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## 2 **Insight on non-coding RNAs from biofluids in ovarian tumors**

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14 **Simple summary:** Ovarian cancer is the most lethal gynecologic cancer since often diagnosed at  
15 advances stages. Current tools for diagnosis are currently insufficient and include physical exami-  
16 nation, ultrasound and pelvic magnetic resonance imaging as well as algorithm combining  
17 thoraco-abdomino-pelvic scans and blood markers. In this context, there is a need for new tools  
18 not only to assess the diagnosis but also to predict response to chemotherapy and detect recur-  
19 rences. Previous studies have highlighted the potential value of non-coding RNAs (ncRNA) in tis-  
20 sue samples, but rarely in biofluids. In this review, we aimed to summarize the literature existing  
21 on ncRNAs and ovarian tumors in biofluids. Most studies focused on serum and blood with no  
22 data in other biofluids and with few ncRNAs investigated using qRT-PCR or microarray, not per-  
23 mitting reflecting the heterogeneity of ovarian cancers.

24 **Abstract:** Ovarian tumors are the most frequent raising diagnostic and therapeutic issues linked to  
25 a large spectrum of tumors with a continuum from benign to malignant tumors. So far, none of the  
26 available diagnostic tools have proven efficient to decide strategy and no consensus exists on the  
27 best strategy between ‘single test’, ‘dual testing’, ‘sequential testing’, ‘multiple testing options’ and  
28 ‘no testing’. In addition, there is a need of prognostic tool such as biological markers of recurrence  
29 and theragnostic tools to detect non-responding women to chemotherapy to adapt therapies. Non-  
30 coding non-coding RNAs are classified in small or long based on their nucleotides count. Non-  
31 coding RNAs have multiple biological functions such as a role in tumorigenesis, gene regulation  
32 and genome protection. These ncRNAs emerge as new potential tools to differentiate benign from  
33 malignant tumours and to evaluate prognostic and theragnostic factors. In the specific setting of  
34 ovarian tumors, the goal of the present work is to offer an insight on the contribution of biofluid  
35 non-coding RNAs (ncRNA) expression.

36 **Keywords:** Ovarian tumor; non-coding RNA; borderline ovarian tumor; ovarian cancer  
37

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### 38 **1. Introduction**

39 Adnexal masses represent a wide spectrum of tumors of various origins (ovary, fal-  
40 lopian tube, and pelvic organs), among them ovarian tumors are the most frequent rais-  
41 ing diagnostic and therapeutic issues linked to a large spectrum of tumors with a con-  
42 tinuum from benign to malignant tumors. The true incidence of ovarian tumors in the  
43 general population is unknown as most of them are asymptomatic hence undiagnosed  
44 [1]. It is estimated that 10% of women will undergo surgery for an ovarian mass in their  
45 lifetime [2].

46 Ovarian tumors are generally detected at physical examination or at pelvic imaging  
47 for various reasons in asymptomatic patients. Less frequently, an ovarian tumor can be

48 source of symptoms, acute pain (torsion of the adnexa), or chronic pelvic pain related to  
49 compression of neighboring organs [1]. Sometimes, the diagnosis can be made in the  
50 context of ovarian cancer (OC) often diagnosed at an advanced stage faced to ascites,  
51 bloating, weight loss with peritoneal carcinomatosis [3,4].

52 OC is the fifth cancer and the most lethal gynecologic malignancy with 313,959 new  
53 cases per year and 207,252 death per year in 2020 [5]. Epithelial ovarian cancer (EOC)  
54 represents more than 95% of all OC [6]. During their lifetime, approximately one in sev-  
55 enty women will develop the disease. The median age at diagnosis is 68 years with a  
56 maximum incidence in women in their 70s. The disease behaves as a chronic condition  
57 with relapses and therefore iterative chemotherapies which lengthen survival [7]. The  
58 disease survival remains poor of 40% at 5 years and 32% at 10 years as more than 75% of  
59 patients are diagnosed at advanced stage disease while the 5-year survival rate for  
60 women diagnosed at an early stage reaches 90% underlining the potential benefit of bi-  
61 omarkers of early stages as well as to detect the transition of borderline tumor into inva-  
62 sive cancer [5].

