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Review

Potential microRNA-related Targets for Therapeutic Intervention with Ovarian Cancer Metastasis

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Abstract. *Treatment of disseminated epithelial ovarian cancer (EOC) is an unmet medical need. Therefore, the identification along with preclinical and clinical validation of new targets is an issue of high importance. In this review we focus on microRNAs that mediate metastasis of EOC. We summarize up-regulated metastasis-promoting and down-regulated metastasis-suppressing microRNAs. We focus on preclinical in vitro and in vivo functions as well as their metastasis-related clinical correlations. Finally, we outline modalities for therapeutic intervention and critical issues of microRNA-based therapeutics in the context of metastatic EOC.*

In 2016, approximately 22,000 women were diagnosed with ovarian cancer in the U.S. and about 14,000 have died from this disease (1). Ninenty percent of ovarian carcinomas are epithelial tumors referred to as epithelial ovarian cancer (EOC) with subtypes such as serous (more than 50%), endometrioid, clear cell, mucinous and undifferentiated or unclassifyable tumors (1). Other types of ovarian cancer are germ cell and sex-cord stromal tumors arising from egg-prducing oocytes or from estrogen and progesterone producing stromal cells. After surgical debulking, EOC patients are treated with intravenous and/or intraperitoneal platin or taxane-based chemotherapy; however, patients typically relapse within two years of the initial treatment (2, 3). For treatment of platinum-sensitive recurrent ovarian cancer, the targeted agent, Avastin, a humanized antibody directed against vascular endothelial growth factor, isoform A, (VEGF-A) has been approved in combination with chemotherapy (4). Numerous other agents such as: tyrosine kinase inhibitors that target both VEGFR and other proangiogenic receptors, a peptide-Fc fusion protein that inhibits binding of angiopoietins 1 and 2 to the Tie-2 receptor, several poly ADP ribose polymerase (PARP) inhibitors and a cytotxic agent targeting the α-folate receptor are under clinical investigation (5, 6). Very recently, FDA has approved rucaparib, a PARP inhibitor, for treatment of breast cancer 1/2 mutation (BRCA) ovarian cancer that has not responded to at least two chemotherapy drugs (7). In order to further highlight pathways and targets for therapeutic intervention, we review the role of microRNAs (miRs) in metastasis of EOC.

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Metastasis

EOC is a tumor entity arising from tissue on the surface of the ovary that can metastasize *via* transcoelomic, hematogenous and lymphatic routes (8). In this review we will focus on the role of miRs in transcoelomic dissemination, which is generally the preferred mechanism of metastasis of EOC. The process of metastasis starts with the shedding of single cells or multicellular aggregates (spheroids) into the peritoneum after expression of anoikis-inhibiting proteins and morphological conversion by epithelial-mesenchymal transition (EMT) (2, 9). Several mechanisms of suppressing an immune response against disseminating ovarian cancer cells are implemented by the tumor cells, such as secretion of Fas-ligand, which induces apoptosis in Fas-expressing immune cells (10). Tumor cells are passively transported by ascitic fluid which contains an abundant source of metastasis-promoting factors and its formation is enhanced by tumor-cell secreted VEGF (11). Eventually nodules are formed in the omentum and peritoneum originating from interactions of tumor cells with the mesothelium (2, 8, 9). The mesothelium is composed of a single layer of specialized epithelial cells

with luminal microvilli that are attached to a basement membrane composed of collagens of type I and IV, fibronectin and laminin (2, 8, 9). A number of interactions have been shown to be crucial for adhesion of tumor cells to mesothelial cells, for example: the interaction of tumor cell Integrin β1 with fibronectin expressing mesothelial cells, mesothelial cell expressed vascular cell adhesion molecule (VCAM) with tumor-cell α4β1, and tumor cell expressed cluster of differentiation 44 (CD44) with hyaluronic acid on mesothelial cells (12-14). An essential step for colonization of secondary sites is the recruitment of endothelial cells (EC) by tumor-secreted pro-angiogenic factors (15). In addition, adipocytes which are a major constituent of the microenvironment of ovarian cancer have been shown to promote tumor growth and metastasis (16). There is evidence that cancer stem cell (CSC)-related subpopulations are involved in ovarian cancer metastasis and chemotherapy resistance (17, 18). In this review we focus on the role of miRs in the metastatic cascade of EOC in order to identify possible new targets with an impact for treatment of EOC. Angiogenesis is one essential aspect for ovarian cancer metastasis, however it is also involved in other steps of the pathogenesis of ovarian cancer, therefore we will not discuss miRs modulating angiogenesis in detail in this review (19).

microRNA

miRs are evolutionary-conserved small non-coding RNAs comprising of 18-25 nts (20-23). They interact with their target mRNAs through a 6-8 nt seed sequence at their 5'end by base-pairing with a complementary sequence often located in the 3'-untranslated region (3'-UTR) of their target mRNA, which results in their cleavage, degradation or inhibition of translation (22). Approximately 1,000 miR genes have been identified. After transcription by RNA polymerse II, miRs undergo a number of processing steps, which include capping at their 5'end, polyadenylation at their 3'end, cleavage and sometimes splicing. The corresponding genes can be located in exons, introns or intergenic regions (24). miRs are synthesized as precursor mRNAs that are processed to mature miRs by several sequential steps. Pri-miRNA, the hairpin-shaped primary transcript comprising several hundred nts is first converted to double-stranded, hairpin-shaped pre-miRNA by the action of RNAse III enzyme DROSHA and its cofactor DiGeorge syndrome critical region 8 (DGCRG8) (25). Pre-miRNA (60-70 nts) is exported to the cytoplasm by Exportin 5 through a nuclear pore (26) and subsequently its loop is cleaved by RNAse DICER and TAR RNA binding protein (TRBP) resulting in a miRNA duplex (27, 28). In the next step the miRNA duplex is incorporated into the RNA-induced silencing complex (RISC). Processing of the 18-25 nts miR-miR* duplex is mediated by the argonaute family of proteins (AGO) in conjunction with several co-factors. After unwinding and strand selection, the mature miR can interact with its cognate target(s) and excert its action as described above. An alternative mechanism for generation of functional miRs has emerged (29). In this context, mirtrons arise from spliced out introns and circumvent cleavage by the microprocessor complex (29). Since miRs can hit several targets, their inhibition may result in modulation of several distinct pathways and disturb regulatory networks (30).

miRs are involved in several steps of the pathogenesis and dissemination of cancer (31, 32). A crucial step in this context was the demonstration of involvement of miR-15a and miR-16-1 in the pathogenesis of B-cell chronic lymphocytic leukemia (B-CLL) (33,34,35). Tumor suppressors are frequently deleted in B-CLL on chromosome 13q14, a locus containing miR-15a and miR-16-1 (33-35). In a proof-of-concept experiment, deletion of miR-15a and miR-16-1 cluster in mice recapitulated the human disease phenotype of B-CLL in mice (33-35) by circumventing the cleavage of the mRNA coding for the anti-apoptotic protein Bcl2. miRs are involved in several steps of the pathogenesis of ovarian cancer (36, 37). In this review we focus on their involvement in metastasis of EOC and their role as possible targets for therapeutic intervention.

