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MicroRNA in Ovarian Cancer: A short review

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Abstract: *Ovarian cancer represents the most fatal among gynaecological malignancies. The high mortality rate may be due to its late-stage diagnosis in lack of relevant diagnostic markers for early detection. There is a strong need for biomarkers that facilitate detection at an early stage. MicroRNAs (miRNAs), representing a new class of biomarkers are being explored. They are single-stranded short sequence RNAs that do not encode proteins but regulate target genes post-transcriptionally. They play a role as suppressors and promoters of ovarian carcinoma being involved in growth, inhibition of apoptosis, metastasis, invasion, and angiogenesis. The research done in this field has shown that miRNAs can facilitate discrimination of patients with ovarian carcinoma from healthy controls suggesting their use as diagnostic biomarkers. This review will summarize the current knowledge and clinical relevance of circulating miRNAs supporting their use in early diagnosis and prognosis of ovarian cancer.*

Keywords: *Circulating miRNA, Ovarian cancer, diagnosis, prognosis*

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I. Introduction

Ovarian carcinoma is lethal among malignancies of female reproductive system with incidence rate of approximately 2,40,000 diagnosed per year.[1] Majority of Ovarian carcinoma (approximately 90%), are epithelial in origin with five most common morphological subtypes such as high grade and low grade serous constituting 70% and 5% respectively, mucinous (3%), endometroid and clear-cell (10%) each, besides others. Serous carcinoma is the most common subtype constituting approximately 80% of all ovarian tumors. [2,3] There are no specific clinical symptoms in early stage so, often detected at a late stage presenting with metastasis and invasion and 5- year life expectancy rate of 42.9% approx. Over 80% of advanced ovarian cancer patients shows relapse, representing poor prognosis .[4,5]Estimation of serum CA-125 and Transvaginal ultrasound(TVUS) is being done to diagnose Ovarian cancer. But, they do not increase viability in symptomless women with no genetic risk mutation. Instead, ovarian cancer screening with CA-125 and TVUS often carries the risk of false positive results leading to surgeries and associated complications that may lead even to death .[6] CA-125 has limited diagnostic sensitivity and specificity.[7]Studies are undergoing to find out molecular alterations that are occurring in ovarian cancer. So, that better diagnostic strategies for early diagnosis can be find out. In this regard, microRNAs, the small non-coding RNA of 19-25 nucleotides representing next-generation biomarkers are being investigated for diagnosis of ovarian cancer. miRNAs are found to increase or decrease their expression in some cancer types. miRNAs are regulating expression of more than half of the protein coding genes in human constituting approximately 60%.[8] So, are impacting natural processes such as cellular growth, cell differentiation, metabolism, ageing, inflammation and immune response.In this way, miRNA are involved in development and advancement of the tumor.[9-13] The review will summarize association of miRNA with various aspects of ovarian cancer.

BIOGENESIS OF MICRORNA

microRNA precursors are in clusters and are found in many portions of the human genome. They are most frequently found within stretches of DNA sequences between the genes and intervening sequences within coding sequence of protein coding genes. These regions are basically referred as junk DNA as their function is unknown. They are infrequently found in exons of RNA transcripts and antisense transcripts.[14,15]

miRNAs are transcribed by RNA II polymerase and Initially, long primary miRNAs (Pri-miRNA) are formed. Primary miRNA has 33bp stem and terminal loop with flanking segments.[16,17]Drosha, required for processing has two domains consisting of RNA polymerase III and ds RNA binding component.[18-20] Within nucleus, Drosha in association with a microprocessor complex including DGCR8, KSRP, P68 proteins