63 Except from patients with deleterious mutation for whom a risk reducing surgery is  
64 recommended, no screening of OC in the general population has proved its relevance  
65 [8]. In routine practice, first line transvaginal ultrasound is used to differentiate benign,  
66 borderline or malignant ovarian tumors [9]. Van Calster et al, evaluating the clinical util-  
67 ity of six prediction models for ovarian malignancy [10], found that the ADNEX models  
68 with and without cancer antigen 125 (CA125) determination and SRRisk were the best  
69 calibrated. However, previous studies have underlined that 18% to 31% of ovarian tu-  
70 mors remain indeterminate after ultrasonography using International Ovarian Tumor  
71 Analysis (IOTA) Simple Rules or other ultrasonography scoring systems [9,11,12]. MRI  
72 is the second line imaging technique to characterize ovarian tumors. Ovarian-Adnexal  
73 Reporting Data System Magnetic Resonance Imaging (O-RADS MRI) score consists of 5  
74 categories according to the positive likelihood ratio for a malignant neoplasm [13] with a  
75 sensitivity of 0.93 and a specificity of 0.91. However, these results were based on an ob-  
76 servational study without randomization, and the score was not integrated into clinical  
77 decision-making limiting its utility.

78 CA125 is the most used biomarker to determine the nature of ovarian tumors  
79 [14,15] although normal levels has been reported in as high as 50% of early stages ovar-  
80 ian cancers [16] [17,18]. A recent Cochrane review has evaluated several algorithms to as-  
81 sess the risk of malignancy of ovarian tumors, including biological markers and imaging  
82 [19]. However, none of these scoring systems had a sufficient relevance to characterize  
83 ovarian tumors [19].

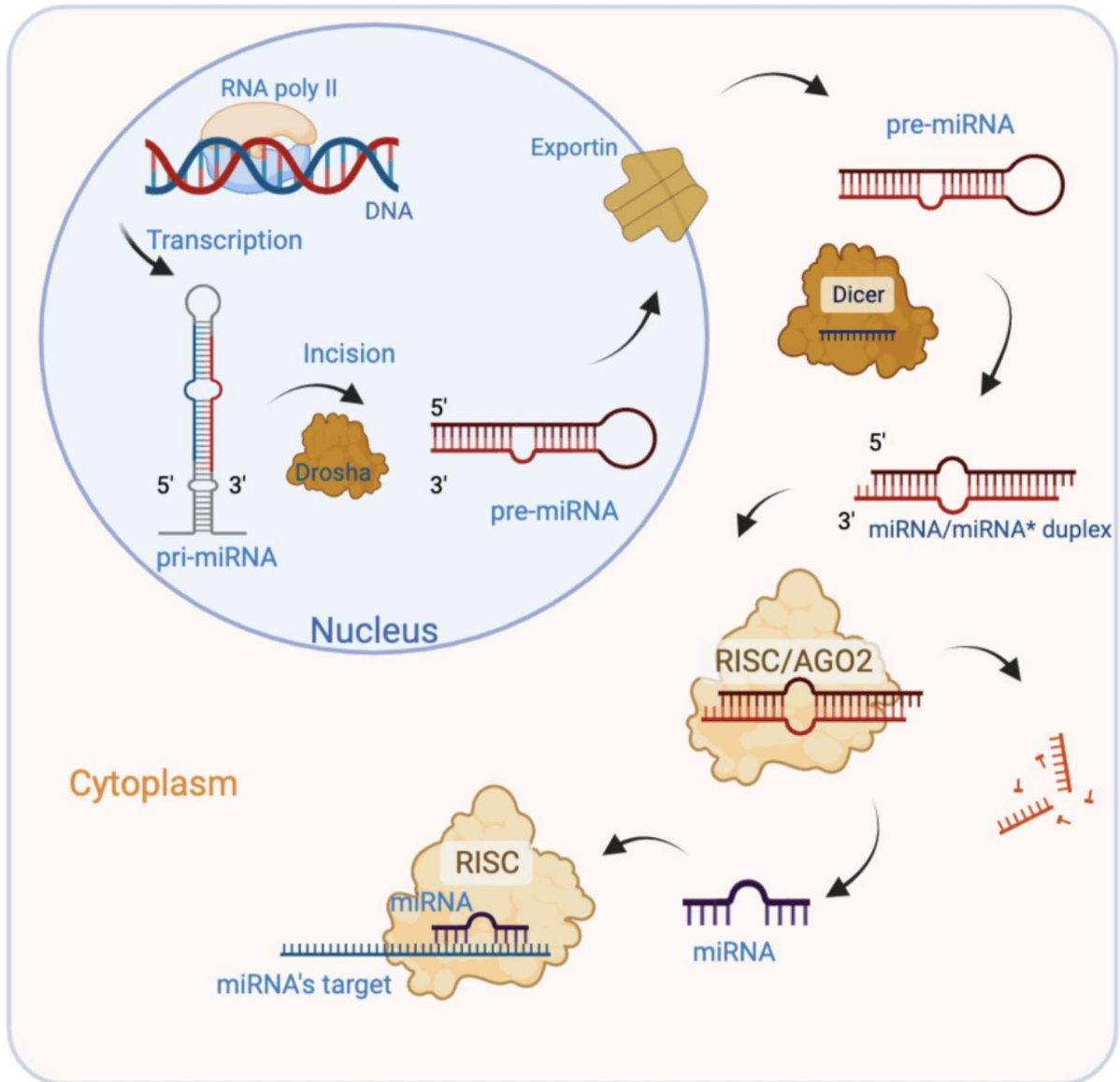
84 Finally, a recent review of Funston et al analyzing 18 documents from 11 countries  
85 showed that transabdominal/transvaginal ultrasound and the CA125 were the most  
86 widely advocated as initial tests [20]. However, no consensus exists on the best strategy  
87 to improve diagnostic performance: 'single test', 'dual testing', 'sequential testing', 'mul-  
88 tiple testing options' and 'no testing'. This further underlines the need for new biological  
89 tools to diagnose ovarian cancer in the general population as early as possible. In addi-  
90 tion, there is a need of prognostic tool such as biological markers of recurrence and  
91 theragnostic tools to detect non-responding women to chemotherapy to adapt therapies.

