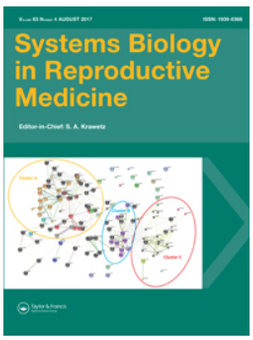

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REVIEW ARTICLE

RNA-based ovarian cancer research from 'a gene to systems biomedicine' perspective

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ABSTRACT

Ovarian cancer remains the leading cause of death from a gynecologic malignancy, and treatment of this disease is harder than any other type of female reproductive cancer. Improvements in the diagnosis and development of novel and effective treatment strategies for complex pathophysiologies, such as ovarian cancer, require a better understanding of disease emergence and mechanisms of progression through systems medicine approaches. RNA-level analyses generate new information that can help in understanding the mechanisms behind disease pathogenesis, to identify new biomarkers and therapeutic targets and in new drug discovery. Whole RNA sequencing and coding and non-coding RNA expression array datasets have shed light on the mechanisms underlying disease progression and have identified mRNAs, miRNAs, and lncRNAs involved in ovarian cancer progression. In addition, the results from these analyses indicate that various signalling pathways and biological processes are associated with ovarian cancer. Here, we present a comprehensive literature review on RNA-based ovarian cancer research and highlight the benefits of integrative approaches within the systems biomedicine concept for future ovarian cancer research. We invite the ovarian cancer and systems biomedicine research fields to join forces to achieve the interdisciplinary caliber and rigor required to find real-life solutions to common, devastating, and complex diseases such as ovarian cancer.

Abbreviations: CAF: cancer-associated fibroblasts; COG: Cluster of Orthologous Groups; DEA: disease enrichment analysis; EOC: epithelial ovarian carcinoma; ESCC: oesophageal squamous cell carcinoma; GSI: gamma secretase inhibitor; GO: Gene Ontology; GSEA: gene set enrichment analyzes; HAS: Hungarian Academy of Sciences; lncRNAs: long non-coding RNAs; MAPK/ERK: mitogen-activated protein kinase/extracellular signal-regulated kinases; NGS: next-generation sequencing; ncRNAs: non-coding RNAs; OvC: ovarian cancer; PI3K/Akt/mTOR: phosphatidylinositol-3-kinase/protein kinase B/mammalian target of rapamycin; RT-PCR: real-time polymerase chain reaction; SNP: single nucleotide polymorphism; TF: transcription factor; TGF-β: transforming growth factor-β

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Introduction

Ovarian cancer (OvC) remains the leading cause of death from a gynecologic malignancy, and treatment of this disease is harder than any other type of female reproductive cancer [American Cancer Society 2015]. The estimated death ratio for all cancer cases is 5% in the US, and the five-year survival rate for women with OvC is 40% ± 5% [Siegel et al. 2014]. The incidence rate of this disease is approximately 6.1 per 100,000 women, with 3.8 deaths per 100,000 women worldwide [Didžiapetrienė et al. 2014]. Early diagnosis offers the prospect of higher survival rates and can prevent 10% of deaths; however, less than 30% of women are diagnosed in stage I and only 20% of patients who are diagnosed in stage III survive up to five years [Buys et al. 2011; Hippisley-Cox and Coupland 2012].

In the context of early diagnosis and targeted therapeutics, OvC is amenable to research across multiple 'omics' such as genomics (i.e., genome-wide association studies and linkage-based approaches), epigenomics (i.e., DNA methylation studies), transcriptomics (i.e. expression profiling by microarrays or RNA-seq technologies), proteomics (i.e., immunoassays), and metabolomics (i.e., mass spectroscopy) approaches. These studies generate new information that can help in understanding the mechanisms behind disease pathogenesis, to identify new biomarkers and therapeutic targets and in new drug discovery.

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Even though reductionist approaches have improved our understanding of components (genes, mutations, SNPs, transcripts, proteins, non-coding RNAs (ncRNAs), metabolites, etc.) linked to cancer, the evaluation of disease progression mechanisms with a systematic approach and mapping the interactions of biological components have had a meagre impact on understanding the mechanisms underlying these complex pathologies. To provide information about how developmental and pathological processes occur in human, animal, and cell models, a systems biomedicine concept has emerged in recent years [Liu and Lauffenburger 2009; Antony et al. 2012]. This concept aims to decipher the multilevel, hierarchical nature of disease models (molecule, organelle, cell, tissue, organ, individual/genotype, environmental factor, population, and ecosystem) by discovering and selecting the key factors at each level and integrating them into models that reveal the global, emergent behavior of the biological process under consideration. In this respect, there is an emergent need for systems biomedicine approaches and methods in order to highlight the effecting mechanism of OvC progression.

The current RNA-based OvC review focuses on the expression profiling studies at transcript (mRNA) and ncRNA (long non-coding RNA (lncRNA) and miRNA) levels. The results of the studies are also evaluated at the pathways level. In addition, OvC research is analyzed from the systems biomedicine perspective to identify biomarkers and drug targets and to illuminate the potential mechanisms behind OvC pathogenesis. The benefits of integrative multi-omics approaches are also emphasized so as to bring about a systems medicine approach to diagnosis, treatment, and when possible prevention of ovarian cancer in the future.

Expression profiling of mRNA transcripts in ovarian cancer

The genomic reprogramming under OvC has been analyzed over the last two decades through microarrays, next-generation sequencing (NGS) methods, such as RNA-seq technology, and real-time polymerase chain reaction (RT-PCR) techniques using either OvC cell lines or tumor biopsies. A group of prognostic genes were identified; however, these gene signatures were not sufficient to define each OvC subtype. In other words, previous studies identified multiple genes which were differentially expressed between normal ovarian tissue and OvCs of varying histology. Gene expression studies demonstrated that OvC patients have distinct gene expression patterns, and therefore, OvC should be considered as a molecularly heterogeneous disease. Gene expression profiling studies on OvC cell lines were mostly focused on investigating the anti-cancer and anti-viral activities of various drugs in OvC. These include cisplatin [Li et al. 2009], paclitaxel [Dezső et al. 2014], MT19c [Stuckey et al. 2011], interferon-alfa [Christian et al. 2012], trastuzumab and pertuzumab [Sims et al. 2012], NSC319726 [Yu et al. 2012a], and eribulin [Dezső et al. 2014]. In addition to drugs, the effect of the enzymatic activity of topoisomerase I, which is a proven target for cancer therapeutics, was investigated in several cancer cell lines including OvC cell lines [Pfister et al. 2009]; the promoter effect of the estrogen hormone on lymph node metastasis and aggressiveness of tumor was studied in human epithelial OvC cell lines [Spillman et al. 2010] and the promoter role of CD157, a bone marrow stromal cell antigen, in mesenchymal differentiation was shown in OVCAR-3 [Morone et al. 2012].

Systematic comparisons of OvC cell lines were also performed using mRNA profiling. In a comprehensive study, the usability of six OvC cell lines (IGROV1, OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8, and SKOV3) as models for neoplastic diseases was analyzed together with 54 different cancer cell lines [Ross et al. 2000]. The main conclusion of this study was that gene expression patterns appeared to be related to the origin of the cell lines. However, OvC cell lines were clustered together and the genes in this cluster were related to epithelial cell biology. The chemotherapeutic vincristine-sensitive OvC cell line SKOV-3 was compared with the vincristine-resistant SKVCR-2, and it was shown that multiple genes, including ATP-binding cassette genes, were activated to increase vincristine resistance in SKOV3 and the activation of a multidrug-resistant phenotype was a complex process [Buys et al. 2007]. mRNA expression profiling studies on OvC biopsies were generally intended to: (i) identify diagnostic and/or therapeutic molecular markers and gain insights into disease mechanisms, (ii) predict molecular responses to chemotherapy treatments, and (iii) find the molecular differences between tumor subtypes and/or grades. Multiple gene expression studies have been performed to develop effective novel biomarkers, which may also assist in identifying the underlying mechanisms in disease formation and progression (Table 1). These biomarkers include kallikreins and claudins [Bignotti et al. 2006]; tumor suppressor genes such as KiSS-1 and SIRT7 [Hata et al. 2007; Wang et al. 2014]; receptors such as AXOR12, PDGFRA, AR and ROR1 [Hata et al. 2007; Merritt et al. 2009; Aragon-Ching 2014; Zhang et al. 2014a]; inhibitors such as SLPI and DKK1 [Merritt et al. 2009; Wang and Zhang 2011]; signaling proteins such as WNT7A, AKAP4, KIF14, SMAD2, and SMAD3 [Merritt et al. 2009; Agarwal et al. 2013; Thériault et al. 2012; Shi and Massaque

Table 1. The gene expression studies that identify biomarkers of ovarian cancer disease mechanisms.