Metastasis-promoting miRs with Preclinical *In Vivo* Efficacy

In this category we discuss miRs -182, -205 and -141.

miR-182. Anti-miR-182 treatment inhibits invasion, proliferation and anchorage-independent cell growth of EOC cell lines SKOV-3, HEY and OVCAR3, as well as the growth and size of tumors resulting from *i.p.* injected OVCAR3 cells (38). The impact of miR-182 on EOC cell metastasis was investigated by intrabursal implantation of pellets derived from OVCAR3 cells, where anti miR-182 treatment resulted in a five-fold reduction of nodules in peritoneal organs compared to controls (38). Another study investigated the role of miR-182 in T29 and T80 (surface epithelium), FTE 187 (fallopian tube) and HEY, SKOV3 and OVCAR3 (EOC) cell lines, and showed that miR-182 increased transformation and invasiveness, but had no impact on proliferation. In an experimental metastasis model with SKOV-3 cells overexpressing miR-182 and corresponding controls, significantly larger and increased number of lung metastases were observed with the transfectants (39). miR-182 exerts its metastasis-promoting effects through down-regulation of BRCA1 and concomittant up-regulation of high-mobility group AT-hook2 (HMGA2) and further through negative regulation of metastasis suppressor 1 (MTSS1) as direct targets (Figure 1). HMGA2 is an oncogenic transcription factor with a documented role in promoting EMT during EOC progression (40). MMTS1 has

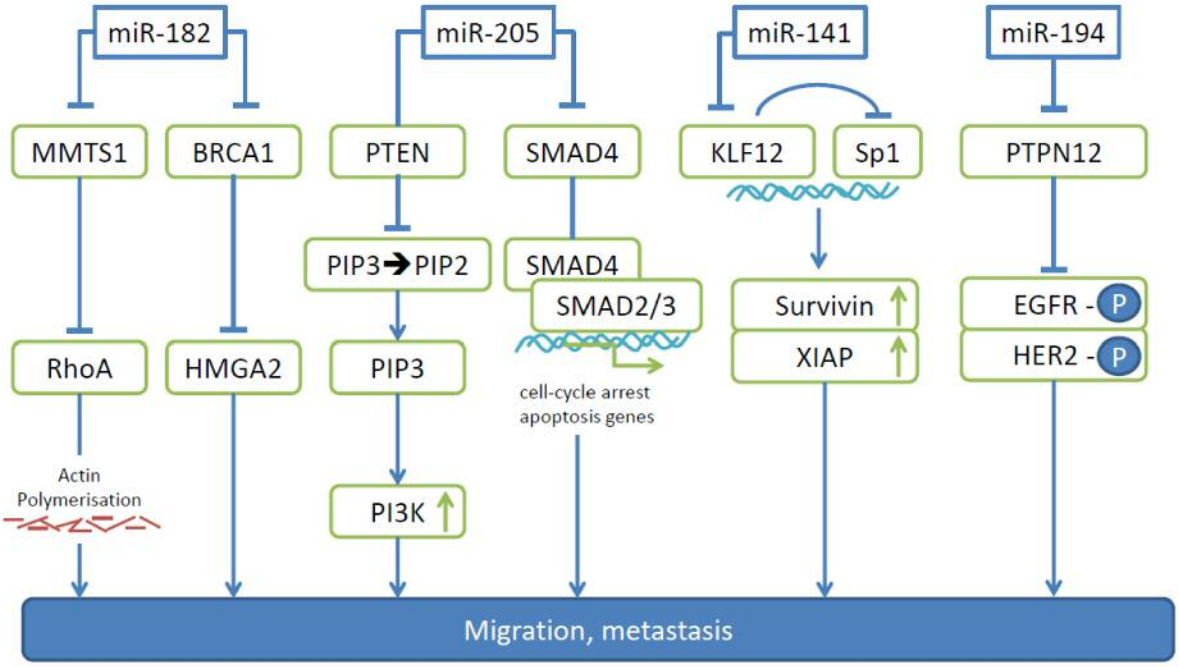

Figure 1. *The role of microRNAs -182, -205, -141 and -194 as mediators of migration and metastasis in ovarian carcinoma. Pathways leading to migration and metastasis of ovarian carcinoma activated by individual miRs are indicated. BRCA1, Breast cancer antigen1; EGFR-P, phosphorylated epidermal growth factor; HER2-P, phosphorylated human epidermal growth factor 2; HMGA2, high mobility group AT-hook 2; KLF12, krüppel-like factor 12; MMTS1, metastasis suppressor 1; PIP2, phosphatidyl-inositol 4,5 biphosphate; PIP3, phosphatidyl-inositol 3,4,5 triphosphate; PI3K, phosphoinositide-3 kinase; PTEN, phosphatase and tensin homolog; PTPN12, tyrosine phosphatase non-receptor 12; RhoA, ras homolog A; SMAD4, suppressor of mothers against decapentaplegic 4; Sp1, transcription factor Sp1, XIAP, X-linked inhibitor of apoptosis.*

an impact on cellular migration of EOC cell lines and acts as a scaffold protein that interacts with multiple partners to regulate actin dynamics (41, 42). In addition, suppression of MMTS1 has been shown to activate ras homology A (RhoA), a small GTPase, which promotes breast cancer metastasis (43). miR-182 is overexpressed in EOC compared to corresponding normal tissue (44). Data correlating its expression with clinical outcome are still pending.

miR-205. miR-205 is up-regulated in EOC and its overexpression correlates with poor survival (45). miR-205 promotes EOC cell proliferation, migration and invasion as shown with HO-8910 and SKOV-3 cells as well as resistance against cisplatin. Suppressor of mothers against decaplentaplegic 4 (SMAD4) and phosphatase and tensin homolog (PTEN) have been identified as direct targets of miR-205 in EOC cells (Figure 1) (45-47). Smad4 is a key regulator of transforming growth factor β (TGFβ)-signaling. After TGFβ binds to its receptor, Smad4 forms a complex with Smad2/3 and translocates to the nucleus where it binds DNA and up-regulates the expression of target genes that cause cell-cycle arrest and apoptosis (46). PTEN is a key modulator of phosphoinositide-3 kinase (PI3K/AKT) signaling by catalysing the conversion of membrane-bound second messenger phosphatidyl-inositol 3,4,5 triphosphate (PIP3) to PI 4,5 biphosphate (PIP2) (47). HO-8910 cells stably expressing miR-205 gave rise to increased number of nodules in omentum, peritoneum, bowel mesentery, liver and ovary in nude mice after *i.p.* injection in comparison to the control cell line (45).