92  
93 Among ncRNAs, those with less than 50 nucleotides are defined as small RNAs  
94 (sncRNAs) and those with more than 200 nucleotides are defined as long non-coding  
95 RNAs (lncRNAs). SncRNAs are further classified into microRNAs (miRNAs), Piwi in-  
96 teracting RNAs (piRNAs), transfer RNAs (tRNAs), small nuclear RNAs (snRNAs), and  
97 small interfering RNAs (siRNAs) [21,22]. LncRNAs are classified into intergenic ncRNAs  
98 (lincRNAs), some circular RNAs (circRNAs), and ribosomal RNAs (rRNAs) [23,24].  
99 Numerous studies indicate that ncRNAs, representing 98% of the transcriptome, are es-  
100 sential for tumorigenesis by regulating the expression of tumour-related genes [25–32].  
101 These ncRNAs emerge as new potential tools to differentiate benign from malignant tu-  
102 mours and to evaluate prognostic and theragnostic factors. In the specific setting of

ovarian tumors, the goal of the present work was to offer an insight on the contribution of biofluid non-coding RNAs (ncRNA) expression.

## 2. miRNAs

miRNAs are small intracellular RNAs, 22 nucleotides long, capable of inducing the silencing of gene expression by post-transcriptional regulatory mechanisms [33] or alternatively by binding miRNAs to the 5'UTR regions inducing either activation or repression of translation. The miRNAs synthesis is presented in Figure 1.



**Figure 1.** miRNAs synthesis. Biogenesis of miRNAs is a multistep process, beginning with the transcription of primary miRNAs (pri-miRNAs) by RNA polymerase II. The pri-miRNAs are transformed into precursor miRNAs (pre-miRNAs, 70 nucleotides long) by the RNase III Drosha-DGCR8-DDX5 microprocessor complex, and are then exported to the cytoplasm by Exportin (a Ran-GFP-dependent transporter). In the cytoplasm, pre-miRNAs are cleaved by the RNase Dicer-TAR RNA-binding protein (TRBP) complex, producing mature miRNA. Not all miRNAs pass through the canonical miRNA biogenesis pathway. Special miRNAs called mirtrons are produced from spliced introns with structural features like pre-miRNAs and undergo a miRNA processing pathway that bypasses the Drosha-mediated cleavage step.

Numerous studies focusing on tissue samples have demonstrated the role of miRNA in OC characterized by a wide-scale deregulation of miRNAs, and aberrant ex-

pression of miRNAs correlated with histotype, histological grade, lymphovascular space involvement, lymph node and distant metastasis as well as FIGO stages [34–37]. Dhar Dwivedi et al reported 53 miRNAs upregulated, and 68 miRNAs downregulated in OC. In the upregulated miRNAs group, a total of 7605 gene target were found. Among them, miRNA-20a-5p and miRNA 106a-5p regulate 14.1% and 9.4% of target genes, respectively. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis enrichment was performed for these upregulated miRNAs targets genes identifying 67 and 24 pathways as enriched. Similarly for downregulated miRNAs, a total of 9287 gene targets were identified. miR-26b-5p, miR-519d, miR-15a, and miR-15b regulated respectively 20.8%, 11.3%, 8.6%, and 8.9% of the target genes with 41, 95, and 38 enriched pathways [38].