processes pri-miRNA to form 70 nucleotide precursor microRNA(pre-miRNA) [16,17]Drosha cleaves both the ends of primiRNA and form two nucleotide sticky ends at 3'end. [18-20] Exportin-5, a Ran GTP dependent ds RNA binding protein transports pre-miRNA to cytoplasm where Dicer, a RNA specific ribonuclease processes it to miRNA duplex. [16,17] Factor like TRBP (Transactivating response RNA binding protein) is also required for regulating Dicer processing.[21]The twostrands ofmiRNA uncoil and fully mature miRNA clusters into RNA induced silencing component (RISC).The miRNA functions as guiding strand and base pairs with selected mRNA.[16,17] The miRNA circulating in blood are in bound form with AGO_2 ,a protein which is required for functional activity of RISC complex. With this complex, miRNA enter recipient cells and modulate gene expression. miRNA regulate the expression of genes at post transcription level by binding to 3'-UTR of target mRNA.[22] Binding of miRNA with high complementarity, leads to cleavage and degradation of mRNA target and if binds with low complementarity, inhibition of translation is the outcome.[23] The degradation of mRNA starts by canonical deadenylation machinery known as P-bodies that causes shortening of Poly A tail[24,25]

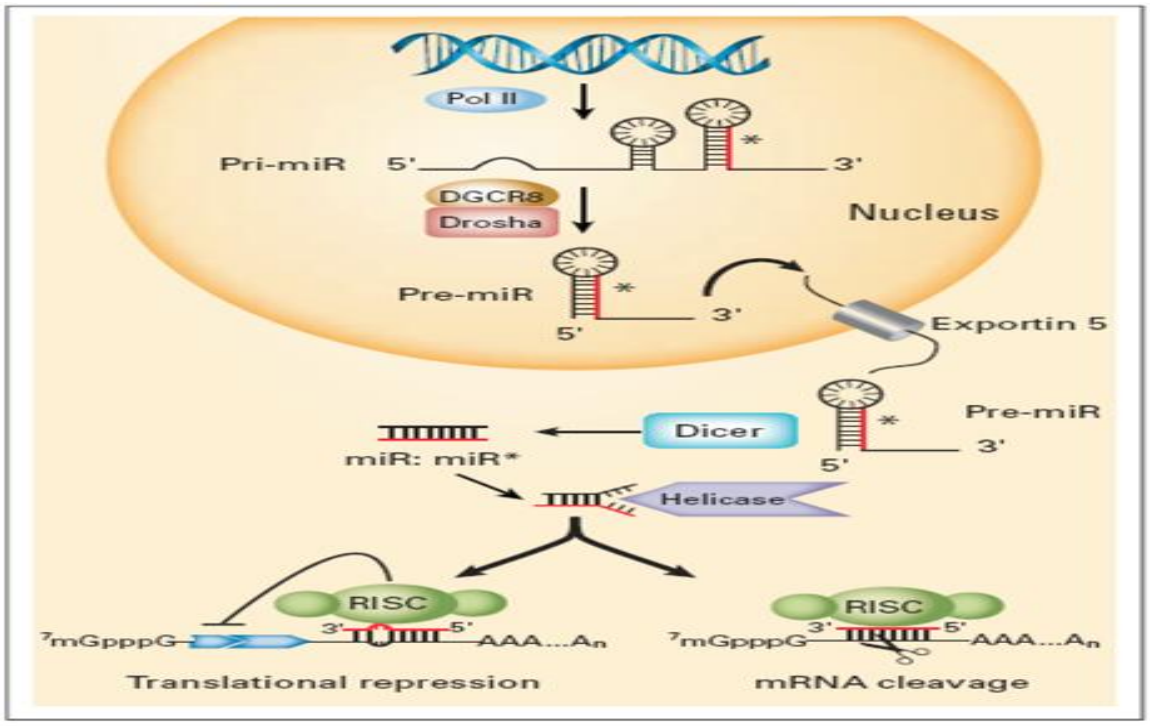

Figure:1:Biogenesis of microRNA[95]

MOLECULAR DYSREGULATIONS OF MICRORNA IN OVARIAN CARCINOMA

Dysregulationof microRNAs is a common event in all stages and types of cancers. Explaination of this dysregulation is given by different mechanisms:alterations in chromosomes of miRNA gene like deletion, amplification, point mutations etc., variation in epigenetic mechanism regulating miRNAs, transcriptional modulation, variations in transcriptional and post transcriptional machinery in charge of microRNA formation .[26]