miR-141. In EOC cell lines and clinical samples the mean expression level of miR-149 is approximately 10-fold higher than that of human ovarian surface epithelium (HOSE) cell lines and normal ovarian tissues (48). In A2780, SKOV3 and OVCA433 cells, miR-141 augments anchorage-independent growth and survival (48). One of the direct targets of miR-141 that has been identified is Krüppel-like factor 12 (KLF12) (Figure 1) (48). KLF12 is a member of the KLF family of transcription factors which are involved in EMT, survival and development (49, 50). In EOC cells, KLF12 exerts a tumor-suppressive effect (48). KLF12 antagonizes transcription factor Sp1 which up-regulates survival factor survivin (51). Overexpression of miR-141 or loss of KLF12 enhances anoikis resistance by modulating the Sp1/survivin/ X-linked inhibitor of apoptosis (XIAP) intrinsic apoptotic pathway (48). *In vivo* studies were performed by injection of SKOV3 cells

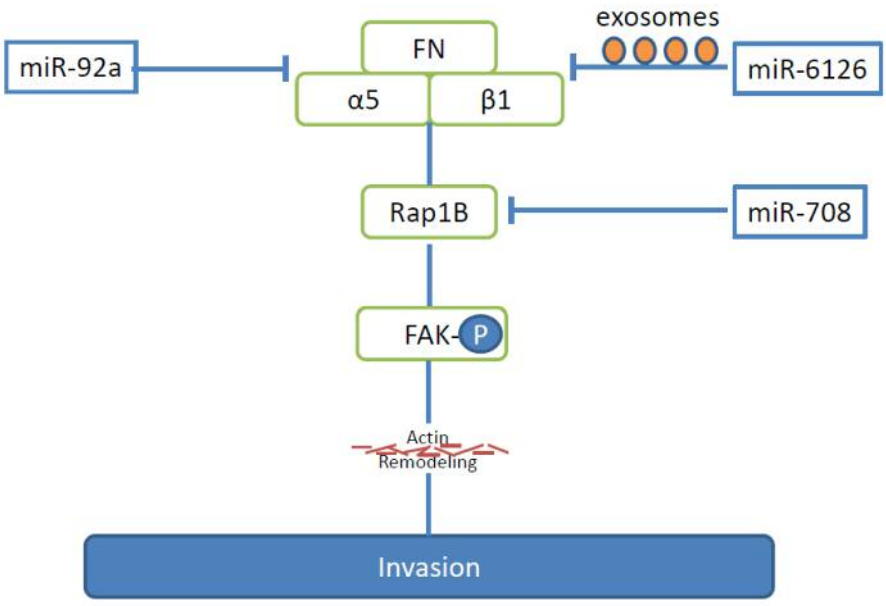

Figure 2. *miRs -92a, -708 and -6126 inhibit integrin-related pathways of metastases in ovarian cancer. The pathways outlined lead to inhibition of FAK and actin remodeling. a5, Alpha5, integrin subunit; b1, beta1, integrin subunit; FAK-P, phosphorylated fokal adhesion kinase; FN, fibronectin; Rap 1B, ras-related protein-1B.*

stably expressing miR-141 into nude mice. Significantly more nodules were observed across the peritoneal cavity with the transfected cell line (48). Increased survival, enhanced metastatic capability, or a combination of both might be responsible for the observed effects. Clinical data correlating expression of miR-141 with survival are not yet available.

Other EOC Metastasis-promoting miRs not yet Validated in Preclinical *In Vivo* Models

miR-194 is up-regulated in EOC compared to normal ovarian tissue and enhances proliferation, migration and invasion of SKOV3 and OVCAR3 cells (52). Protein tyrosine phosphatase non-receptor 12 (PTPN12) was identified as a direct target of miR-194 (Figure 1) (52). PTPN12 plays an important role in adhesion and motility in several types of cancer (53, 54). Due to loss of PTPN12 several tyrosine kinases are activated in breast cancer, including EGFR and human epidermal growth factor receptor 2 (HER2). PTPN12 suppresses growth and metastasis of PTPN12 deficient breast cancer cells and low PTPN12 correlates with poor prognosis and tumor recurrence in breast cancer patients (52).

miR-146a and miR-150 promote survival and spheroid formation as well as cisplatin resistance of EOC cells (55). Both of them exhibit significantly increased expression in omental metastases in comparison to the corresponding normal tissues (52). miR-196a is overexpressed in EOC compared to normal ovarian surface tissue and correlates with international federation of gynecology and obstetrics (FIGO)-stage, tumor size, lymph node metastases and high levels are associated with poor survival (56).

Metastasis-suppressive miRs with *In Vivo* Activity in Preclinical Models

miR-92a. Identification of miR-92a was catalysed by the finding that high integrin α5 expression is a predictor for reduced survival for patients with advanced EOC (57). Based on bioinformatic information, integrin α5 was identified as a direct target of miR-92a. Integrin α5 predominantly binds to integrin β1 to form integrin α5β1, which recognizes the arginine-glycine-aspartate motif of its ligand fibronectin (FN), one of the most abundant proteins in the extracellular matrix (ECM) of the omentum and peritoneum (Figure 2) (58). miR-92a inhibits the adhesion to FN, invasion and proliferation of EOC cell lines SKOV3, A2780, OVISE and HeyA-8 (57). Mir-92 inhibits tyrosine phosphorylation of focal adhesion kinase (FAK) (59), a kinase involved in integrin signaling, and subsequently down-regulates matrix metalloprotease 2 (MMP2) (57). HeyA-8 EOC cancer cells stably transduced to express miR-92a, gave rise to reduced numbers of peritoneal metastases and tumor burden after *i.p.* injection into nude mice (57). However, the function of miR-92a in EOC is a controversial issue. An independent study suggests a down-regulation of miR-92a in EOC, linking it to tumorigenesis or progression of EOC (60).