In contrast to miRNAs expression extensively analyzed in tissue samples, relatively little data are available on their expression in biofluids. This point is particularly important as it could allow preoperative tumor assessment, improving therapeutic strategy and share making decisions. There are published evidences that serum miR-221 [39], mir-205 [40], mir-375 [41], mir-210 [42], mir-34a-5p [43], mir-92 [44], mir-93 [45], mir-141 [46] mir-7 [47] and mir-429 [48] are upregulated in biofluids of patients with different types of ovarian cancers. On the other hand expression of microRNAs let-7f [49], mir-93 [46], mir-199a [50] and mir-148a [51] is downregulated in biofluids of patients with ovarian tumours.

From the diagnostic point of view, Oliveira et al [52] evaluated the profile of plasma miRNAs on a panel of 46 candidates finding 4 upregulated miRNAs (miR-200c-3p, miR-221-3p, miR-21- 5p and miR-484) and two downregulated (miRNA-195-5p and miRNA-451a). However, only 2 miRNAs (miRNA-200c-3p and miRNA-221-3p) were confirmed in a validation cohort. Savolainen et al [53], on a short series of 9 patients, found that miRNA-200a, miRNA-200b and miRNA-200c both in tumor tissue and plasma allowed discrimination between malignant and benign samples. In addition, a correlation was found between the expression of miRNA-200 in urine and plasma with the malignant status of tumors. Another study reported a higher level of miR-590-3p in OC plasma compared to a control group [54], Chang et al [55] observed for germ cell tumors of the ovary (OGCT) and sex cord (SCST) specific expression profiles of miRNAs in 9 OGCTs (2 malignant and 7 benign) and 3 SCST. Overexpression of miRNA-373-3p, miRNA-372-3p and miRNA-302c-3p and underexpression of miRNA-199a-5p, miRNA-214-5p and miRNA-202-3p were reproducibly observed in malignant OGCT versus benign OGCT or SCST. Yokoi et al reported a plasma signature composed of 6 miRNAs selected after RT-qPCR (miRNA-200a-3p, miRNA-766-3p, miRNA-26a-5p, miRNA-142-3p, let-7d-5p and miRNA-328 -3p) able to successfully distinguish patients with ovarian cancer from healthy controls (AUC: 0.97; sensitivity, 0.92; and specificity, 0.91) paving the way for screening ovarian cancer [56]. Among five miRNAs, Zhu et al observed that only serum miRNA-125b could distinguish benign controls and EOC patients [57]. Moreover, among miR-200 family, Meng et al [58] identified that serum levels of miRNA-200a (p=0.0001), miRNA-200b (p=0.0001), and miRNA-200c (p=0.019) could distinguish benign from malignant ovarian tumors. Resnick et al [59], confirmed that miRNAs in serum could be used as a marker for ovarian cancer in a series of 28 patients based on over-expression of miRNA-21, miRNA-92, miRNA -29a, miRNA-93 and miRNA-126, and underexpression of miRNA-99b, miRNA-127 and miRNA-155. In a meta-analysis on the diagnostic value of serum miRNA-21 expression, including 6 studies with limited sample size, Qiu & Weng reported a pooled respective sensitivity, specificity, and AUC of 0.81 (95%CI: 0.73–0.88), 0.82 (95%CI: 0.75–0.87), and 0.89 (95%CI: 0.85–0.91) imposing further validation [60]. Recently, Wenyu Wang developed a plasma signature for malignant tumors using extracellular vesicle and identified a panel of eight miRNAs (miR-1246, miR-1290, miR-483, miR-429, miR-34b-3p, miR-34c-5p, miR-145-5p, miR-449a). Their model had a respective AUC of 0.9762 and 0.9375 in the training and the validation set [61]. In contrast to several studies focusing on serum miRNAs, Kai Berner et al

177 focused on urinary expression of twelve microRNAs. In their experience, miR-15a was  
178 upregulated whereas let-7a was down-regulated in ovarian cancer patients [62].