The chromosomal alteration has been identified for several miRNA genes.About 50% of them are found at heritable point on a chromosome that may tends to break due to replication stress and at regions of amplification, deletion, or chromosome break points.[27] An elaboration of miR-182 region and removal of miR-15 region is found in ovarian carcinoma.[28] Loss of heterozygosity also contributes to ovarian cancer. The loss of normal copy ofgenes atloci let-7a-3/let-7b and miR-143/miR-145 has also been seen in 50 and 22% of 90 ovarian carcinoma respectively.[29]Zhang and colleagues established by genomic hybridization analysis of 227 human tumor samples that in, ovarian cancer, breast cancer and melanomas,certain specific fixed positions on a chromosome containing genes of miRNAwere frequently altered. 26 miRNAs were found to be associated with increase in copies of the gene and 15 miRNAs with copy number loss of the gene.[30] High grade serous epithelial ovarian cancer bestowwith mutations in *Tp53*, *BRCA1* and *BRCA2*.Low grade serous epithelial ovarian cancer present with mutations in *KRAS, BRAF, PIK3CA, CTNNB1* and *PPP2RIA*.[31,32]TP53 mutations are seen in about 96% of high grade serous ovarian cancer. The expression of tumor suppressor miRNA 34a, 34b and 34c, was reduced 100% and 72% respectively with TP53 mutation.[33]The most of these genetic variations are missense, 30% areframeshift mutations, nonsense or splice junction variants leading to total inadequacy of p53

protein.[34]About one –fifth of subjects with ovarian carcinoma have hereditary disease related with germinal mutations of BRCA1 and BRCA2.[35,36] The variant allele of miR-146a is produced by G to C polymorphism of precursor miR-146a.It can increase its expression and modulates expression of BRCA1/2 by binding to 3'-UTR of BRCA1 mRNA.[37] Epigenetic alterations are an important reason for dysregulation in miRNA.Expression of certain miRNA genes is also regulated via epigenetic mechanism including CpG island methylation within promoter region.[38]Methylation is involved in regulating 11% of miRNA genes.[39] The decrease in expression of miR-34 in ovarian carcinoma had also been found due to hyper methylation of tumor suppressor genes 34a ,34b and 34c.[40,41]loria and colleagues suggested by his study on ovarian cell lines OVCAR3 that overexpressed miRNA like miR-21, miR-203 and miR-205 in ovarian cancer might be regulated by methylation.[42]Some miRNA are regulated by transcription control like miR-200 family. This is also operated by transcription control in ovarian carcinoma.ZEB1/2,transcription factors binds to promoters of miR-200 clusters and blocks transcription.[43] Expression of miR-17-92 cluster is operated by transcription factor c-Myc.[44]Drosha and Dicer mutation is another mechanism which explains dysregulation of miRNA in ovarian cancer. In 39% of ovarian cancer tissue analyzed, a 60% decrease of dicer mRNA and 51% decrease of drosha mRNA levels has been evaluated.[45] In high grade and high stage ovarian carcinoma, a marked down regulation of dicer expression has been seen.[46]A recurrent somatic missense mutation of DICER1has been discovered in non-epithelial ovarian tumor. These mutations are highly prevalent (60%) in sertolileydig cell tumour.[47]

ROLE OF MICRORNA IN TUMORIGENESIS

Many studies has been done so far to suggest the role of microRNA in ovarian carcinoma. microRNA may act as tumor suppressor genes or oncogenes or involved in biological behaviour in ovarian cancer development. They are also involved in invasion and metastasis of ovarian cancer cells by promoting epithelial to mesenchymal transition (EMT), angiogenesis, regulating extracellular matrix (ECM) or by regulating cellular growth factors. There is down regulation of expression of certain miRNA in tumor tissues suggesting their role as tumor suppressors. Tumor suppressors genes are known to inhibit tumor formation by inhibiting proliferation of cells, promoting differentiation and inhibiting migration of cells. miRNA may serve as proto-oncogenes which are involved in cell growth, reproduction, proliferation, differentiation. Certain miRNA shows significant up regulation in their expression in tumor tissues suggesting their role as proto-oncogenes. Their up regulation lead to unusual cell behavior and malignant growth of cells.