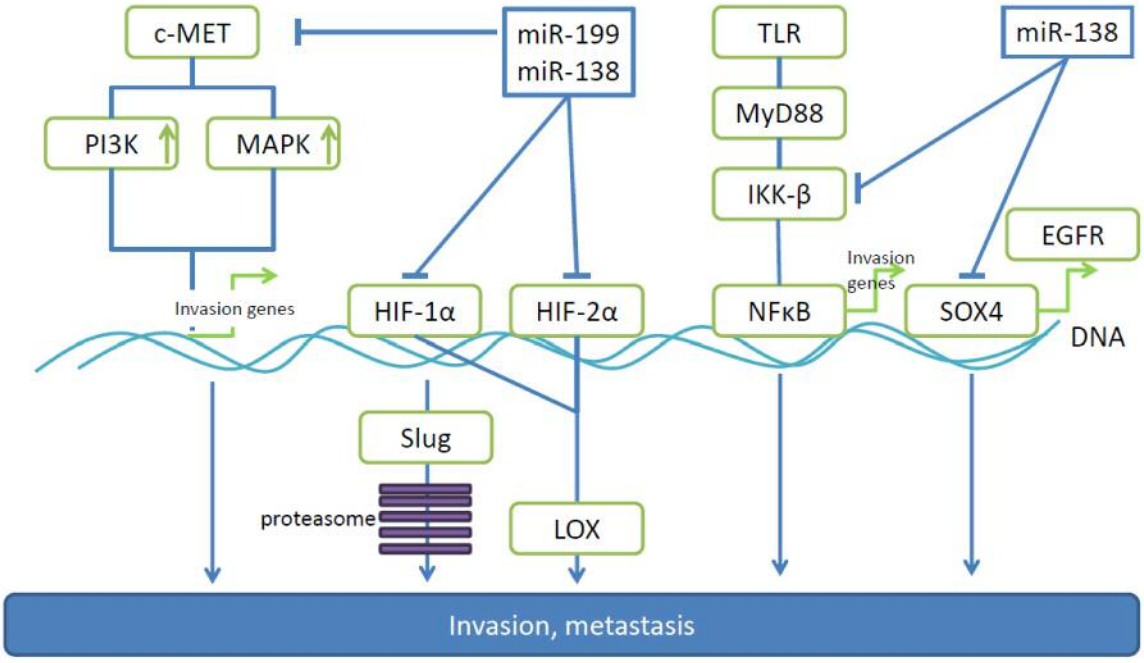

Figure 3. *miRs -138 and -199 are down-regulated in ovarian cancer and target pro-metastatic genes. miR-138 and -199 related pathways leading to invasion and metastasis of ovarian carcinoma are shown. EGFR, Epidermal growth factor receptor; HIF-1α, hypoxia-inducible factor 1α; HIF-2β, hypoxia-inducible factor 2β; IKKβ, Iκ kinaseβ; LOX, lysyl-oxidase; MAPK, mitogen-activated protein kinase; MET, MET tyrosine receptor kinase; MyD88, myeloid differentiation factor 88; NFκB, nuclear factor κB; PI3K, phosphoinosite-3-kinase; slug, transcription factor slug; SOX4, SRY-box4; TLR, toll-like receptor.*

miR-6126. miR-6126 is secreted in exosomes by several EOC cell lines and targets integrin β1 directly (Figure 2) (61). Integrin β1 has been identified as a key mediator of EOC metastasis (6, 62, 63). Ectopic expression of miR-6126 impairs invasion in HeyA8 and HeyA8-MDR EOC cells (61). Low integrin β1 and high miR-6126 co-expression are correlated with longer survival in EOC patients (61). *In vivo* investigations of the role of miR-6126 were performed in the orthotopic HeyA8 EOC metastasis model. Tumor cells were inocculated (*i.p.*), followed by tail vein injection of liposomes carrying a miR-6126 mimetic. Tumor weight in the mimic-treated mice was significantly smaller than in the control miR group (61). Inhibition of tumor cell proliferation and angiogenesis as well as reduced integrin β1 levels were observed in the xenografts. miR-6126 mimic treatment resulted in increased miR-6126 and decreased integrin β1 levels in the exosomes (61).

miR-138. Making use of isogenic pairs of low and high invasive EOC cell lines, mir-138 was found to be down-regulated in highly invasive cells (64). In vitro experiments have identified miR-138 as an inhibitor of migration and invasion based on targeting of SRY-related high mobility group box 4 (SOX4) and hypoxia-inducible factor 1α (HIF1α) (Figure 3) (64). Overexpression of SOX4 (2,3) and HIF-1α (4) reverse miR-138 mediated suppression of cell invasion. SOX4 activates pro-metastatic EGFR through trancriptional control (65-68) and HIF-1α mediates proteosomal degradation of EMT-promoting transcription factor slug (64, 69). *In vivo* properties of miR-138 were evaluated in an orthotopic model after intrabursal injection of SKOV-16iv cells stably expressing miR-138 and a corresponding control cell line. No effect on primary tumor weight was noted, however, lower incidence of peritoneal metastases and ascites formation was observed with the transfected cell line (64). In patient derived EOC cells, miR-138 low/SOX4 high expression correlates with lymph node metastases, higher tumor grade and larger ascites volume (64).

miR-199. miR-199 is down-regulated in the majority of EOCs and has been shown to directly target pro-metastatic proteins such as c-MET, HIF-1α, HIF-2β and Iκ kinase β IKKβ in this tumor entity (Figure 3) (70-72). In EOC cell lines, miR199 inhibits proliferation, invasion and adhesion as well as extracellular signal regulated kinase and nuclear factor κB (NFκB) signaling (70-72). Inhibition of HIF levels, down-regulates lysyl-oxidase (LOX), a matrix remodeling enzyme which cross-links collagens (73). c-MET is a well-validated target for anti-metastatic therapy in OVC (74, 75).

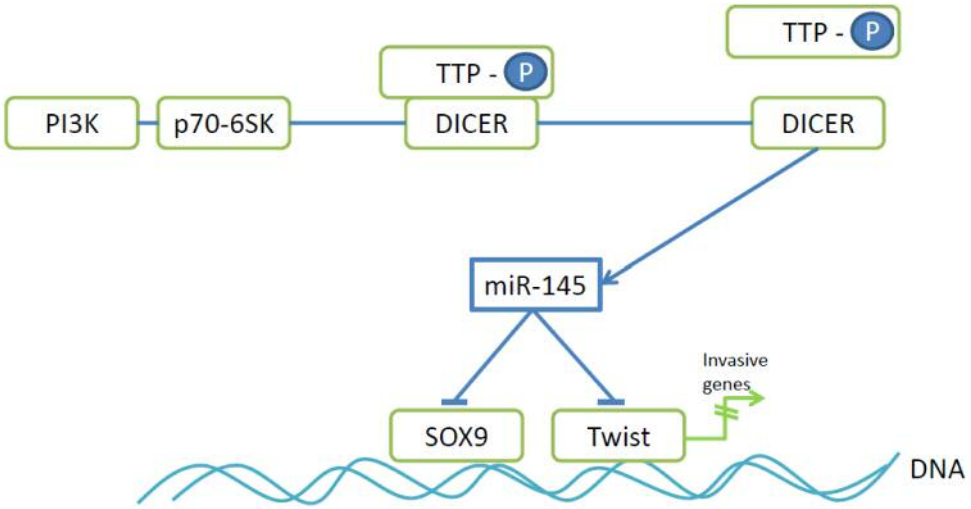

Figure 4. *Mode of action of anti-metastatic miR-145. P70-6SK phosphorylates TTP leading to dissociation of the TTP-DICER complex resulting in processing and activation of miR-145 by DICER. DICER, Microprocessor complex; PI3K, phosphoinosite 3-kinase; p70-S6K, p70 S6 kinase; SOX9, SRY-box 9; TTP-P, phosphorylated tristetraprolin; Twist, transcription factor Twist.*