Sample size and clinical type	Methods	Findings	Proposed mechanism	Reference
172 high-grade serous ovarian carcinoma and 12 normal ovarian tissues	RT-PCR	Compared with normal ovarian tissue, the level of ELOVL6 mRNA was significantly lower in high-grade serous ovarian carcinoma.	Low expression of ELOVL6 may correlate with the poor differentiation and drug resistance in high-grade serous ovarian carcinoma.	Li et al. 2016b
66 high-grade serous carcinoma patients effusions	RT-PCR	HuR is widely expressed in metastatic high-grade ovarian serous carcinoma at the mRNA level.	Higher HUR mRNA levels were significantly related to poor overall survival.	Davidson et al. 2016
44 ovarian tumor tissues and 7 fallopian tube tissues as a control	RT-PCR	Fibulin-5 was down-regulated in ovarian carcinomas compared with control tissues.	It was suggested that fibulin-5 act as a tumor suppressor by inhibiting by migration of tumor cells.	Heo et al. 2015
40 human primary epithelial ovarian carcinoma tissues	RT-PCR	CCNI and KDR mRNA expression was detected in all EOC tissues.	A significant positive correlation between the gene expression of KDR and CCNI.	Cybulski et al. 2015
52 benign ovarian tumors, 106 EOC samples and 30 specimens of normal ovaries	RT-PCR	PRSS3 mRNA levels were significantly higher in both epithelial ovarian cancers and benign tumor tissues relative to normal tissues.	PRSS3 overexpression can be used as a predictor of clinical outcome in patients with ovarian cancer and may therefore represent a new prognostic marker.	Ma et al. 2015
140 epithelial ovarian cancer and 20 normal ovarian tissue samples	RT-PCR	SLP-2 mRNA was expressed at higher levels in all epithelial ovarian cancer tissues compared to adjacent noncancerous tissues.	SLP-2 overexpression was associated with disease progression and poor survival outcomes for patients with epithelial ovarian cancer therefore SLP-2 may be regarded as a potential prognostic factor.	Sun et al. 2015
72 tumor, 15 para-carcinoma and 10 normal ovarian tissues	RT-PCR	IGF2 is frequently increased in human ovarian tissues.	High expression of IGF2 may be a significant prognostic factor for poor survival in ovarian cancer.	Dong et al. 2015
24 tumor and 9 healthy tissues	Microarray	CASP8 and BAD genes were under expressed in tumors biopsies vs. normal samples.	Down regulation of apoptosis signaling pathways in ovarian cancer.	Borhani et al. 2014
18 normal ovaries, 28 benign tumors, 55 serous borderline ovarian tumors, and 135 EOC	RT-PCR	GOLPH3 expression is up-regulated in cancerous tissues vs. control.	GOLPH3 will involve in ovarian cancer formation.	Ma et al. 2014
30 ovarian (15 high and 15 low stage) cancer samples and 9 healthy tissues	RT-PCR	ROR1 expression is relatively higher in cancerous tissues when compared to control.	ROR1 expression is associated with worse prognosis and have potential to be a prognostic marker in ovarian cancer.	Zhang et al. 2014a
53 ovary tumors and 30 healthy tissues	RT-PCR	Mammaglobin A, lipophilin A, lipophilin B and RYD5 gene expressions are considerably high in ovarian cancers relative to healthy tissues.	Lipophilin B over-expression has a potential to be a prognostic biomarker in ovarian cancer.	Bignotti et al. 2013
38 ovarian carcinoma and 21 non-diseased samples	RT-PCR	AKAP4 was generally expressed (89%) in diseased samples but not by controls.	AKAP4 gene as a candidate therapeutic target in ovarian cancer.	Agarwal et al. 2013
90 ovarian carcinoma tumors with 10 healthy samples	RT-PCR	KIF14 expression was raised in tumor samples.	KIF14 is a potential therapeutic target and prognostic marker for ovarian cancer.	Thériault et al. 2012
4 mm-thick paraffin sections of ovarian tumor biopsies contained 146 samples	RT-PCR	EPCR gene expression was detected the presence of in ascitic cell clusters of ovarian cancers.	EPCR expressed by ovarian cancer cells could be a possible biomarker of cancer.	Ducros et al.2012
32 ovarian serous papillary adenocarcinoma and 10 healthy ovarian tissues	RT-PCR	DKK1 was up-regulated in ovarian cancer tissues relative to healthy tissues.	DKK1 attended in tumor invasion and have a potential to be a prognostic biomarker in ovarian serous papillary adenocarcinomas.	Wang and Zhang 2011
78 ovarian tumor and 12 normal ovarian surface tissues	RT-PCR	CHD5 expression was down-regulated by at least twofold in 32 of 72 (41%) invasive EOC.	CHD5 is down-regulated and appears to be an adverse predictor candidate of ovarian cancer disease.	Wong et al. 2011
28 invasive and 7 low malignant potential serous ovarian tumors with the 7 serous benign ovarian tumors and 4 healthy tissues	Microarray	C6orf31, PDGFRA were down while SLPI and WNT7A were up regulated in LMP and invasive group when compared with other two control groups.	C6orf31, PDGFRA, SLPI and WNT7A genes may play a significant role in ovarian cancer.	Merritt et al. 2009
177 tumor samples	Microarray and RT-PCR	Microarray analysis identified a profile of 34 differentially expressed genes. High BTF4 and GCS expression is related to better prognosis.	BTF4 and GCS could be a potential prognostic marker in EOC.	Le Page et al. 2008
20 patients EOC tissues	RT-PCR	SPAG9 mRNA expression was detected in 90% of EOC tissues.	SPAG9 could be a potential target for the development of diagnostic and therapeutic methods in EOC.	Garg et al. 2007
76 epithelial ovarian cancer surgical specimens	RT-PCR	Different expressions profile of metastin and AXOR12 were detected in ovarian cancer samples.	Metastin/AXOR12 signaling might suppress the invasive ovarian cancer phenotype.	Hata et al. 2007
19 ovarian serous papillary carcinomas (OSPC) and 15 controls	Microarray	Kallikreins 6/7/8/10/11, claudin 3/4 and B7-H4 genes were significantly up-regulated in tumor samples.	Kallikreins 6/7/8/10/11, claudin 3/4 and B7-H4 genes were proposed candidate diagnostic and therapeutic biomarkers.	Bignotti et al. 2006

2003; Xue et al. 2014]; transmembrane proteins such as PRRT1 encoded by C6orf31 [Merritt et al. 2009]; enzymes such as PTGS encoded by COX-2 and GOLPH3 [Lin et al. 2011; Ma et al. 2014]; secretoglobin family members such as lipophilin B [Bignotti et al. 2013]), and pro-apoptotic genes such as CASP8 and BAD [Borhani et al. 2014].

Many OvC patients experience recurrence after chemotherapy treatment. Transcriptome studies were performed to predict genes associated with chemo-response, and results from these studies may lead to the identification of chemo-resistance mechanisms and the development of convenient treatment strategies [Ju et al. 2009; Choi et al. 2012]. Several differentially expressed genes (such as ABCF2, ADPRTL1, ASS, BCAT1, CCNA2, CDCA8, CENPE, COL3A1, ETV4, GRIA2, GRP, ITGAE, LBR, MUC1, STK6, SGPP1, PCNA, PRDX2, TOP2A, TRA1, and TRF4-2) are associated with chemo-sensitivity and chemo-resistance. It has been shown that p53-mediated cell-cycle arrest prevents the DNA damaging-based chemotherapeutic treatment in OvC; thus, the inhibition of p53 during chemotherapy has been proposed as a strategy to improve treatment outcome [Moreno et al. 2007]. Possible roles for the PI3K/Akt, NF-κB, and ERK pathways in chemo-resistance have also been reported [Koti et al. 2013].