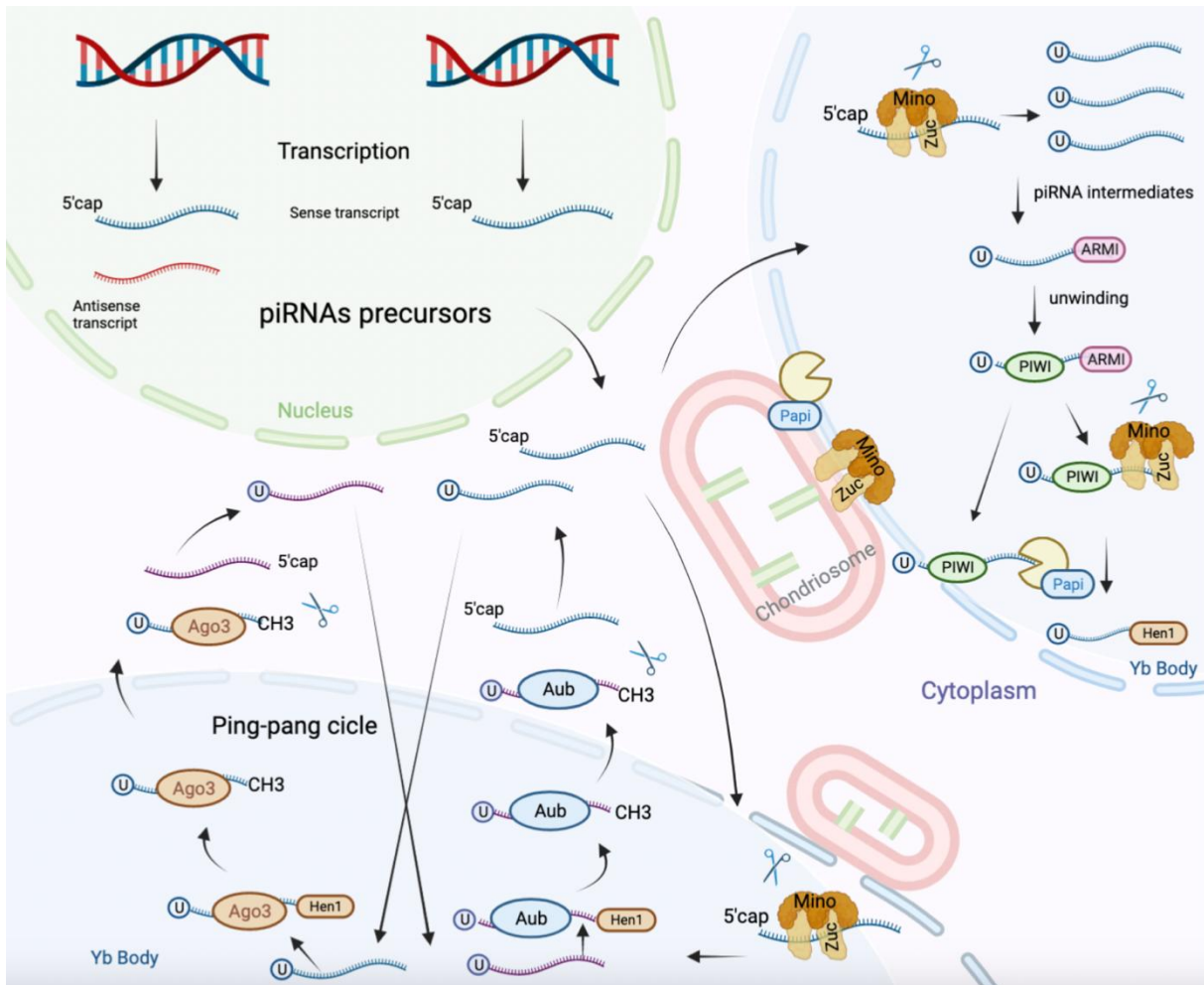
179 From the prognostic point of view, Zhu et al [57] found that elevated serum  
180 miRNA-125b levels were higher in patients with early OC stages (FIGO stages I-II), and  
181 with no residual tumor after surgery. In addition, elevated serum miR-125b were corre-  
182 lated with progression-free survival ( $p = 0.035$ ). Meng et al reported high levels of  
183 miRNA-200b and miR-200c were associated with poorer overall survival ( $p=0.007$ ,  
184  $p=0.017$ , respectively) [58]. Gao et al. [63] including 74 serum samples of OC patients, 19  
185 of borderline tumors and 50 of healthy controls, found that elevated serum miRNA-200c  
186 were correlated with improved two-year survival while decreased serum miR-145 levels  
187 was associated with disease progression [64]. Finally, Zuberi et al. observed in OC an as-  
188 sociation between high expression of serum miR-125b and lymph node and distant me-  
189 tastases[65].