Luo et.al indicated tumor suppressor like effect of miR-126 on SKOV3 cell lines in ovarian cancer.It acts by inhibiting expression of PAK4.[48] miR-1 /miR-133a has a tumor suppressor like role in endometrial cancer. They regulate phosphodiesterase 7A (PDE7A) and bring inhibition of metastasis and invasion. Its levels are significantly downregulated in endometrial cancer.[49]Let -7 family hinders growth and invasion of tumor cells by inhibiting expression of proteins such as RAS, c-Myc ,HMG-A2,c-Dc 25A,Cdk 6,cyclin-2 encoded by proto-oncogenes.The ovarian cells with more invasion and metastatic potential seems to have low let-7f expression.[50]

Fan et al. found that inhibition of miR-20a subdues the invasion by acting on Amyloid precursor protein(APP).[51]Zou et al. established that increased expression of miR-197 is related with tumor invasion and metastasis in OC by targeting nemo like kinase (NLK) and bringing its downregulation.[52] Depending upon cellular context miRNA may act as tumor suppressor or oncogene like miR-429 levels are increased initially in epithelial ovarian cancer but decrease with distant migration and metastasis.[53] Tumor cells metastasize by promoting EMT.EMT induces changes in cells like loss of morphological characteristics, reorganization of cytoskeleton and attainment of motile phenotype.[54]miR-200 family participate in epithelial to mesenchymal transition and invasion by targeting E-cadherin transcription repressors like ZEB1/ZEB2 to increase E-cadherin expression and in turn epithelial phenotype.[55] It also targets transcription factor snail. That also leads to enhanced E-cadherin expression in ovarian carcinoma.[56] E-cadherin is a glycoprotein that in normal circumstances helps in cell-cell adhesion along with β–catenin.[57] Tumor cells after getting induced by TGF-β or PDGF-D increase ZEB1/ZEB2 expression and as a result decrease in miR-200 promoting EMT.[58] Dong et.al found that miR-137 and miR-34a function as unmediated suppressors of Snail (zinc finger transcription factor) in OC cells and suppress EMT phenotype and sphere formation of OC cells.[59]miR-205 shows increase in late stage of ovarian cancer.[60] It inhibits TCF-21 and increase ability of ovarian cancer cells to metastasize.[61]miR-205 down regulatesEzrin and lamin A/C after stimulation by VEGF resulting in proliferation, invasiveness and inhibition of apoptosis.[62]Overexpression of miR-125, miR-181b is related with invasion and metastasis of ovarian cancer cells by acting on large tumor repressor 2 (LATS2).[63,64]Li et.al established that in OC cells with low metastatic capability expression of miR-183 and miR-22 is more compared to ovarian cells with highmetastatic potential. Risein expression of miR-183 and miR-22 decreases the expression of Ezrin protein and in ezrin mediated way hinders ovarian cancer metastasis. [65]miR-543 causes transcription inhibition of MMP-7 mRNA by binding to its 3'-UTR and reduces metastasis and invasion.[66] MMPs are proteases involved in tumor invasion by cleaving components of ECM .Their increased expression is related with advancement