A limited number of gene expression profiling studies have been performed to clarify the cancer subtype or grade, which is an important determinant for accurate diagnosis and treatment. It was reported that mRNA expression of ILF3 and UBE2I are relatively higher in OvC tissues compared to that in normal tissues. In addition, to uncover gene expression patterns in different subtypes, patterns of ILF3 and UBE2I gene expression were compared within OvC subtypes and grades. Considerably higher expression signatures for both genes were observed in serous carcinomas relative to mucinous, endometrium, and clear-cell carcinomas, and the gene expression levels were higher in advanced stages compared to early stages. Therefore, the researchers proposed possible roles for ILF3 and UBE2I in tumorigenesis and subtype differentiation [Zhu and Yu 2010]. In addition to ILF3 and UBE2I, the PAX2 gene was also proposed as a potential biomarker to distinguish low-grade OvCs from high-grade OvCs [Tung et al., 2009]. More recently, in a microarray study, researchers analyzed the molecular differences among three subtypes (serous, endometrioid, and clear-cell) of OvC and reported that the mechanisms underlying serous carcinomas were relatively more similar to endometriod carcinomas compared to clear-cell carcinomas [Pamula-Pilat et al. 2014]. Overall, these studies reported that low- and high-grade ovarian serous carcinomas may have different gene expression profiles and developmental pathways.

Recent studies concerning the prognostic significance of cancer-associated fibroblasts (CAFs) in human cancer have gradually increased to better define the tumor microenvironment, and are reviewed in the paper by Poulsson and Micke [2014]. CAFs are located in the tumor stroma, and it is unclear how cancer cells transform normal fibroblasts into CAFs. For example, Ko et al. [2012] investigated the expression of HOXA9 to understand how EOC cells easily adapt to the peritoneal environment. They reported that HOXA9 promoted OvC growth by stimulating CAFs. In a more recent study, using both *in vitro* and *in vivo* models of CAFs in OvC development, Lawrenson et al. (2015) showed that NPPB is a novel candidate biomarker expressed by CAFs and is essential for accurate clinical diagnosis of EOC.

Expression profiling of non-coding RNAs in ovarian cancer

One of the most important discoveries of the post-genomic era is that a large fraction of the genome transcribes a heterogeneous population of ncRNAs. Their crucial roles in RNA silencing and post-transcriptional regulation of gene expression have been suggested [Bartel 2004], and the identification of the roles of ncRNAs (especially miRNAs and lncRNAs) in human diseases is a hot topic. The associations of various miRNAs with OvC pathogenesis have been reported in the literature (Table 2). Most of these reports employed antisense-miRNA transfection strategies, while others determined differentially expressed miRNAs using microarray technologies.

In the last decade, expression patterns of miRNAs were analyzed in OvC biopsies and cell lines (especially OVCAR3, OV167, PE01, and OV202) via miRNA microchips [Iorio et al. 2007; Kan et al. 2012; Nam et al. 2012; Peng et al. 2012; Yang et al. 2012; Yang et al. 2013a; Pink et al. 2015; Shields et al. 2015]. Significant alterations were detected in expression levels of numerous miRNAs including miR-19a, miR-28, miR-34a, miR-34b, miR-34c, miR-100, miR-125a, miR-125b1, miR-140, miR-141, miR-145, miR-146a, miR-182, miR-199a, miR-200a, miR-200b, miR-200c, miR-205, miR-296, miR-506, miR-519, miR-1181, miR-1202, and miR-1207-5p. Furthermore, differential expressions of miR-19a, miR-100, miR-141, miR-199a, miR-200a, miR-200b, and miR-200c were observed in almost all analyses. Among those, miR-100 was proposed as a tumor suppressor [Peng et al. 2012] and the

Table 2. The expression profiling studies of non-coding RNAs (i.e., miRNAs and lncRNAs) of the ovarian cancer.

Sample size and clinical type	Methods	Findings	Proposed mechanism	Reference
miRNAs				
135 epithelial ovarian cancer patients and 54 benign ovarian tumor patients	TaqMan low density miRNA arrays, RT-PCR	expression levels of serum miRNA-20a, miRNA-125b, miRNA-126, miRNA-355, and let-7c were significantly different between malignant and benign ovarian tumor patients	miRNA-125b has the potential to become a novel biomarker for early diagnosis and prognosis prediction of epithelial ovarian cancer	Zhu et al. 2017
Ovarian cancer cell line A2780 and its cisplatin-resistant derivative CP70	Microarrays	miR-21-3p directed increased resistance to cisplatin in a range of ovarian cell lines	miR-21-3p can induce cisplatin resistance in ovarian tumours	Pink et al. 2015
A2780, HEY, SKOV3 cells and primary human ovarian cancer samples	TaqMan RT-PCR, Immunoblotting,	miR-181a was up-regulated and promotes epithelial-to-mesenchymal transition in ovarian cancer	miR-181a promotes TGF-β-mediated epithelial-to-mesenchymal transition via repression of its functional target, Smad7	Parikh et al. 2014
33 ovarian papillary serous cystadeno-carcinoma and 7 normal ovarian tissues, OVCAR3 and A2780 lines	Taqman RT-PCR and RT-PCR	miR-199a and miR-125b were downregulated in ovarian cancer tissues and cell lines	provides a rationale for new therapeutic approach to suppress tumor angiogenesis using miR-199a and miR-125b	He et al. 2013
98 epithelial ovarian cancer tissues and 15 adjacent normal epithelial tissues	TaqMan RT-PCR	miR-100 is downregulated in human epithelial ovarian cancer	low miR-100 expression may be a poor prognostic factor	Peng et al. 2012
4 cell lines 28 serous epithelial ovarian cancer and 28 healthy donors	miRNA expression profiling	miR-200a, miR-200b and miR-200c were highly overexpressed	identified serum microRNAs able to discriminate patients with high grade serous epithelial ovarian cancer	Kan et al. 2012
CD133(+) spheroid-forming subpopulation of the OVCAR3 human ovarian cancer cell line	miRNA microarray and RT-PCR	miR-205, miR-146a, miR-200a, miR-200b were significantly up-regulated while miR-205, miR-146a, miR-200a, miR-200b, and miR-3 were significantly down-regulated	indicate that dysregulation of miRNA may play a role in the stem cell-like properties of ovarian cancer stem cells	Nam et al. 2012
SKOV3 and SKOV3/CIS cells	miRNA microarrays	miR-130a was upregulated in SKOV3/CIS compared to the parental SKOV3 cells	provides important information for the development of targeted gene therapy	Yang et al. 2012
83 human epithelial ovarian cancer samples	RT-PCR	miR-34a expression is decreased in 100%	miR-34 family plays an important role in EOC pathogenesis	Corney et al. 2010
15 normal ovarian tissue sections and 69 malignant tissues	miRNA microarray technologies	most significantly overexpressed miRNAs were miR-200a, miR-141, miR-200c, and miR-200b, whereas miR-199a, miR-140, miR-145, and miR-125b1 were among the most down-modulated miRNAs. miR-21, miR-203, and miR-205, up-modulated in ovarian carcinomas compared with normal tissues	indicate that miRNAs might play a role in the pathogenesis of human epithelial ovarian cancer and identify altered miRNA gene methylation as a possible epigenetic mechanism involved in their aberrant expression	Iorio et al. 2007
A2780, 3AO, OVCAR3, SKOV3, and HO-8910 cell lines and 11 pathologically confirmed ovarian cancer tissues	qRT-PCR, MTT assay, Western blotting, Knockout™ RNAi System, Immunohistochemical staining	HOTAIR overexpression promoted cell cycle progression (and thus cell proliferation) by activating the wnt/β-catenin signaling pathway	HOTAIR might be a potent therapeutic target for ovarian cancer treatment	Li et al. 2016a
109 ovarian cancer and 45 normal ovarian tissue samples and cell lines (SKOV3, IGROV1, A2780, OVCAR3 and HOSE 6.3)	qRT-PCR	CCAT2 in ovarian cancer tissues and cell lines were significantly higher compared with values obtained for adjacent non-tumor tissues and normal ovarian epithelial cells	CCAT2 is a novel factor involved in ovarian cancer progression, and constitutes a potential prognostic biomarker and therapeutic target for patients with ovarian cancer.	Huang et al. 2016
Ovarian cancer tissues and adjacent normal tissues and HO-8910 and OVCAR3 cells	qRT-PCR, western blot assays	AB073614 expression was significantly up-regulated in 85.3% (64/75) cancerous tissues compared with normal counterparts	lncRNA AB073614 acts as a functional oncogene in ovarian cancer development	Cheng et al. 2015
SKOV-3, HO8910 and highly metastatic sublines SKOV-3.ip1, HO8910-PM	microarray analysis and western blotting	ANRIL was highly expressed in both SK-OV-3.ip1 cells and HO8910-PM cells	ANRIL plays an important role in serous ovarian cancer invasion/metastasis and could represent a novel biomarker	Qiu et al. 2015
Epithelial ovarian cancer tissues and SKOV3.ip1, HO8910-PM, and HEY-A8 cell lines	A series of in vitro and in vivo assays	HOTAIR expression was elevated in epithelial ovarian cancer tissues, and HOTAIR levels were highly positively correlated with the FIGO stage	HOTAIR plays a vital role in epithelial ovarian cancer metastasis and could represent a novel prognostic marker and potential therapeutic target	Qiu et al. 2014
SKOV3 and SKOV3.ip1 cell lines	Microarray and RT-qPCR	MALAT1, H19, UCA1, CCAT1, LOC645249, LOC100128881, and LOC100292680 were deregulated	indicates that some lncRNAs might exert a partial or key role in epithelial ovarian cancer metastasis	Liu et al. 2013
Ovarian cancer cell lines (SKOV3 and OVCAR5), tumor tissues and their normal counterpart	Microarray and qPCR	LSINCT5 is overexpressed in ovarian cancer cell lines and tumor tissues, relative to their normal counterpart.	a novel lncRNA LSINCT5 enhances cellular proliferation and may play a significant role in multiple processes in ovarian cancer	Silva et al. 2011

