchymal subtype associated with poor overall survival in 459 cases of serous ovarian cancer from TCGA and 560 cases from independent cohorts and identified eight key miRs, including *miR-25*, *miR-506*, *miR-29c*, *miR-182*, *miR-128*, *miR-101*, *miR-141* and *miR-200a*, which were predicted to regulate 89% of the targets in this network [19]. Furthermore, they used a nanoparticle delivery of miR-506 in orthotopic ovarian cancer mouse models leading to E-cadherin induction and reducing tumor growth [19]. Therefore, the role of miR-21 in ovarian cancer needs further confirmation, but there is no doubt that *miR* can be used in ovarian cancer, not only a diagnostic tool, but also as a predictor for outcome [2,19].

CSCs control the development and progression of different malignancies

Unlike the aberrant *miR* expression in somatic cells, which can promote tumorigenesis, altered expression of *miR* in germline cells may predispose to cancer development [2]. One emerging hypothesis for cancer development appeared to be the existence of CSCs (or also called tumor initiating cells or tumor progenitor cells) that were believed to be fully responsible for tumor formation and progression, and have the ability of self-renewal [20]. Several signaling pathways and molecules were designated to modulate CSCs, such as

Hedgehog, *Notch*, *Wnt/β-catenin*, *c-Myc*, *c-Met*, *Bcl-2* and *Bmi-1* [21]. CSCs in different cancers could be identified by different methods, such as fluorescent-activated cell sorting (FACS) by cell surface markers, efflux of Hoechst dye for isolating side population cells, overexpression of enzyme alcohol dehydrogenase or single colony selection. Ovarian CSCs, identified by cell surface markers CD44 and CD117, or CD133, were demonstrated to have tumorigenic potency, stemness ability, chemoresistance and the ability to induce distant metastasis in many previous studies [20]. The expression of CD133 defined a tumor initiating subpopulation of human ovarian cancer in the NOD/SCID model [21]. Moreover, anti-CD133 targeted toxin used in an *in vivo* ovarian cancer model could markedly reduce the progression of intraperitoneal ovarian cancer despite the low percentage of CD133 expression [22].

miRNAs can affect functions of CSCs

Several studies have recently confirmed that miRNAs also play a vital role in affecting the function of CSCs. For brain cancer, miR-34 was involved in the survival, apoptosis and self-renewal of CSCs through its target gene, such as *Wnt3*, *MYC*, *Notch* and *Bcl-2*. Restitution of *miR-34* could inhibit tumor sphere growth *in vitro* and tumor formation *in vivo* [23]. Moreover, restitution of *miR-34* also inhibited the growth of CSCs with surface markers of $CD44^+/CD133^+$. Likewise, overexpression of miR-199-5p could decrease tumor development of medulloblastoma through reducing $CD133^+$ subpopulation cells and targeting *HES-1*, a transcription factor of the Notch signaling pathway. In addition to confirming the suppression of the properties of prostate CSCs, CD44, a cell marker for prostate CSCs, was proven to be a direct and relevant downstream target of *miR-34a* simultaneously. The protein level of CD44 could be reduced in overexpression of *miR-34a*. In breast CSCs, *let-7* could also regulate the characteristics of stem cells, including self-renewal and differentiation [24]. Overexpression of *let-7* could inhibit mammosphere formation, tumor formation, distant metastasis in the NOD/SCID model and even reduce the proportion of undifferentiated cells *in vitro*. However, recent studies suggest that other *miRs*, in addition to *let-7*, might simultaneously play a role in regulating breast CSCs because overexpression of *let-7* alone was not sufficient to completely block the function of CSCs. More complete inhibition of self-renewal and mammosphere formation in breast CSCs could be achieved when *let-7* was simultaneously introduced with *miR-30* compared with either one alone. This synergistic inhibition effect of *let-7* and *miR-30* on breast CSCs suggests that multiple miRNAs might concertedly regulate the function of CSCs.

Association between miRNA-21 and CSCs

Strong associations between *miR-21* and CSCs were confirmed in different types of cancer. Overexpression of *miR-21* not only contributed to epithelial–mesenchymal transition by activation of mesenchymal cell markers (N-cadherin, Vimentin, α-SMA) and inhibition of the epithelial cell marker, E-cadherin, in the MCF-7 cell line but also increased subpopulation cells expressing surface markers ($ALDH1^+$, $CD44^+/CD24^{-/low}$) and the ability of sphere formation [25]. Epithelial–mesenchymal transition reversed by antagonism of *miR-21* indicated the key role of *miR-21* in regulating CSC-associated features [26]. In hepatocellular carcinoma side population CSCs, *miR-21* was shown to be upregulated in regulating the ability of invasion and migration [27]. Furthermore, *miR-21* could maintain the chemoresistance of these side population CSCs. Inhibition of *miR-21* by temozolomide, an alkylating agent, used as a chemotherapeutic agent for treating glioblastoma, significantly enhanced apoptosis of glioblastoma cells [28]. Finally, *miR-21* was also shown to play an important role in ovarian CSCs [29]. When using the miRNA microarray to analyze the expression of miRNAs in $CD133^+$ spheroid-forming cells of the OVCAR3