from benign to malignant ovarian cells.[67] They modulate cell adhesion molecules (CAM), growth factors(GF) and their receptors.[68] Angiogenesis is a physiological process required for cancer succession and metastasis by supplying oxygen and required nutrients. It is represented by continuous growth of new blood vessels from preexisting ones. Blood supply is crucial for cancer growth.[69]PTEN(Phosphatase and tensin homolog) is a tumor suppressor gene that mediates PI3K/AKT pathway required for normal blood vessel development.[70] PTEN converts phosphatidyl Inositol (3,4,5) triphosphate into Phosphatidyl inositol (4,5) bisphosphate.The PI3K deregulation causes activation of AKT.Activation of AKT signaling results in unrestricted proliferation and neoplastic angiogenesis.PTEN is required for stoppage of AKT signaling induced by oncogenes. miR-222 also targets PTEN and promote metastasis and invasion.[71-73] miR-205 induce angiogenesis by repressing PTEN and activating downstream AKT pathway.[74] Interleukin-8 (IL-8) and Chemokine Ligand-1(CXCL-1) secreted by tumor epithelial cells are main players of tumor vasculature and angiogenesis.miR-200 family targets IL-8 and CXCL-1 and inhibits formation of blood vessels.[75]Tumor angiogenesis also results from imbalance between proangiogenic and antiangiogenic factors specially of VEGF. In majority of ovarian carcinoma VEGF express at high levels.[76]Upregulated expression of miR-27a inhibits ZBTB 10 expression and in this way indirectly regulates expression of VEGF and VEGFR (receptor) leading to tumor growth and neoangiogenesis.[77]miR-125 b and miR-199 a acts as tumor suppressors and targets HIF-1α and VEGF and decrease angiogenesis.[78] Xu et.al seen that miR-145 has a suppressing effect on neoangiogenesis and is found repressed in tissues and cell lineage of ovarian carcinoma.[79]Inhibition of apoptosis is also a reason of ovarian carcinoma.The apoptotic suppressor such as survivin member of Inhibitors of apoptosis (IAP) family has an inhibitory action on caspasescascade,The activators of apoptosis such as (Smac/Diablo) neutralizes the inhibitory action of IAPs on caspases and bring cellular apoptosis.Survivin suppress apoptosis by sequestration of Smac/Diablo.High serum survivin levels thus correlate with late stage, grade, ascites, peritoneal metastasis of serous ovarian cancer and level of cytoreduction.[80-82]

MICRORNAs AS DIAGNOSTIC AND PROGNOSTIC BIOMARKERS

In human,miRNAs present in circulation are stable and are protected from endogeneousRNase activity.[83].Majority of miRNAs are released in body fluids via binding to lipoproteins like HDL or by forming non-vesicular Ago_2ribonucleoprotein complexes and as small extracellular membranous vesicles called exosomes.[22] Their stability and specificity make them potential diagnostic biomarker in cancer. [84]In miRbase (version 21,june17), 2588 mature human miRNA and 1915 mature mouse miRNA have been identified.[8]miRNArepresents only ~ 0.01% of total RNA by weight. Average expression of individual miRNA species is around 500/cell that is greater than the expression of mRNA species.[85] Various studies has shown that microRNA can serve as diagnostic markers in ovarian cancer as they are related to various aspects of ovarian cancer occurrence.

Hausler et.al evaluated 24 patients of serous ovarian cancer and 15 normal healthy controls on microarray and found higher expression of miR 30c-1-3p and lower expression of miR181a-3p, miR450-5p, miR 342-3p in relapsed serous ovarian cancer group.[86]

Kan et.al performed expression profiling and found higher expression of miR-182,miR-200a,miR-200b,miR-200c in serous epithelial ovarian cancer cell lines in contrast to control group i.e normal human ovarian surface epithelial cells.miR-200a, miR-200b,miR-200c when individually normalized to serum volume and miR-103 showed greater expression in serum of serous epithelial ovarian cancer group. miR 200b and 200c when combined and normalized to miR-103 and serum volume were found to be positive classifiers of Serous epithelial ovarian cancer .[87]

Chung et.al suggested that miRNA can serve as a unique biomarker of epithelial ovarian cancer.He found underexpression of miR-132, miR-26a,miR-145 and let -7b in serous ovarian cancer group in contrast to controls.[88]Zheng et.al scanned miRNA by Taqman low density array and validated them by real time PCR assay.He found increased expression of miR-205 and under expression of let -7f in ovarian cancer group compared to controls .A combined use of miR-205 and let-7f can be helpful in diagnosis of EOC in patients of stage-1 disease.[54]

Zuberi et.al found higher expression of miR-200a, miR-200b,miR-200c in epithelial ovarian cancer group compared to controls.[89]

Table 1: microRNAas Diagnostic biomarkers

Tumor type	Sample type	UpregulatedmiRNA	Downregulated miRNA	Control group	References
SAC	Whole blood	miR-30c-1-3p	miR-181a-3p,miR-342-3p,miR-450-5p	Healthy controls	86
MAC, SAC	Plasma	miR-205	Let-7f	Healthy controls	54
MAC	Serum	miR-200a,miR-200b,miR-200c		Healthy controls	89