IKKβ promotes function of the toll-like receptor-myeloid differentiation factor-NFκB (TLR-MyD88-NFκB) pathway, which enhances the inflammatory microenvironment, a prerequisite for EOC progression and dissemination (72, 76-78). This function of IKKβ is based on inhibition of inhibitor of NFκB (IκB), by promoting its degradation through the proteasome and inhibiting the nuclear translocation of NFκB (76). *In vivo*, miR-199 inhibits growth and peritoneal seeding of ovarian tumors after *i.p.* injection of SKOV3 and A2780 cells (70, 71). In these models total tumor burden and number of metastases on the peritoneal surface, omentum, small bowel mesentery and both ovaries were reduced. Clinical data correlating miR-199 levels with prognosis and overall survival are not yet available.

miR-145. miR-145 has the capacity to suppress multicellular spheroid (MCS) formation of ovarian cancer cells by preventing the up-regulation of N-cadherin expression (79,80). N-cadherin expression is regulated by Twist and SOX9 and both have been identifed as direct targets of miR-145 (79). Twist is an EMT-promoting transcription factor and its expression correlates with bad prognosis in ovarian cancer patients (81), whereas transcription factor SOX9 promotes pro-tumoral and metastatic signaling in ovarian cancer cells (82). miR-145 belongs to a subset of miRs whose expression is promoted by the interaction of microprocessor DICER (83) and zinc finger protein tristetraprolin (TTP) (Figure 4) (84). p70 S6 kinase (p70-S6K), a downstream effector of PI3K signaling (85) and frequently constitutively active in EOC disrupts this interaction by phosphorylating TTP and thus down-regulating expression of miR-145 (79). Meta-analysis in the Oncomine database has indicated that high levels of p70-S6K and low TTP levels are associated with ovarian cancer progression (79). *In vivo* anti-metastatic activity of miR-145 was shown in nude mice after *i.p.* injection of SKOV3 cells stably transduced with miR-145. The number and size of tumor nodules in the peritoneal cavity as well as the volume of ascites fluid were reduced with transfectants in comparison to the control cell line (79).

miR-708. miR-708 is induced by glucocorticoids (GC) in EOC cells (86). GC are used in conjunction with chemotherapy of EOC to prevent hypersensitivity reactions (87). miR-708 is down-regulated in metastatic OVC and patients with high miR-708 expression show significantly better survival (86). miR-708 inhibits migration and invasion of EOC cell lines as shown by wound healing and transwell Boyden chamber assays (86). Ras-related protein-1B (Rap-1B), a small GTPase, was identified as a direct target of miR-708 (Figure 2) (86). Rap-1B facilitates integrin-mediated signaling and actin remodeling *via* FAK and paxillin and stimulates EOC cell invasion and metastasis (88, 89). miR-708 or depletion of Rap-1B decreases adhesion of EOC cells to FN and collagen type I, reduces number and density of focal adhesions and rescues miR-708 suppressed cell growth and invasion (86). miR-708 transfectants of SKOV-I6iv cells gave rise to reduced lung metastatic activity after tail vein injection and orthotopic injection into the mouse ovarian bursa and significantly reduced abdominal metastasis with transfectants in comparison to the control cell line as shown by

bioluminescence imaging (86). GCs also suppress metastasis of SKOV-I6iv cells in the orthotopic model described above.

miR-26b. miR-26 is down-regulated in EOC and low expression is associated with FIGO stage, poor disease free survival, higher risk of distant metastases, recurrence and overall survival (90). Karyopherin α2 (KPNA2) was identified as one of its targets (90). KPNA2 is a nuclear transport protein (91) and its down-regulation promotes expression of stem cell pluripotency homeobox transcription factor 4 (OCT4) (90, 92, 93). Overexpression of KPNA2 in EOC correlates with poor prognosis (94). An inverse correlation between KPNA2 and miR-26a expression in EOC has been observed (90). The miR26/KPNA2/OCT4 axis inhibits EOC proliferation, migration and sphere-forming ability *in vitro* and *in vivo* (90). Ectopic expression of miR-26b down-regulates OCT4 and vimentin levels and up-regulates E-cadherin expression (90). However, overexpression of KPNA2 could not completely counteract the effect of miR-26b indicating involvement of additional targets (90). *In vivo* experiments were performed with OVCAR3 cells stably expressing miR-26b. Tumor growth was inhibited in the transfectant cell line in comparison to mice injected with the control cell line after injection into the dorsal flank. Tail vein injection experiments resulted in fewer and smaller micrometastases in the lungs with the transfectant cell line.

miR-448. miR-448 inhibits proliferation and invasion of SKOV3 and A2780 EOC cell lines and is down-regulated in human EOC (95). CXC chemokine ligand 12 (CXCL12) was identified as one of the direct targets of miR-448 (Figure 5) (95). CXCL12 is a chemokine that mediates interaction of tumor cells with the microenvironment, angiogenesis, tumor progression and metastasis (96, 97). miR-448 inhibits proliferation, migration and invasion of SKOV3 and A2780 cells *in vitro* (95). miR-448 transfected SKOV3 cells exhibited suppressed cell growth in nude mice in comparison to the control cell line. Additional studies are need to investigate the *in vivo* anti-metastatic activity of miR-448. miR-448 is down-regulated in human EOC (95), further correlations with clinical parameters are not yet available.

miR-214. miR-214 was identified as an important mediator of the tumor- and metastasis-promoting role of cancer-associated fibroblasts (CAFs) in EOC (98). miR-214 (99) was down-regulated in normal human ovarian fibroblasts during co-culturing with HeyA8 EOC cells resulting in their conversion to CAFs (98). The induced CAFs promoted enhanced invasiveness of HeyA8 cells. CAFs increased growth and invasion of co-injected HeyA8 cells and replaced normal ovarian structures such as follicles or fallopian tubes in an orthotopic mouse model of EOC (98). It was shown that miR-214 acts on CC chemokine ligand 5 (CCL5) mRNA as a direct target and that the *in vivo* effects could be blocked by an antibody directed against CCL5 (Figure 5) (98). In EOC, CCL5 levels correlate with tumor progression (100). Similar observations in breast cancer cells were reported earlier (101). Overexpression of CCL5 in fibroblasts was sufficient to promote metastasis of admixed with breast cancer cells (101).