miR-200 family, miR-28, miR-34a, miR-125a, miR-296, and miR-519 as tumor suppressors [Iorio et al. 2007; Korpal et al. 2008; Grammatikakis et al. 2013]; the inhibitory effect of miR-199a in OvC proliferation and metastasis was presented in Joshi et al. [2014]. It was proposed that elevated levels of miR-19a may lead to angiogenesis by suppressing the anti-angiogenic factor TSP-1 [Dews et al. 2006] and that aberrant miR-34 levels may be related to migration, invasion, and cellular proliferation in OvC [Corney et al. 2010]. The targets of miR-34 include c-myc, CDK6, Notch-1, MET, E2f3, Bcl2, and cyclinD1 [Suzuki et al. 2009], and miR-34 is regulated by p53 [He et al. 2007].

Expression of miR-21-3p and miR-214 are associated with chemo-resistance in OvC. miR-21-3p expression is associated with cisplatin resistance in OvC tumors [Pink et al. 2015]. In a previous study, it was demonstrated that up-regulation of miR-214 leads to chemo-resistance and cell survival by targeting PTEN, which is a tumor suppressor that is mutated in a large number of cancers at a high frequency [Yang et al. 2008]. Recently, researchers undertook a comprehensive study in which genome-scale miRNA mimic toxicity screens were employed in a diverse spectrum of OvC cell lines. They found that the toxicity profile was robust, but a small cohort of commonly toxic mimics (i.e., miR-124 and miR-517a) was identified [Shields et al. 2015].

The dual role of miRNAs in the regulation of tumorigenesis has been reported in the literature, where down-regulated miRNAs can behave as tumor suppressors, whereas up-regulated miRNAs can act as tumor enhancers during cancer progression. OvC-related miRNAs and their targets have roles in uncontrolled cell proliferation, abnormal apoptosis, angiogenesis, and inflammation processes (Figure 1). A previous study revealed that miR-9 directly targeted NF-kappaB1, which has a main role in the inflammatory response, and that inhibition of miR-9 caused up-regulation of NF-kappaB1 expression [Guo et al. 2009]. Additionally, miR-199a repressed NF-kappaB1 activity via suppression of IKKβ expression [Chen et al. 2008], and was reported to suppress the pro-inflammatory factor COX-2 [Chakrabarty et al. 2007]. The study also reported that down-regulation of miR-199a in OvC repressed tumor angiogenesis via HIF-1α and the VEGF pathway [He et al. 2013].

Although many studies center upon miRNA signatures in OvC cells, only a few have focused on miRNA signatures in ovarian CAFs. Studies on CAFs showed that dysregulation of miRNAs in the stromal microenvironment may affect tumor growth [Chou and Werb 2012; Mitra et al. 2012].

Recently, it was discovered that cell-free miRNAs circulate in the body fluids (such as serum, plasma, whole blood, and urine) of healthy and diseased patients, suggesting that they may serve as promising biomarkers for early detection, prognosis, and sensitivity to chemotherapy of cancers [Nakamura et al. 2016]. Cell-free miRNA signatures were found to parallel those from the originating tumor cells, indicating that circulating miRNA profiles may reflect not only the existence of OvC but also tumor histology, stage, and prognoses of the patients [He et al. 2008; Nakamura et al. 2016]. Several circulating miRNAs were presented as potential diagnostic and prognostic biomarkers in OvC. These include let-7f, and miR-21, miR-29a, miR-92, miR-93, miR-99b, miR-126, miR-127, miR-155, and miR-205 for OvC diagnosis [Fernandez-Mercado et al. 2015]; let-7f, miR-21, miR-23b, miR-29a, miR-141, miR-145, miR-200b, miR-200c, miR-221, miR-429, and miR-1290 for OvC prognosis [Nakamura et al. 2016].

Studies which investigated the associations between lncRNAs and OvC were at the initial stages and very limited. Researchers reported the overexpression of LSINCT5 in OvC cell lines (i.e., SKOV3 and OVCAR5) [Silva et al. 2011]. In another study, differential expression of several lncRNAs in SKOV3 was examined. Seven of the analyzed lncRNAs (MALAT1, H19, UCA1, CCAT1, LOC645249, LOC100128881, and LOC100292680), which possess different metastatic potentials, were identified as dysregulated [Liu et al. 2013]. Moreover, in another study, it was suggested that HOTAIR was significantly up-regulated in epithelial OvC tissues relative to normal tissues. Furthermore, the researchers suggested that HOTAIR plays an essential role in OvC metastasis and proposed it as a candidate prognostic and therapeutic target [Qiu et al. 2014]. HOTAIR is the most studied lncRNA in OvC and other cancer types [Hajjari and Salavaty 2015]. It was reported that the overexpression of HOTAIR promotes chemo-resistance by activating the Wnt/β-catenin pathway [Li et al. 2016a] and supports the proliferation of serous OvC via regulating the cell cycle and apoptosis [Qiu et al. 2015]. Other lncRNAs associated with OvC are ANRIL, AB073614, RP11-284N8.3.1 and AC104699.1.1. ANRIL promotes metastasis in serous OvC [Qiu et al. 2015], whereas AB073614 acts as an oncogene (promotes tumorigenesis) in OVC pathogenesis [Cheng et al. 2015]. RP11-284N8.3.1 and AC104699.1.1 are involved in immune system activation and anti-tumor-related processes in the OvC microenvironment [Guo et al. 2015]. Recently, a regulatory association between miRNA, let-7b, and lncRNA, HOST2, in OvC was reported; to date, this is the first