190 From the theragnostic point of view, most studies are based on cell cultures [66,67].  
191 Yang et al [68] found that protein kinase B (AKT) pathway activation was regulated by  
192 miRNA-214 and miRNA-150. Moreover, Echevarria-Vargas et al reported a cisplatin re-  
193 sistance associated with miR-21 expression [69]. Lu et al [70] observed that let-7a expres-  
194 sion was significantly lower in OC patients sensitive to platinum and paclitaxel com-  
195 pared to those resistant to these agents. Langhe et al reported a panel of 4 miRNAs (let-  
196 7i-5p, miRNA-122, miRNA-152-5p and miRNA-25-3p) significantly down-regulated in  
197 OC with potential contribution to drug resistance [71]. Finally, in a recent review, Saburi  
198 et al [72] noted a relation between miRNA-30a-5p, miRNA-34a, miRNA-34a-5p, miRNA-  
199 98-5p, miRNA-142-5p, miRNA-338-3p, miRNA-708 and cisplatin resistance. Similarly, a  
200 relation was noted between miRNA -136, miRNA-338-5p, miRNA-503-5p, miRNA-1246,  
201 miRNA-1307 and paclitaxel resistance. Finally, a relation was noted between  
202 miRNA509-3p and platinum resistance and between miRNA-744-5p and carboplatin re-  
203 sistance. However, it is important to note that none of these miRNAs have been evaluat-  
204 ed in biofluids while this could be a major contributor to adapt chemotherapy.

205 From the analysis of the literature on miRNAs in biofluids, it appears that there are  
206 arguments to suggest their role in physiopathology, in the differential diagnosis between  
207 benign and malignant tumors and to a lesser degree with borderline tumors as well as to  
208 support their diagnostic, prognostic and theragnostic values. However, these analyses  
209 were mainly performed by microarray with validation by RT-qPCR with potential biases  
210 linked to the methodology as proven in the context of endometriosis [73]. Moreover,  
211 the small number of studies with limited sample size focusing on the specific evaluation  
212 of miRNAs expression in biofluids of patients with ovarian tumors limit their potential  
213 clinical utility. Indeed, Langhe et al [71] pointed out that miRNAs are abundant in tis-  
214 sues but often rare in plasma and serum. For the quantification of miRNAs in plasma,  
215 the authors stressed that it was essential to use a high-sensitivity platform such as Next  
216 Generation Sequencing (NGS). However, no study using NGS and bioinformatic tools to  
217 analyze miRNA content in large blood, serum, urine or saliva series are available to de-  
218 termine their role in routine practice.

### 219 3. PiRNAs

220 piRNAs are small ncRNAs of 24 - 32 nucleotides [74]. piRNA biosynthesis is sum-  
221 marized in Figure 2 [74,75]. Dysregulation of piRNAs and proteins (e.g. PIWI family  
222 proteins) has been observed in various cancers including OC [75,76]. The main function  
223 of piRNAs is to protect the genome from transposons. Giulio Ferrero et al analyzing  
224 piRNA expression in urine, plasma exosomes, and stool observed that urine samples ex-  
225 hibited the highest piRNAs expression [77]. The piRNAs production and function are  
226 presented in Figure 2.



**Figure 2**: piRNAs synthesis and function. Mature piRNAs are generated from the processing of single-stranded RNAs transcribed from piRNA clusters in the genome representing the largest class of non-coding RNAs found in most species. piRNAs can be also generated in the cytoplasm by a mechanism called the "ping-pong" cycle involving piRNA-directed antisense primary cleavage of transposon transcripts by Aubergine and PIWI proteins. piRNAs can modulate histone modifications and DNA methylation in a sequence-specific manner, leading to alterations in chromosomal conformation and gene expression regulation.

Singh et al. [78] found that piRNAs distinguish endometrioid from serous OC with 159 and 143 piRNAs differentially expressed, respectively. Among these piRNAs, 74 were upregulated and 77 down-regulated in endometrioid OC, and 56 upregulated and 81 downregulated in serous OC. piR-52,207 was found to be upregulated in endometrioid OC, and both piR-52,207 and piR-33,733 in serous. Interestingly, among 20 biofluids evaluated by Hulstaert et al [79], saliva has the highest fraction of piRNAs. So far, in the specific setting of OC, little data are available on piRNA expression in blood sample allowing to evaluate their potential diagnostic and prognostic value and no study has evaluated saliva piRNA expression.

#### 4. Transfer-RNAs (tRNAs)

Transfer RNAs (tRNAs) are a source of small regulatory RNAs (tsRNAs) acting on protein translation [38,80]. Based on the cleavage site, tsRNAs are divided into transfer RNA-derived RNA fragments (tRFs) and tiRNAs [81] with tumorigenesis functions [82–86] [87,88]. tRFs are also involved in gene expression, oncogene activation and ovarian cancer progression through association with Ago and PIWI proteins [89].