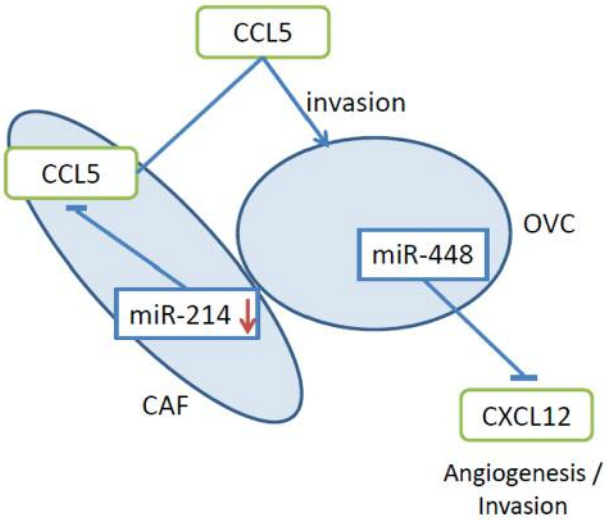

Figure 5. *miR-s -214 and -448 inhibit chemokines mediating angiogenesis and invasion of ovarian carcinoma cells. miR-448 inhibits CXCL12. miR-214 down-regulates CCL5 and is decreased in CAFs after their interaction with ovarian cancer cells. CAF, Cancer-associated fibroblast; CCL5, CC chemokine ligand 5, CXCL 12, CXC chemokine ligand 12.*

miR-373. miR-373 is down-regulated in EOC and its expression levels inversely correlate with clinical stage and histopathological grade of EOC (102). In cells transfected with miR-373 EMT is inhibited and *in vitro* invasion of SKOV3 is mitigated (102). *In vivo*, *i.p.* injected miR-373-expressing SKOV-3 cells gave rise to fewer metastases in the peritoneal cavity, peritoneal wall, small intestine, colon, stomach, liver and diagraphm (102). Rab22 was identified as a direct target of miR-373 (Figure 6) (102). Rab22 is a small GTPase and member of the Rab family proteins which are involved in the endocytic pathway (103). Rab22 activates Rab5 which is functionally involved in degradation of EGFR and plays a key role in migration of cancer cells through the integrin-mediated pathway (104-106). There is evidence that miR-373 may suppress TGFβ signaling through the Rab22-Rab5 pathway (107).

miR-193b. Studies addressing the interaction between EOC cells and a 3D culture model which mimics human omentum revealed the down-regulation of miR-193 in tumor cells after

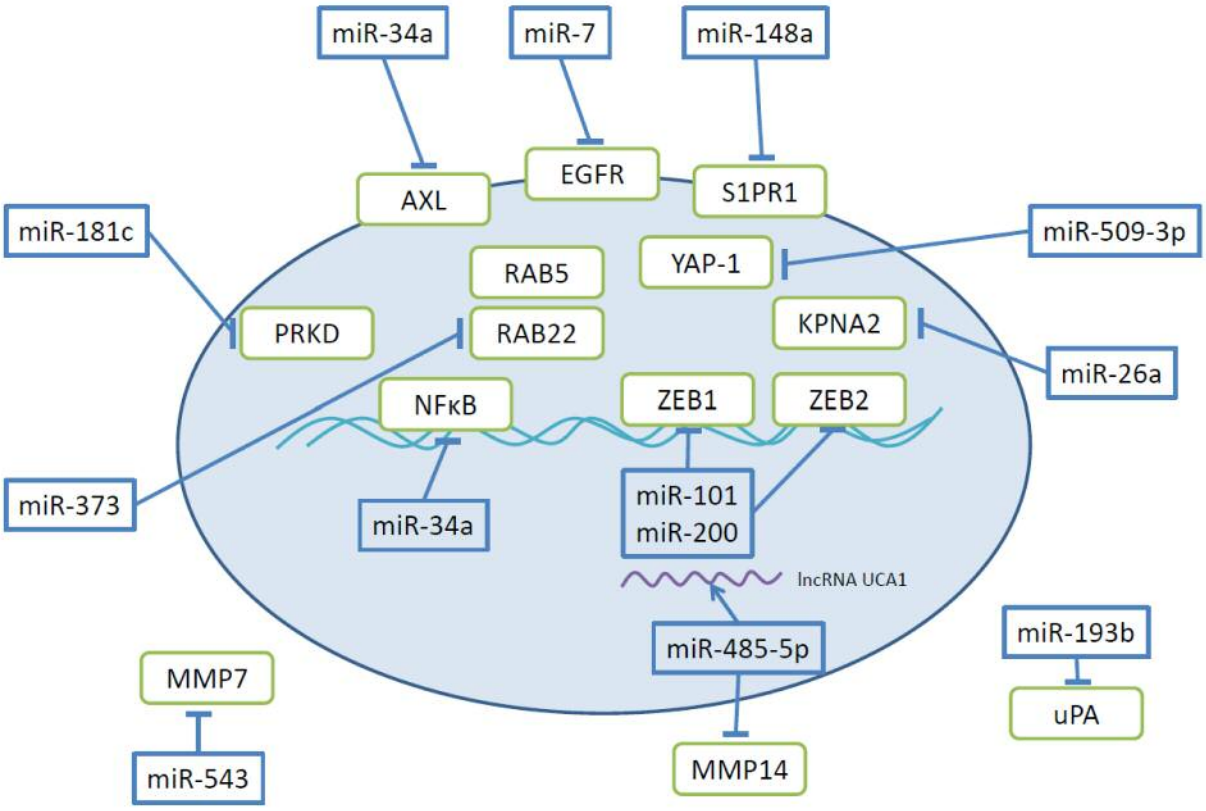

Figure 6. *Further miRs and their targets involved in modulation of invasion and metastasis of ovarian cancer. The oval circle represents an ovarian carcinoma cell. AXL, Transmembrane tyrosine kinase AXL; EGFR, epidermal growth factor receptor; KPNA2, karyopherin; lncRNA, long non-coding RNA; MMP 7,14, matrix metalloproteinase 7, 14; NFκB, nuclear factor κB; PRKD, protein kinase C delta; RAB 5,22, RAB family GTPase 5,22, S1PR1, shingosine-1-phosphate-receptor; UCA-1, urothelial cancer associated-1; uPA, urokinase plasminogen activator; YAP, yes-associated protein.*

interaction of both components (108, 109). DNA methyltransferase 1 (DNMT1) was found to be responsible for methylation of the miR-193b promoter (108). miR-193b impairs colony formation and invasion through 3D cultures in Hey8 cells (108). Human urokinase plasminogen activator (uPA) was identified as a direct target of miR-193b (Figure 6). The effects observed are at least partly due to inhibition of uPA, because blocking of uPA mimics most of the effects of miR-193b (108). uPA is a well validated target as a mediator of invasion and metastasis (110-113). Hey8 cells transfected with miR-193b gave rise to a 50% decrease of tumor burden after *i.p.* injection in comparison to the control cell line (108). Data connecting miR-193b to clinical parameters are not yet available.