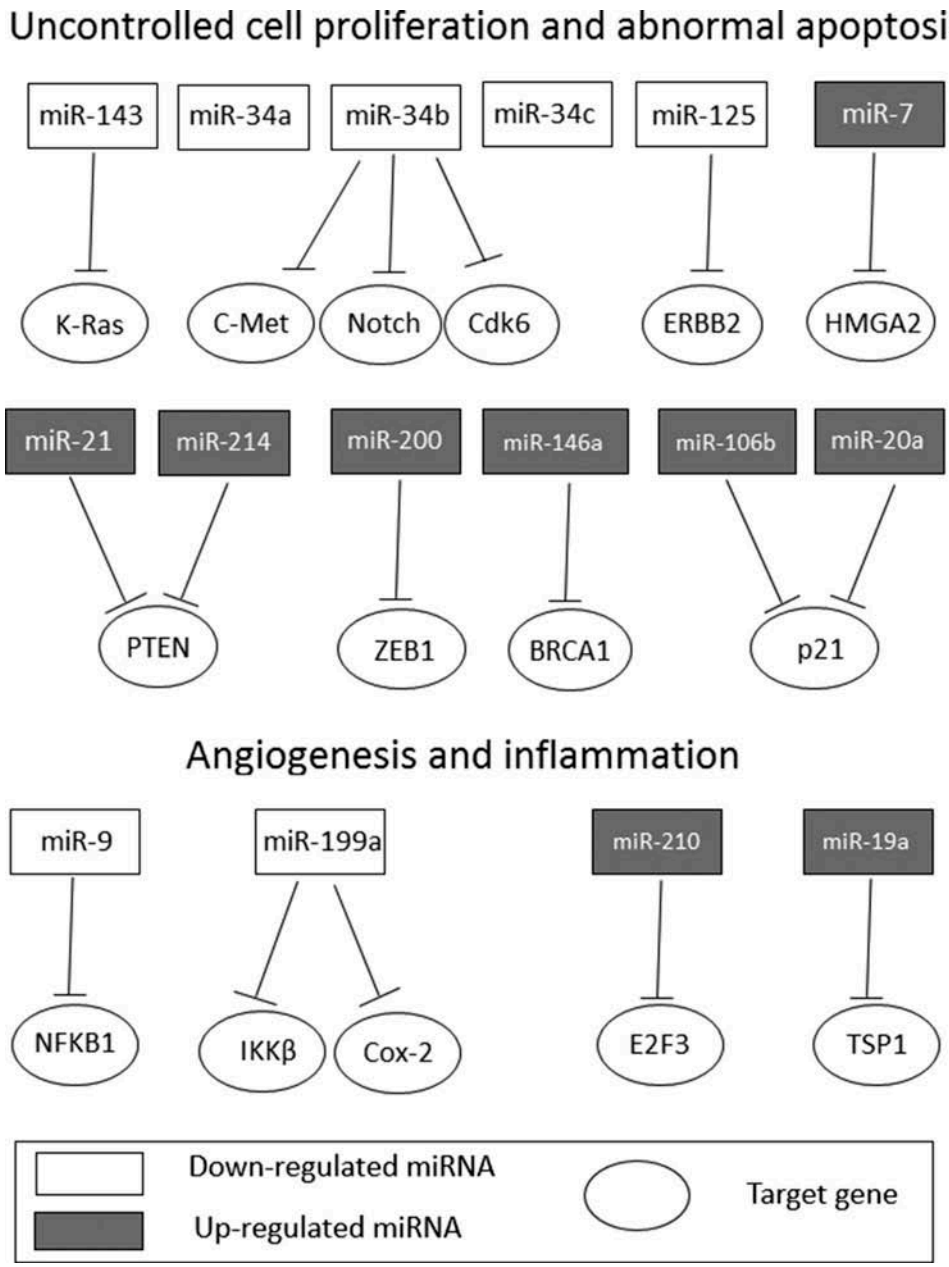

Figure 1. Ovarian cancer associated miRNAs and their target in uncontrolled cell proliferation, abnormal apoptosis, angiogenesis, and inflammation processes.

and only study which investigates the miRNA-lncRNA interaction in OvC [Gao et al. 2015].

Similar to circulating miRNAs, lncRNA released into the extracellular environment and the presence of lncRNAs in body fluids were also suggested in recent studies [Qi et al. 2016]. As a consequence, there has been great effort to identify circulating lncRNAs as biomarkers for early cancer diagnosis, disease evolution, and poor prognosis. Although circulating lncRNAs were reported in several cancers, such as PCA3 in prostate cancer [Lee et al. 2011], uc003wbd and AF085935 in hepatocellular carcinoma [Lu et al. 2015], and RP11-445H22.4 in breast cancer [Xu et al. 2015], to date circulating lncRNAs have not been studied in OvC. Unlike microchip or antisense-miRNA strategies, NGS technologies will allow detection of novel ncRNAs in OvC. RNA-Seq technology was employed in two recent studies to analyze expression profiles in the A2780 cell line [Parikh et al. 2014] and its cisplatin-resistant derivatives, MCP1 and CP70 [Samuel et al. 2016]. They reported that miR-181a plays a key role in OvC via inducing epithelial-to-mesenchymal transition, which is responsible for OvC formation. Furthermore, the enhancing roles of miR-31

and KCNMA1 in cisplatin resistance in OvC were reported.

Different signaling pathways associated with ovarian cancer

Understanding the underlying signaling pathways is fundamental in disease research due to the important regulatory roles these pathways play in numerous cellular events including cancer pathogenesis and formation. OvC research has revealed the important roles of several signaling pathways in cancer formation and progression, which include p53, phosphatidylinositol-3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR), the transforming growth factor-β(TGF-β), Notch, Wnt/β-catenin, and mitogen-activated protein kinase/extracellular signal-regulated (MAPK/ERK) pathways.

Mutation of the p53 gene is one of the most well-known and common alterations underlying human malignancies such as cancers [Mirzayans et al. 2012]. p53 gene mutations are observed in more than 50% of human cancer cases and alterations in Mdm2 and p14Arf, which are two constituents of the p53 signaling pathway, are observed in the remaining 50% of cases [Brachova et al. 2013; Stegh 2012]. p53 mediates the consistent removal of damaged cells via cell senescence or death, and may ensure survival and repair of damaged cells [Vousden and Prives 2009]. Thus, activation of the p53 signaling pathway through DNA-damage associated factors can enable both checkpoint activation and apoptotic cell death [Mirzayans et al. 2012].

The PI3K/Akt/mTOR signaling pathway, comprised of phosphatidylinositol-3-kinase (PI3K), a protein kinase (Akt) and mammalian target of rapamycin (mTOR), is mainly responsible for cell growth and survival; thereby, it is directly associated with tumorigenesis and metastasis [Dobbin and Landen 2013; Porta et al. 2014]. An appreciable role of this pathway in OvC cancerogenesis, progression, and chemoresponse has been suggested [Dobbin and Landen 2013]. Even though the PI3K/Akt/mTOR signaling pathway is the most frequently dysregulated pathway in cancer after the p53 signaling pathway, it is usually altered in OvC [Leary et al. 2013]. It is estimated that this signaling pathway is activated in 70% of OvCs [Li et al. 2014] in multiple ways including PIK3R1/2 mutations, gain-of-function mutation amplifications of PIK3CA, mutations or amplifications of AKT1/2/3, loss or inactivating mutations of the tumor suppressors (TSC or LKB1), and loss or mutations of PTEN in cancer pathogenesis [Cheaib et al. 2015; Teplinsky and Muggia 2015].

The multi-functional cytokine, TGF-β, is involved in cell proliferation, differentiation, apoptosis, and carcinogenesis. Its role as a proto-oncogene or anti-oncogene in tumor cells is dependent on the type and stage of the tumors [Kubiczkova et al. 2012]. TGF-β effectively prevents uncontrolled cell proliferation, and therefore can be considered as a potential drug to treat malignancies. However, alterations in TGF-β signaling may cause growth arrest resistance [Moustakas et al. 2002] and accordingly, can lead to cancerous cells. Consequently, irregularities in TGF-β can potentially change its tumor suppressor activity to a tumor promoter activity [Tian et al. 2011]. TGF-β signaling is induced in various cancer types including OvC [Kubiczkova et al. 2012]. Also, the three ligands of TGF-β (TGF-β1, TGF-β2, and TGF-β3) are significantly over-expressed in OvC [Bauckman et al. 2012]. When the gene expression patterns of TGF-β1 and its two receptors (TβR1 and TβR2) were assessed using RNase protection, significantly higher levels of TGF-β1 expression were observed, and thus, elevated TGF-β1 expression was proposed as a biomarker for OvC prognosis [Komiyama et al. 2011].