SAC	Serum		miR-132 miR-26a, let-7b, miR-145	Healthy controls	88
SAC	Plasma	miR-106b, miR-126, miR150,miR17,miR-20a,miR-92a		Benign neoplasms	90
SAC,MAC,CCAC,and EAC and other OC	Serum exosomes	miR-375,miR-1307		Healthy controls and benign neoplasms	91

SAC:Serousadenocarcinoma,MAC:Mucinousadenocarcinoma,CCAC:Clear cell adenocarcinoma, EAC:Endometroidadenocarcinoma,OC:Ovarian carcinoma

Shapira et.al supported the fact that miRNA can differentiate women with Ovarian cancer from benign mass.They generated miRNA profiles from plasma of 42 women with SEOC,36 women with benign neoplasm and 23 age matched healthy controls.They found 22 miRNAs that showed differential expression between healthy controls and ovarian cancer group. Six miRNA profiles (miR-106b, miR-126, miR-150,miR-17,miR-20a,miR-92a)were able to differentiate between benign and OC group. [90]

Su et.al found up regulated expression of miR-375 and miR-1307 in serum exosomes of ovarian cancer patients in contrast to benign and healthy groups. An association of miR-1307 and miR-375 was found with tumor staging and lymph node metastasis respectively. Moreover, both have considerable prospective as targets of OC chemoresistance.[91]

Many studies have shown that miRNA can serve as biomarkers of prognosis in patients with ovarian cancer.

Zuberi et al.found association of up regulated expression of miR-200a with tumor histology and stage. Overexpression of miR-200c is related with metastasis to lymph nodes. miR-200a ,miR-200b and miR-200c were able to anticipate the prognosis and overall survival in epithelial ovarian cancer.[89]

Table 2: MicroRNA as Prognostic biomarkers

Tumor type	Sample type	Up regulated microRNA	Down regulated microRNA	End point	References
SAC,MAC,CCAC,EAC and Other ovarian carcinomas	Serum	miR-141	miR-200c	OS	93
SAC and others	Serum	miR-221	-	OS	94
MAC, SAC	Plasma		Let-7f	PFS	54
MAC	Serum	miR-200a ,miR-200b and miR-200c		OS	89

SAC: Serousadenocarcinoma, MAC:Mucinousadenocarcinoma,CCAC:Clear cell adenocarcinoma, EC:Endometroidadenocarcinoma,OC:ovarian carcinoma OS:Overall survival PFS:Progression free survival

Chen et.al performed Kaplan–meier overall survival analysis using TCGA data and showedmiRNA (hsa-miR135,miR-150,miR-340,miR-625,miR-1908,miR-31,miR-87,miR-96,miR-196b,miR-449 andmiR-1275) are related with high survival of patients with SOC.[92]

Gao et.al found that increased miR-200c expression is related with higher 2 year probability of survival and low miR-141 expression with significant higher survival rate. [93]

Zheng et.al indicated that decreased levels of let-7f might be predictive of unfavorable prognosis in EOC.[54] Hong et al. seen that overexpression of miR-221 come about as unfavorable self-sufficient factor of prognosis .It also has a role as diagnostic marker.[94]

II. Conclusion

Ovarian cancer is relatively manageable if diagnosed at an early stage. The mechanism underlying its etiology is still incompletely understood. Till date, no reliable biomarker is known that can assist in early stage diagnosis. miRNAs are related to various aspects of ovarian cancer and are stable in circulation. They behave as oncomirs or tumor suppressors by regulating cell proliferation, metastasis, invasion, angiogenesis and apoptosis. The emerging evidences have suggested that circulating miRNAs hold great capability as upcoming non-invasive diagnostic and prognostic biomarkers. It has been seen in different studies that miRNAs even from the same tumor type shows inconsistent pattern. This might be due to lack of standardized protocols of selection of internal controls. Further studies at large scale with standardized protocols are required to include miRNAs in current testing regime for early detection and screening of ovarian cancer.

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