miR-200. miR-200 is a family of miRs with a high degree of sequence homology with only one nucleotide difference in their seed sequence. The family is composed of miR-200a, -200b, -200c, miR-141 and miR-429 (114). Due to the homology in the seed sequences they share many targets. Inhibition of EMT seems to be a shared property of the miR-200 family. Investigations with the 60 NCI cell line panel and additional studies have identified transcription factors zinc E-box binding homeobox 1 and 2 (ZEB1 and ZEB2) as direct target of miR-200 (115,116,117). Zn-finger transcription factors ZEB1 and ZEB2 bind to the E-box of the E-cadherin promoter and inhibit its expression. Ectopic expression of miR-200 mediates up-regulation of E-cadherin and reduces motility of the corresponding cell lines (115). For EOC inconsistent correlations between expression of miR-200 and disease progression has been reported (114, 118, 119). One of the reasons for these discrepancies is the use of varying types of normal cells in the profiling studies ranging from whole ovary (ovarian surface epithelium only 1% of the cells), to immortalized ovarian surface epithelial cells and primary cultures of human cells from the surface of normal ovaries (114, 118, 119). Another complicating issue might be the dynamic variation of miR-200 expression during disease progression (118, 120). A current model suggests high miR-220, low ZEB1+2 and high E-cadherin expression in primary ovarian carcinoma and low miR-200, high ZEB1+2 expression in ascites and metastatic EOC (118,

120). Anti-metastatic function of miR-200c was demonstrated *in vivo* with $CD117^+$, $CD44^+$ CSCs isolated from SKOV3 cells (121). Overexpression of miR-220c in these cells leads to inhibition of EMT, CSC growth and lung metastases after s.c. injection (121). It is notworthy to mention that pro- and anti-metastatic functions have been described for miR-200 (122, 123). Further studies are needed to resolve the function of miR-200s in EOC.

Other EOC-related Metastasis-suppressing miRs

In this chapter we describe EOC metastasis-related miRs with promising preclinical *in vitro* data and a varying degree of clinical validation and pending validation in preclinical *in vivo* models. They are involved in regulation of diverse pathways, transcription factors and regulation of MMPs.

miR-7 and miR-34a target transmembrane receptor tyrosine kinases EGFR and AXL (Figure 6). miR-7 inhibits EGFR, a driver of EOC cell migration and proliferation (124, 125). Investigation of miR-7 expression in 17 paired EOC versus normal tissues inversely correlates miR-7 levels and EOC metastasis. In HO-890 and ES2 EOC cells transfected with miR-7, invasion and migration was suppressed *in vitro* as well as AKT/ERK1/2 pathway activation in an EGFR-dependent manner (126). miR-7 was shown to be down-regulated in the highly metastatic EOC clone HO-8910pm in comparison to the original cell line HO-8910. miR-34a inhibits AXL as a direct target (127). AXL mediates proliferation-, invasion- and angiogenesis-related functions in cancer (128). Overexpression of miR-34a in HO-890 and SKOV3 EOC cells resulted in inhibition of proliferation, invasion and migration, and in addition decreased expression of N-cadherin and up-regulation of E-cadherin (127). miR-34a is down-regulated in EOC compared with adjacent non-neoplastic tissue.

miR-340 has been identified to directly target NFκB1 in EOV (129). NFκB1 is a homodimer of p50 and regulates cell-cycle, apoptosis, immune responses and tumorigenesis (130, 131). Decreased levels of miR-340 were noted in the EOC cell lines OVCAR3, SKOV3, HO-8910 and ES2 in comparison to FTE 187 cells derived from normal human immortalized fallopian tube (129). miR-340 restrains proliferation by impeding G_1/S transition and inhibits invasion by down-regulation of MMP2, MMP9, N-cadherin, vimentin and up-regulation of E-cadherin (129). Data for EOC specimens are not yet available.

Sphingosine-1-phosphate-receptor (S1PR) was identified as a direct target of miR-148a (Figure 6) (132). S1P/S1PR signaling has been shown to play a role in a number of cellular functions including cell growth, migration and invasion and inhibiting EOC invasion potential (133, 134). Expression of miR-148 is reduced in SKOV3, OVCAR and A2780 EOC cells in comparison to normal ovarian tissue-derived cell line HUM-CELL-0088 (132). miR-148a expression is also reduced in EOC in comparison to normal ovarian tissues (135).

Protein kinase C delta (PKCD) has been identified as a direct target of miR-181c (Figure 6) (136). PKCD is involved in pro- and anti-tumoral functions depending on the tumor type (137). miR-181 inhibits proliferation and invasion of A2780 cells and is down-regulated in EOC tissues in comparison to normal tissues (136).

Yes-associated protein (YAP) (138, 139), an effector of the Hippo pathway, was identified as a direct target of miR-509-3p (Figure 6) (140). miR-509-3p attenuates migration and disrupts multi-cellular spheroids in HEY8, OVCAR3,4,8 and SKOV3 cells (140). miR-509-3p is more abundant in patients with favorable prognosis. Its target, YAP1, is functionally associated with the ECM through its non-canonical Hippo-independant role as a mechanotransducer. YAP1influences how tumor cells sense and respond to the mechanical properties of the ECM and their microenvironment and thus impacts cell proliferation, differentiation, migration and migration (141-143).

miR-101 directly targets transcription factors ZEB1 and ZEB2, inhibiting EMT, invasion and migration of SKOV3 cells (144). miR-543 and miR-485-5p are involved in MMP-related interactions. miR-543 inhibits translation of MMP7 by binding to its 3'-UTR (22). In EOC, placental growth factor (PlGF) mediates decrease in miR-543 (145). MMP-7 is an important mediator of invasion of EOC cells due to its induction by mesothelin (146, 147). miR-485-5p targets MMP14 and is neutralized by binding to lncRNA urothelial cancer associated 1 (UCA-1) acting as a sponge (Figure 6) (148).