Dhar Dwivedi et al. [38] observed that tsRNAs can predict abnormal cell proliferation with high accuracy in serum samples from a cohort of patients healthy controls and

benign and malignant tumors [90]. Eric Y. Peng observed that four tsncRNAs differentially expressed in serum samples had a high diagnostic accuracy for malignancy with an AUC of 0.95. Similarly, serum tRF-03357 and tRF-03358 levels are increased in patients with high-grade OC [91,92]. In addition, i-tRF-GlyGCC is linked to advanced FIGO stages, suboptimal debulking and most importantly with early progression and poor overall survival in EOC patients [92].

Despite, a relative abundant literature on tRNA, no study has focused on their diagnostic, prognostic and theragnostic relevance in the specific setting of OC

### 5. Circular RNAs (CircRNAs)

CircRNAs are a large class of ncRNA with more than 70,000 specimen identified in human tissues [93–99] and in many cancerous cell types including OC [95,100–102]. circRNAs have a high prevalence, specificity [103,104], stability [105] and conservation [106] conferring a particular value as biomarkers. Moreover, using 20 biofluids, Hulstaert et al demonstrated that circRNAs are enriched in biofluids compared to tissues [79]. Indeed, the median circRNA read fraction in biofluids was 84.4% vs 17.5% in tissues. circRNAs act as specific miRNA reservoirs or sponges, as protein or peptide translators, as regulators of gene transcription and expression and interact with RNA-binding proteins (RBPs) impacting on transcription and translation of genes.

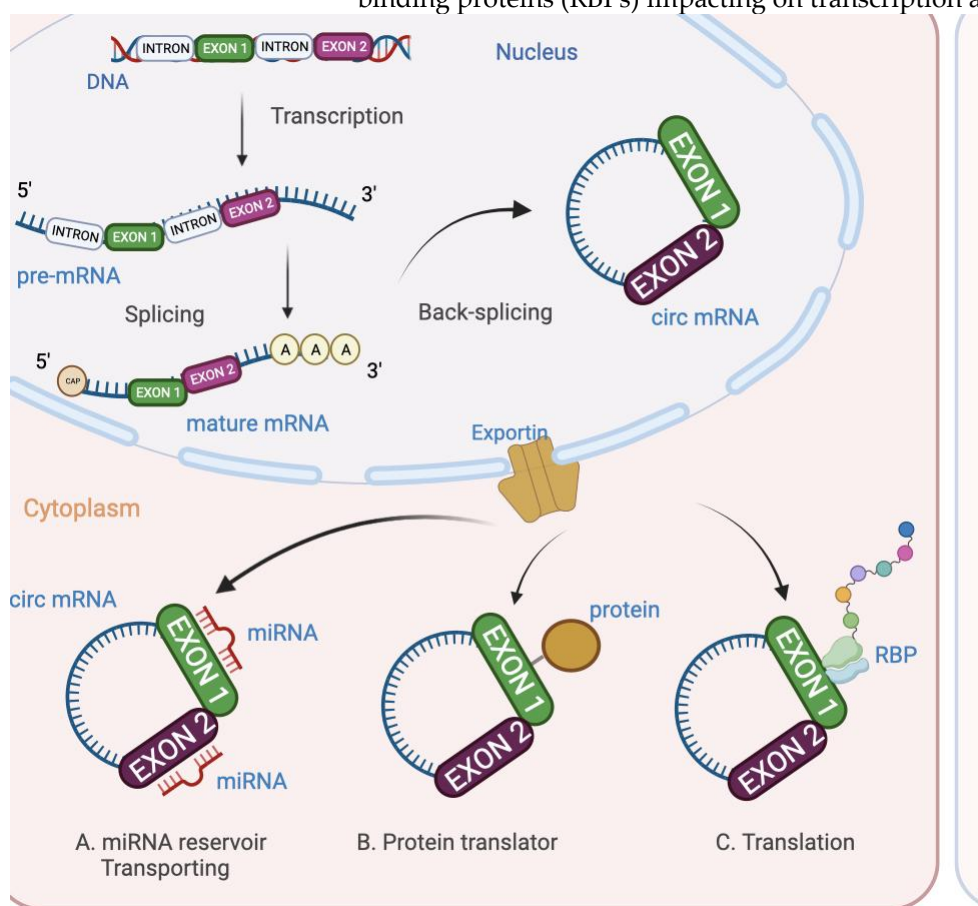


Figure 3: CircRNAs Biosynthesis. Biosynthesis of circular RNA (circ-RNA) are expressed from mostly protein-coding genes. It is a multistep process, first the transcription of pre messengerRNA (mRNA), second splicing into mature mRNA then back-splicing into circ-RNA.

Circ-RNA are then exported to the cytoplasm to A. act as micro RNA (miRNA) reservoir or transport miRNA; B. act as protein or peptide translators; C. Interact with RNA-binding proteins (RBPs) for transcription or translation of genes.