The Notch signaling pathway is another highly conserved pathway which plays a role in cell proliferation, differentiation, apoptosis, and developmental processes. Irregularities in this pathway may lead to malignant neoplasm, and this pathway can act as either an oncogene or a tumor suppressor dependent on tissue and organ type [Lachej et al. 2012]. An oncogenic role for the notch signaling pathway has been reported in OvC [Ntziachristos et al. 2014]. According to the TCGA project, 22% of high-grade serous OvC cases have altered Notch signaling pathway components such as Notch1 and Notch3 receptors [Groeneweg et al. 2014a]. Notch inactivation was suggested as a novel strategy in OvC treatment, and gamma secretase inhibitor (GSI) drugs were proposed for this purpose [Capaccione and Pine 2013]. In another recent study using GSI drugs with chemotherapy in patients with OvC, notably improved treatment outcome [Groeneweg et al. 2014b].

The Wnt/β-catenin signaling pathway, which regulates miscellaneous biological processes including cell proliferation, mobility, and adhesion through differentiation, progression, and homeostasis, is crucial for normal ovarian development and follicular development, and is up-regulated in OvC [Mostowska et al. 2014; Gatcliffe et al. 2008]. Alterations in the expression of several pathway members (APC, Axin 1/2, GSK3β, and CTNNB1) were observed in OvC [MacDonald et al. 2009]. Mutations in the CTNNB1 gene, which codes for β-catenin, were directly linked to epithelial OvC transformation [Gatcliffe et al. 2008].

Furthermore, inhibitors for the Wnt/β-catenin signaling pathway, such as niclosamide, were developed as targeted treatment strategies for OvC. In niclosamide-treated OvC cells, aberrant Wnt signaling was observed and the proliferation rate was decreased [Arend et al. 2014].

The MAPK/ERK signaling cascade (also known as the Ras-Raf-MEK-ERK pathway) is regulated by several factors like DNA damage, metabolic stress, and altered protein concentrations [Burotto et al. 2014]. MAPK1 is a member of the MAPK/ERK signaling pathway which is dysregulated in cancer cells including OvC [Lei et al. 2014]. Mutations in the BRAF and KRAS genes may cause MAPK pathway activation and dysregulation of kinase activity [Teplinsky and Muggia 2015].

Integrative approaches in OvC research

Development of high-throughput technologies that offer functional genomics datasets provide the opportunity for integrative analyses in OvC research to create a holistic view. However, to date, current literature does not cover the potential for integrative analysis. The studies were limited with reconstruction of context-specific, small-scale network models and meta-analysis of mRNA and ncRNA expression to understand cancer pathogenesis and to identify prognostic and therapeutic targets.

In recent years, a few studies have utilized integrative network analyses to present context-specific network models in human OvC. One of the earliest examples is the dynamic inflammatory cytokine network, which includes three key cytokine/chemokine mediators of cancer-related inflammation (i.e., TNF, CXCL12, and IL6) [Kulbe et al. 2012]. A network-based Cox regression model (called Net-Cox), which was used for a large-scale analysis of various OvC datasets to identify gene signatures has been proposed. This suggested FBN1 as a biomarker sensitive to chemotherapy [Zhang et al. 2013]. Using a Bayesian network model, others have used integrative approaches that include the TCGA cancer dataset to identify genetic and epigenetic signatures associated with OvC. With this approach an association between several genes (such as ARID1A, C19orf53, CSKN2A1, COL5A2, PSG11, and GALNT10) and overall survival time of OvC patients [Zhang et al. 2014b] was suggested. More recently, an angiogenesis network model was constructed via categorization of TCGA data into the angiogenic and non-angiogenic subtypes [Glass et al. 2015]. Through differential co-expression and dynamic modularity analyses, researchers presented a network module of 12 genes associated with the cell death mechanisms in ovarian serous cystadenocarcinoma [Jin et al. 2015].

Meta-analysis of 11 transcriptomic datasets associated with OvC was performed to identify potential candidate biomarker genes for OvC progression [Fekete et al. 2012]. Three hormone receptor genes (ESR2, PGR, and TSPAN8) and two genes (MAPT and SNCG) were associated with survival and relapse-free survival, respectively. More recently, a meta-analysis of all single gene probes in the TCGA and Hungarian Academy of Sciences (HAS) in OvC was conducted to identify candidate biomarkers using Cox regression analysis [Willis et al. 2016]. The researchers identified 32 putative biomarkers (such as AXL, APC, RAB11FIP5, LRIG1, SLC33A1, NUCB2, POLD3, and ESR2) with possible roles in ovarian serous carcinoma.

Integrative analyses considering ncRNAs are limited. Integration of the TCGA ovarian data with a miRNA-target gene interaction network presented 34 OvC-related predictive miRNAs along with several anti-correlated mRNA-miRNA pairs [Creighton et al. 2012]. In comparison, to identify epigenetic biomarkers for diagnosis of OvC, others using MeDIP-Chip in A2780 and CaOV3 cell lines observed that a long intergenic ncRNA, LOC134466, was hypermethylated in 81% of serous epithelial OvCs [Gloss et al. 2012].

Ovarian cancer research should meet integrative multi-omics science

High-throughput functional genomics techniques focus on dynamic aspects such as gene transcription (transcriptome), protein–protein and protein–DNA interactions (interactome), transcriptional and post-transcriptional regulations (regulome), translation (proteome), and metabolism (metabolome and fluxome) as opposed to the static view of DNA-based information. Systems biomedicine approaches consider integration of the 'big data' obtained via these high-throughput functional genomics screens with biological networks to decipher disease formation and progression mechanisms [Liu and Lauffenburger 2009]. According to Tseng et al. [2012], two types of data integration strategies exist for such data: (i) horizontal meta-analysis, which combines different sample types under the same conditions, and (ii) vertical integrative analysis, which combines different molecular components usually of the same sample type. Vertical integrative analysis is more favorable for investigating the behavior of pathological processes under variable conditions by exerting the key factors at different omics levels (i.e., mRNA, ncRNA, protein, protein interaction, metabolite, transcription factor (TF), and enzyme).

Publicly available databases which have emerged in recent years provide regulatory information necessary to reconstruct comprehensive transcriptional regulatory networks via integrating TF-miRNA-lncRNA-target gene interactions (Table 3). The information stored in these databases can be used to reconstruct disease- or condition-specific subnetworks as well as to annotate new ncRNAs. As reviewed above, expression profiling studies at transcript (mRNA) and ncRNA levels in OvC cell lines and biopsies have provided several datasets for horizontal meta-analyses and vertical integrative analyses to create a more holistic view of the active transcriptional regulatory subnetworks in OvC.

Several network-based studies have explored the control of gene expression by TFs and miRNAs via reconstruction of transcriptional regulatory networks (TF-miRNA-target gene interactions) and the signal transduction activities via reconstructing protein–protein interaction networks. For instance, in a previous study, researchers performed an analysis by focusing on the expression of relationships among miRNA targets [Gennarino et al. 2012]. Furthermore, researchers reported important tumor-regulating miRNAs and TFs via topological analysis of a combinatorial transcription regulatory network in human cancer [Yu et al. 2012b].

An integrative approach is crucial to detect more reliable RNA biomarkers for diagnosis, treatment of OvC, and to illuminate active pathways and the molecular relationships underlying pathogenesis of the disease. Here, we propose an RNA-based systems biomedicine approach for characterization of disease mechanisms, which consists of two main parts (Figure 2). Integrative statistical analyses of RNA data is performed to elucidate molecular signatures, i.e., disease-related genes (mRNAs), ncRNAs, potential proteins, and metabolites, which indicate significant

Table 3. Data resources for miRNA and lncRNA annotation and their targets interaction.