Therapeutic Aspects, Key Issues and Expert Commentary

We have analysed the steady-state levels of selected miRs in ovarian cancer specimen by summarizing data as derived from TCGA (Figure 7). Notworthy, the poor expression of miRs-26b, -138, -193b, -199, -373, -448, and -708 correlates with their anti-metastatic potential. Furthermore, significant expression of miRs-145, -200a, -200b and -205 correlates with their metastatic propensity. We have outlined *in vitro* and *in vivo* target-validation related experiments for miRs involved in metastasis of EOC in the previous sections. miRs target the mRNAs derived from several genes and corresponding pathways which may translate into enhanced efficacy compared to mono-target based intervention, however this may also result in increased toxicity (149). The mode of therapeutic intervention and corresponding agents are driven by their metastasis-promoting or suppressive properties (27, 28, 150, 151). This issue has been discussed in the context specific miRs in previous chapters of this review and therefore only the key features of therapeutic intervention with miRs will be summarized here.

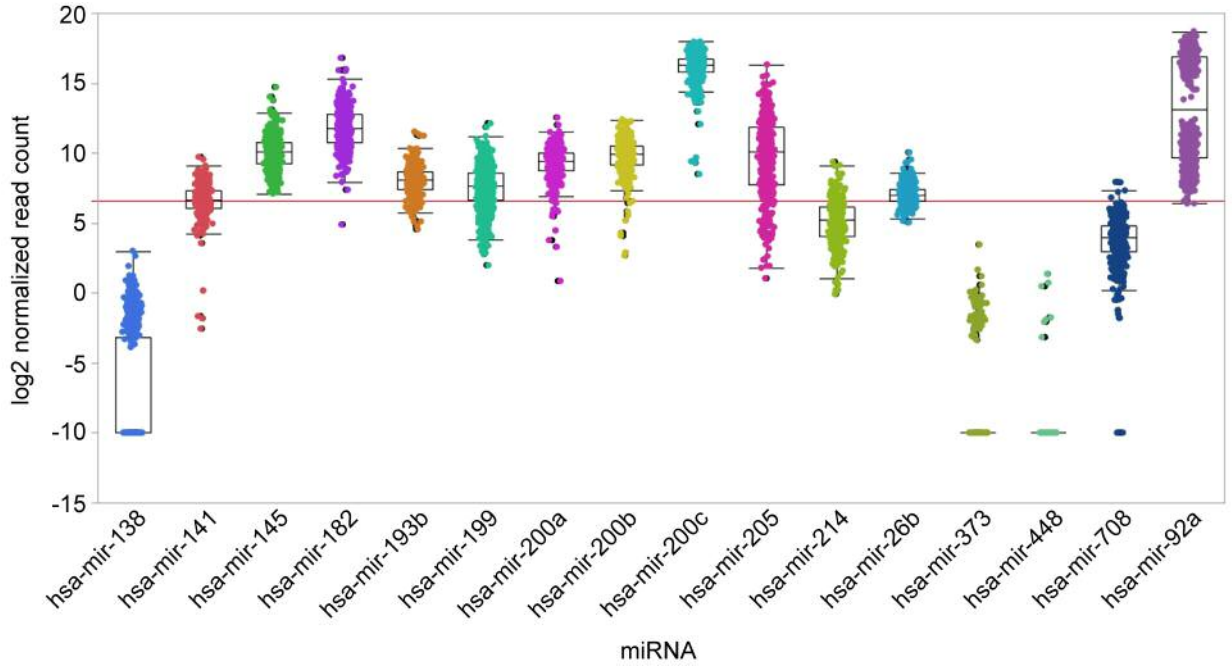

Figure 7. *Steady-state levels of selected miRs in ovarian cancer. Log2 normalized expression counts as derived by small RNA sequencing from the ovarian carcinoma cohort from TCGA are displayed. This cohort comprises data from 453 tumor patients. No matched normal samples are provided. The red line indicates a count of 100 normalized reads and separates very low from higher expression levels. Data are shown as box plots.*

Metastasis-promoting miRs can be inhibited by single-stranded miRs based on first generation antisense oligonucleotides (ASO) or locked nucleic acids (LNA) with complementary sequences to the miRs to be inhibited (27, 28, 150, 151). For improvement of the pharmco-kinetic (PK) and pharmacodynamic (PD) properties, diverse modifications of the nucleotide backbone have been introduced. They also can be inhibited by miR sponges containing reiterated tandem repeats of the target sequence or by masking of the miR-binding site of the target mRNA by making use of single-stranded RNA complementary to the target sequence (150, 152). Tumor-suppressing miRs can be reconstituted by gene therapy or by miR mimetics (synthetic double-stranded RNAs) matching to the corresponding miR sequence. Despite significant progress in delivery techniques, making use of viral vectors, coated and uncoated liposomes, nanoparticles and carrier-related compounds such as polyethylene glycole, synthetic polyethylenimine, cyclodextran, N-acetylgalactosamine and dendrimers, several critical issues remain to be resolved. Key challenges are targeting miRs to the disease site, tumor penetration, effective dose to reach the appropriate target cells, efficacy of endosomal escape, immuno-modulatory off-target effects, toxicty related issues such as liver toxicity, cytokine-release syndrome and a number of additional issues (27, 28, 150, 151).

EOC might be a target-indication for miR-based therapy because some of these issues may be by-passed (153). EOC arises at the surface of the ovary, disseminates into the peritoneum and is therefore amenable to *i.p.* administration of therapeutic agents after debulking of the tumor mass. I.p. injection of the paclitaxel or cisplatin-based standard therapeutic regimen has been shown to improve the clinical outcome of patients after debulking of the tumor in comparison to *i.v.* injection due to increased drug concentration at the site of disease (154, 155). Anti-metastatic activity of selected miRs after *i.p.* administration in several orthotopic EOC models has been described in previous chapters of this review. Also it is expected that *i.p.* administration of miR-related therapeutic agents will decrease systemic toxicity and to mediate vasculature-independent exposure in clinical settings.

Targeting of miR-122 for treatment of Hepatitis C Virus (HCV) infection has proceeded to Phase II clinical studies (Roche/Santaris and Regulon Therapeutics) and is the most advanced miR-related approach (28). A Phase I study with miR-34 mimetic MRX 34 (Mirna Therapeutics) in patients with solid tumors was recently terminated due to side effects caused by cytokine-release syndrome. Clinical studies of miR-related agents in EOC are expected in the near future.

Taken together, prioritization of miR-related targets for treatment of dissemination of EOC should be based on the synoptic view of preclinical target validation data and the role of the corresponding miR in disease progression. From

a technical point of view, *i.p.* delivery of miR-related therapeutic agents is a potential advantage versus *i.p.* delivery. Inhibition of overexpressed miR is a more promising approach than reconstitution of expression of down-regulated miRs. The present repertoire of targets for treatment of EOC (156) will be extended by miRs.

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