Table 1
List of dysregulated miRNAs related to functions of ovarian cancer stem cells.

miRNAs (*miR*)	Up/Downregulation	Potential targets	References
miR-15a, *miR-16a*	Down	*BAZ2A*, *Bcl-2*, *CCND1*, *Wnt3*, *BMI-1*, *ETS1*, *c-JUN*, *MCL1*	[14,27,28]
miR-21	Up	*PDCD4*, *RPS7*, *NCAPG*, *TPM1*, *PTEN*	[29]
miR-34a, *miR-34b*, *miR-34c*	Down	*SIRT1*, *MYC*, *NOTCH*, *Bcl-2*, *CCND1*, *Wnt3*	[14,15,29,31–34]
miR-98	Down	*HMGA2*, *Lin28B*, *HIC2*	[15]
miR-138	Down	*SOX4*, *HIF-1α*	[35]
miR-181a, *miR-181b*	Up	*HOXA11*, *GATS6*, *NLK*, *CDX2*, *TBL1X*, *DPP6*, *KLF2*	[29,33,36]
miR-187	Dual roles	*Dab2*	[37]
miR-377	Down	*REST*, *SOD1*	[31,38]
miR-let-7b, *miR-let-7d*, *miR-let-7e*, *miR-let-7f*	Down	*c-Myc*, *KRAS*, *HMGA2*, *IL-6*, *LiN28B*, *HIC2*	[14,15,29,34,39]

BAZ2A = bromodomain adjacent to zinc finger domain, 2A; Bcl-2 = B cell lymphoma 2; BMI-1 = polycomb ring finger oncogene; CCND1 = cyclin D1; CDX2 = caudal type homeobox 2; cJUN = jun proto-oncogene; Dab2 = Disabled homolog-2; DPP6 = dipeptidyl-peptidase 6; ETS1 = v-ets avian erythroblastosis virus E26 oncogene homolog 1; GATS = stromal antigen 3 opposite strand; HIC2 = hypermethylated in cancer 2; HMGA2 = high mobility group AT-hook 2; HOXA11 = homeobox A11; IL-6 = interleukin 6; KLF2 = Kruppel-like factor 2; KRAS = Kirsten rat sarcoma viral oncogene homolog; Lin28B = lin-28 homolog B; MCL = malyl-CoA lyase/β-methylmalyl-CoA lyase; MYC = myelocytomatosis oncogene homolog; NACAPG = non-structural maintenance of chromosome (SMC) condensin I complex, subunit G; NLK = nemo-like kinase; PDCD = programmed cell death; PTEN = phosphatase and tensin homolog; REST = RE1-silencing transcription factor; RPS = ribosomal proteins; SIR = sirtulin; SOD1 = superoxide dismutase 1, soluble; TBL1X = transducin (β)-like 1X-linked; TPM = tropomyosins; Wnt3 = glycoproteins acting as ligands to produce cell responses playing a variety of important roles 3.

cell line, *miR-21* was found to be significantly upregulated; therefore, it can be supposed that dysregulation of *miR-21* may play an important role in stem cell-like properties of ovarian CSCs.

miRNA-21 and other miRs exert a broad regulatory role on ovarian CSCs

A recent publication from the China Medical University in Taichung, entitled "MicroRNA-21 promotes ovarian teratocarcinoma by sustaining cancer stem/progenitor populations in vitro", by Chung et al, proved that *miR-21* regulates cell growth and sphere formation of the ovarian teratocarcinoma cell line PA1 through CD133 CSCs when knockdown of miR-21, the $CD133^+$ subpopulation and sphere formation were significantly educed [30]. Moreover, overexpression of *miR-21* induced a marked increase in the $CD133^+$ subpopulation as well as sphere formation. These authors provided direct evidence that *miR-21* targeted CD133 to affect the function of the ovarian teratocarcinoma cell line PA1. Actually, other *miRs*, such as *miR-34*, *miR-181* and *let-7*, were also shown to play important roles in ovarian carcinogenesis and the function of cancer stemness, or even directly affecting CSCs besides *miR-21* (Table 1) [14,15,27–29,31–39]. Dysregulation of these *miRs* may be implicated in the development of ovarian cancer, or even CSCs. These new findings improve our understanding of ovarian cancer. Given that ovarian CSCs appeared to be involved in tumorigenesis, distant metastasis and therapy resistance, and that miRNAs exerted a broad regulatory role on CSCs, *miR*-based therapies might add novel firepower in the anticancer weapon store. In addition to developing *miRs* as an anti-CSC therapy, *miR* expression profiling in CSCs or specific subtypes of cancer might also have diagnostic and prognostic value in the future.

Conclusion

The discovery of aberrant expression of *miRs* has defined new pathways in ovarian tumorigenesis and progression, because *miR* profiles presented either in tissues or biological fluids, such as blood, can potentially be used for the purpose of early detection or surveillance of cancers, and target therapy with *miR* might be a promising area, which might not only significantly decrease the toxicity of conventional therapy but also enhance therapeutic effects, as mentioned previously [40,41].

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