Database	Web link	Description	Reference
miRNA			
miRBase	http://www.mirbase.org/	Known functional miRNAs	Kozomara and Griffiths-Jones 2013
MiRDB	http://mirdb.org/miRDB/	miRNA-target predictions	Wang 2008
miRecords	http://mirecords.biolead.org/	Experimentally verified miRNA-target interactions	Xiao et al. 2009
miRTarBase	http://mirtarbase.mbc.nctu.edu.tw/	Experimentally verified miRNA-target interactions	Hsu et al. 2014
starBase	http://starbase.sysu.edu.cn/	miRNA-target predictions	Li et al. 2013
miR2Disease	http://www.mir2disease.org/	Experimentally verified miRNA-target interactions and disease association	Jiang et al. 2009
miRCancer	http://mircancer.ecu.edu/	microRNA Cancer Association Database	Xie et al. 2013
TransmiR	http://www.cuilab.cn/transmir	TF-miRNA interactions	Wang et al. 2010
HMDD	http://www.cuilab.cn/hmdd	Experiment-supported evidence for human miRNA and disease associations	Li et al. 2014
microRNA.org	http://www.microrna.org/	miRNA-target interactions	Betel et al. 2008
ChIPBase	http://deepbase.sysu.edu.cn/	TF-miRNA interactions	Yang et al. 2013b
TargetScan	http://www.targetscan.org/	miRNA-target predictions based on sequence complementarity	Agarwal et al. 2015
PicTar	http://pictar.mdc-berlin.de/	miRNA-target predictions based on sequence complementarity	Chen and Rajewsky 2006
RNAhybrid	http://bibiserv.techfak.uni-bielefeld.de/rnahybrid	miRNA-target predictions based on calculations of mRNA secondary structure	Krüger and Rehmsmeier 2006
StarMir	http://sfold.wadsworth.org/	miRNA-target predictions based on calculations of mRNA secondary structure	Rennie et al. 2014
TarBase	http://diana.cslab.ece.ntua.gr/DianaToolsNew/index.php?r=tarbase	Experimentally verified miRNA-target interactions	Vergoulis et al. 2012
miRGator	http://genome.ewha.ac.kr/	miRNA expression	Cho et al. 2013
miRGen	http://www.microrna.gr/mirgen	TF-miRNA interactions	Alexiou et al. 2009
miRNApath	http://lgmb.fmrp.usp.br/mirnapath/	Pathway analyses	Chiromatzo et al. 2007
LNCipedia.org	http://lncipedia.org/	Human annotated lncRNAs	Volders et al. 2015
lncRNAdb	http://www.lncrnadb.org/	Annotated lncRNAs	Quek et al. 2014
NONCODE	http://www.noncode.org/	An integrated knowledge about non-coding RNA	Zhao et al. 2016
lncRNOme	http://genome.igib.res.in/lncRNome/	Resource about lncRNAs in Human.	Bhartiya et al. 2013
NPInter	http://www.bioinfo.org/NPInter/	Interactions between noncoding RNAs and biomolecules	Yuan et al. 2014
ChIPBase	http://deepbase.sysu.edu.cn/	TF-lncRNA/lincRNA regulatory relationships	Yang et al. 2013b
starBase	(http://starbase.sysu.edu.cn/)	lncRNA and target biomolecules interactions	Li et al. 2013
lncBase	http://diana.imis.athena-innovation.gr/	Experimental and predictive miRNA targets on lncRNAs	Paraskevopoulou et al. 2013
lncRNA2Target	http://mlg.hit.edu.cn/lncrna2target/	Resource about differentially expressed genes regulated by lncRNAs	Jiang et al. 2015
lncRNADisease	http://www.cuilab.cn/lncrnadisease	Experimentally supported lncRNA-disease and predicting novel lncRNA-disease association data	Chen et al. 2013
NRED	http://jsm-research.imb.uq.edu.au/nred	ncRNA Expression Database	Dinger et al. 2009
lncRNAtor	http://lncrnator.ewha.ac.kr/	Expression profile, interacting (binding) protein, integrated sequence curation of lncRNAs	Park et al. 2014

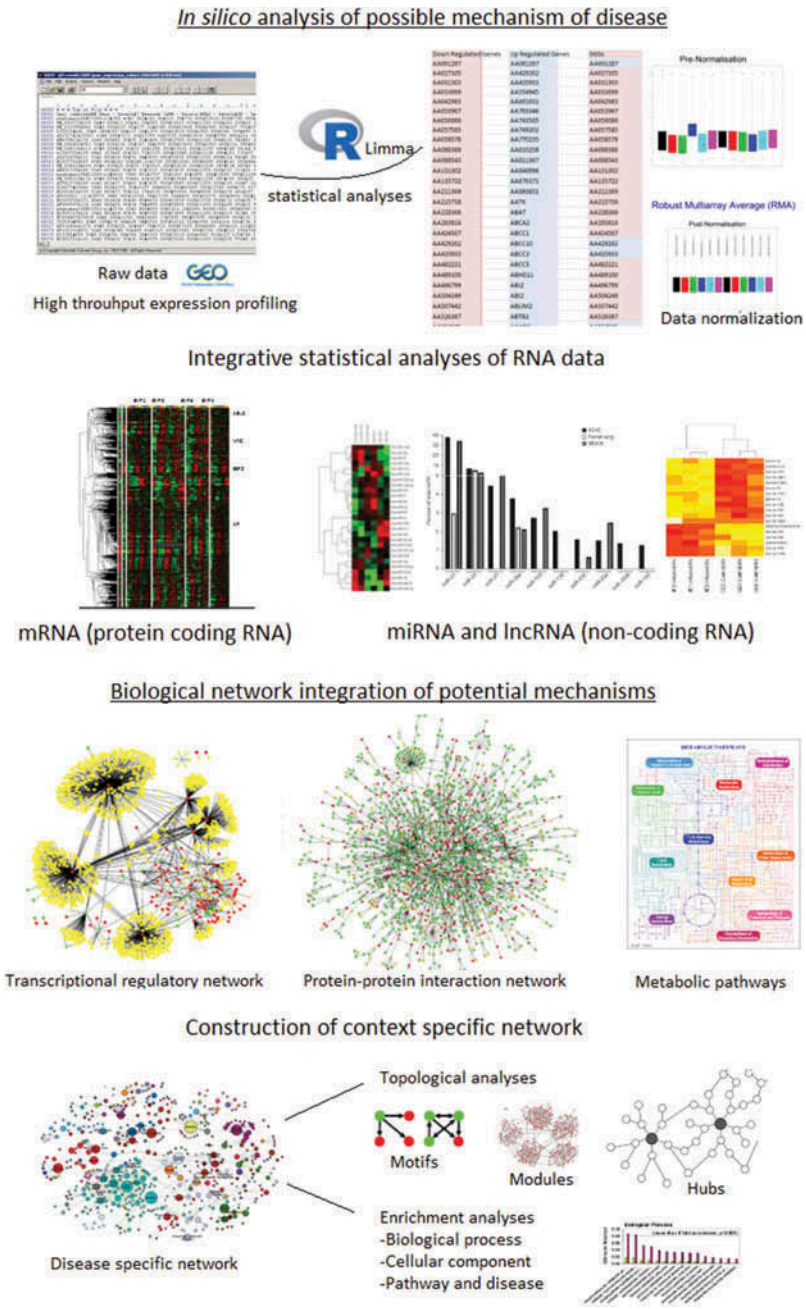

Figure 2. RNA based systems biomedicine approach to understand disease pathogenesis and identify biomarkers.

differences in their expression levels between different conditions (e.g., diseased versus healthy state). These signatures might be considered as diagnostic biomarkers, but would also be helpful in understanding the possible mechanisms of disease formation and progression through coupling with biological network models (protein–protein interaction, transcriptional regulatory, and metabolic) to decipher the active roles of these signatures and their interconnectivity in a holistic manner.

A conventional approach for the detection of diagnostic biomarkers or drug targets is to determine molecules of interest, such as disease-related genes, ncRNAs, TFs, receptors, and metabolites. For this purpose, expression profiling efforts from OvC and healthy tissues present valuable information. Moreover, analysis of the existing RNA expression datasets in a comprehensive manner, i.e., 'horizontal meta-analysis', should result in more robust findings [Karagoz et al. 2015; Calimlioglu et al. 2015; Sevimoglu and Arga 2015; Kori et al. 2016]. Datasets representing differentially expressed miRNAs and lncRNAs are very limited. New efforts, especially in total RNA sequencing, will pioneer the characterization of novel ncRNAs

associated with OvC. Analysis of pathways associated with OvC-related genes through pathway databases such as KEGG [Kanehisa and Goto 2000], Reactome [Croft et al. 2010], GAD [Becker et al. 2004], and gene set enrichment analyses (GSEA) through gene ontology annotations [Ashburner et al. 2000] or Cluster of Orthologous Group categories using bioinformatics tools such as DAVID [Huang et al. 2007], AmiGO [Carbon et al. 2009], and WebGestalt [Wang et al. 2013] will provide invaluable information on the molecular mechanisms (protein complexes, pathways, biological processes, etc.) underlying OvC. In translating molecular findings from high-throughput data to clinical relevance, disease enrichment analysis (DEA) is an important tool [Huang et al. 2009; LePendu et al. 2011]. Coupled with GSEA, DEA provides disease associations of DEGs, which allows biologists to verify disease relevance in a biological experiment and identify unexpected disease associations. Very recently, the association of OvC with other cancers, especially colorectal and bladder and pancreatic cancers, was discovered in this manner [Kori et al. 2016].

Biological network models are necessary to understand the underlying formation and progression mechanisms of human diseases. Several genome-scale models simulating the generic metabolic network, the protein–protein interactome, and the transcriptional regulatory network have already been reviewed in the literature. However, these models are limited in their capability to represent the behavior of the human cell and are still evolving. Among those, metabolic models take the lead. Genome-scale reconstructions of metabolic networks (Recon1, Recon2, HMR, HMR 2.0, etc.), which simulate the generic human cell, were performed [Duarte et al. 2007; Shlomi et al. 2008; Bordbar et al. 2011; Thiele et al. 2013]. These models include information about biochemical transformations (stoichiometry, reversibility, etc.) together with gene-protein (enzyme)-reaction (metabolite) associations. In addition, considering the genomic and proteomic alterations between different tissues, tissue-specific metabolic networks were also constituted [Wang et al. 2012; Uhlen et al. 2015]. These models were implemented in various diseases, such as obesity [Mardinoglu et al. 2013], non-alcoholic fatty liver disease [Mardinoglu et al. 2014], type 2 diabetes [Calimlioglu et al. 2015], ovarian diseases [Kori et al. 2016] and oesophageal squamous cell carcinoma (ESCC) [Karagoz et al. 2016a], to map metabolic responses and to identify reporter metabolites [Patil and Nielsen 2005; Garcia-Albornoz et al. 2014], which can be considered as potential biomarkers and therapeutic targets. Since protein–protein interactions are a fundamental, integral component in the road to the comprehension of the much tangled biological systems, models representing protein–protein interaction networks have an important role in systems biomedicine [Sevimoglu and Arga 2014]. Systems biomedicine makes use of interactome networks to better our understanding of the 'chaotically' organized proteins so as to make inferences about disease networks that will ideally motivate us in the interpretation of their biological functions, and the determination of disease-associated proteins and their subnetworks. The massive amount of interactome data obtained from high-throughput experiments is collected, integrated, and stored in various PPI databases, such as BIND [Bader et al. 2003], HomoMINT [Persico et al. 2005], BioGRID [Chatr-Aryamontri et al. 2015], HIPPIE [Schaefer et al. 2012], STRING [Szklarczyk et al. 2015], and HPRD [Prasad et al. 2009]. In addition, several efforts have been performed to increase the reliability of the models [Kamburov et al. 2012; Lopez et al. 2015; Karagoz et al. 2016b]. These models were integrated with disease datasets (i.e., transcriptome and proteome data) to elucidate the active subnetworks and pathways under disease conditions, and to determine potential biomarkers and therapeutic targets at the protein level in various cases, such as Triple Negative Breast Cancer [Karagoz et al. 2015], type 2 diabetes [Calimlioglu et al. 2015], psoriasis [Sevimoglu and Arga 2015], ESCC [Karagoz et al. 2016a], ovarian diseases [Kori et al. 2016], hepatocellular carcinoma [Budhu et al. 2013], colorectal cancer [Li et al. 2012], and pancreatic cancer [Frampton et al. 2014]. Furthermore, transcriptional regulation of gene expression provides substantial information that correlates genome on protein–DNA interactions required for a given response due to environmental and genetic alterations . Numerous transcriptional regulatory networks have been reconstructed in the literature using various miRNAs, TFs, and their target gene interactions (Table 3), which were obtained by either computational techniques or experimental studies [Qiu et al. 2010; Yu et al. 2012b; Sengupta and Bandyopadhyay 2013; Gov and Arga 2016]. Integration of disease-associated gene expression datasets with the reconstructed transcriptional regulatory network allows us to understand the transcriptional regulatory mechanisms behind the cellular response in the diseased state. Employment of these network models in OvC research would be helpful in understanding the possible mechanisms of OvC formation and progression, as well as presenting potential biomarkers for early diagnosis and novel therapeutic targets for treatment.

The clinical studies on several biomarker candidates that were predicted through systems-based analyses exhibited their high potential in early detection of OvC. For instance, Palmer et al. [2008] selected 14 candidate blood markers of serous OvC, predicted

through gene expression profiling, and evaluated their performance individually and in combination across histological types of epithelial OvC based on sensitivity at high specificity concept. They identified a set of serum markers with adequate performance in identification of OvC survival prior to clinical diagnosis. In another study, the efficacy of three proteomic biomarker candidates, predicted through mass spectrometry based proteomics analysis, was assessed, and a biomarker panel that may significantly improve early detection of OvC was developed [Su et al. 2007]. More recently, Duffy and colleagues [2015] reviewed the main steps in advancing a newly discovered cancer candidate biomarker from pilot studies to clinical application.

An inspirational and descriptive example on how genome-wide and systems-based studies improved development of efficient therapeutic strategies in OvC was presented very recently [Schoeberl et al. 2017]. They summarized their decade-long effort in development of a new therapeutic agent (seribantumab), and emphisized the role of systems biology principles through the discovery process. They started with screening the molecular pathways through high-throughput transcriptome and interactome datasets to identify molecules critically involved in ligand-mediated cancer cell survival. Their efforts highlighted the ErbB network, and computational models predicted ErbB3 as a potential target, which is involved in mediating pro-survival signaling. Modeling was further used to support dose selection and to identify candidate biomarkers for ErbB3 activation, and clinical trials were designed to test and refine their hypotheses. So, they illustrated how systems-level investigations coupled with computational modeling were used to guide the development process of seribantumab as a drug in platinum-resistant OvC.

Current perspective

Improvement in the diagnosis and development of novel and effective treatment strategies for complex pathophysiologies, such as cancers, requires understanding of the generation and progression mechanisms. RNA-level analyses generate new information that can help in understanding the mechanisms behind disease pathogenesis, to identify new biomarkers and therapeutic targets, and to enable drug discovery.

Whole RNA sequencing, coding and non-coding RNA expression array datasets have been used to illuminate the mechanisms of disease processes, and have identified mRNAs, miRNAs, and lncRNAs associated with OvC progression. In addition, these individual efforts have shown that various signaling pathways and biological processes are associated with OvC. Besides the heterogeneity of OvC tissue in/with respect to cancer grade and or subgroup, the gender and/or individual difference of human samples at the genome level provides challenges in data evaluation. Additionally, low overlap in transcriptomics and proteomics results from different experimental studies emphasizes the crucial role of transcriptional and post-transcriptional control mechanisms as well as epigenetic regulations.

All these findings provide evidence for the importance of integrative approaches within the systems biomedicine concept in future OvC research. Integration of total RNA-seq datasets (coupled with data from other omics level analyses) with biological network models will provide molecular signatures, which may be used for screening or therapeutic purposes and the development of bioinformatics tools for integrative analyses, and will be beneficial for understanding etiopathogenesis and biological mechanisms of OvC.

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Notes on contributors

Overall outline of review: EG, KYA; Literature search and writing: EG, MK; Supervision, critical review, and proofreading: KYA; Revision: EG, MK, KYA. All authors approved the final version of the manuscript.

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