278 From the diagnostic point of view, in serum of OC patients, Wang et al. identified 5  
279 circRNAs (circ-0002711; Chr5:170610175-170632616+; circ-0001756; Chr4:147227078-  
280 147230127-; and Chr16:53,175091-53191453+) with diagnostic value [107].

281 From the prognostic point of view, a previous study demonstrated that serum circ-  
282 0049116 released from a cell surface protein (mucin 16) could have a value [108]. In-  
283 creased expression of the circ-MUC16/miR-199a-5p axis positively correlates with ag-  
284 gressiveness of OC. Expressions of circ-FAM35b, circ-051239, circ-ABCB10, circ-0072995,  
285 circ-EEF2, circ-RAB11FIP1, circ-FGFR3, circ-NOLC1 and circ-PGAM1 were correlated  
286 with metastasis of EOC [109–116]. Moreover, circ-0015756, circ-0002711, hsa-circ-  
287 0015326, circ-0001068, circ-0025033 and circ-KIF4A exhibited prognostic value in OC  
288 [117–120]. Serum circ-SETDB1 is positively correlated with lymph node metastasis and  
289 advanced stages of serous OC [121].

290 From the theragnostic point of view, circ-0002711/miR-1244/ ROCK1 and has-circ-  
291 0015326/miR-127-3p/MYB pathways could be potential therapeutic targets [118].  
292 CircRNAs, has-circ-0000714, circ-TNPO3 and circ-NRIP1 are expressed in OC with  
293 Paclitaxel resistance [122–124]. You et al also reported that Circ-0063804 promoted OC  
294 cells proliferation and resistance to cisplatin by enhancing CLU expression via sponging  
295 miR-1276 [125]. In a recent review, Min Liu et al [126] reported the different implications  
296 of circ-RNAs in the pathogenesis of OC and underlined that circRNA-Cdr1as inhibited  
297 OC cell proliferation and promoted cisplatin-induced cell apoptosis while circRNA-  
298 TNPO3 enhanced paclitaxel resistance. Despite the potential contribution of these circ-  
299 RNAs to the diagnostic, prognostic and theragnostic value in patients with OC, no study  
300 has focused on these biomarkers in biofluids in this specific setting.

## 301 6. Small nucleolar RNAs (snoRNAs)

302 Small nucleolar RNAs (snoRNAs) are a class of non-coding RNAs with 60–300 nu-  
303 cleotides, and mainly divided into two classes: C/D box SnoRNAs and H/ACA box  
304 SnoRNAs [127]. Most snoRNAs act as guide RNAs for the post-transcriptional modifica-  
305 tion of ribosomal RNAs by modifying 2'-O-ribose methylation and pseudo-uridylation  
306 of ribosomal RNAs (rRNAs) [126]. Cumulative evidence demonstrated that snoRNAs  
307 play a role in tumorigenesis of various cancer [128–131]. Using microarray on 197 EOC  
308 (162 serous, 15 endometrioid, 11 mucinous, and 9 clear cell), Oliveira et al found that  
309 SNORA68 and SNORD74 were associated with decreased overall survival (OS) and poor  
310 clinicopathological features [132]. In an *in vitro* study Huilong Lin et al. observed that  
311 SNHG5 enhanced the sensitivity of ovarian cancer cells to paclitaxel by sponging miR-  
312 23a [133]. Wenjing Zhu et al developed a signature based on nine snoRNAs (SNORD126,  
313 SNORA70J, SNORD3C, SNORA75B, SNORA58, SNORA11B, SNORA36C, SNORD105B,  
314 SNORD89,) to predict prognosis of OC patients [134]. Finally, Peng-Fei Zhang et al re-  
315 ported that SNHG22 overexpression was associated with poor prognosis and induces  
316 chemotherapy resistance to cisplatin and paclitaxel via the miR-2467/Gal-1 signaling  
317 pathway in EOC [135]. Although the number of dysregulated snoRNAs in ovarian can-  
318 cer is up to 462 [128], one preliminary study investigated the role of snoRNA RNU2-1f in  
319 ovarian cancer. In this study, snoRNA abundance was investigated in serum (n = 10) by  
320 microarray analysis and validated in a serum set (n = 119) by reverse-transcription quan-  
321 titative PCR. They reported abundance of U2-1 snoRNA fragment (RNU2-1f) was signifi-  
322 cantly increased in sera of ovarian cancer patients (P < 0.0001) and paralleled Interna-  
323 tional Federation of Gynecology and Obstetrics stage as well as residual tumor burden  
324 after surgery (P < 0.0001 and P = 0.011, respectively).

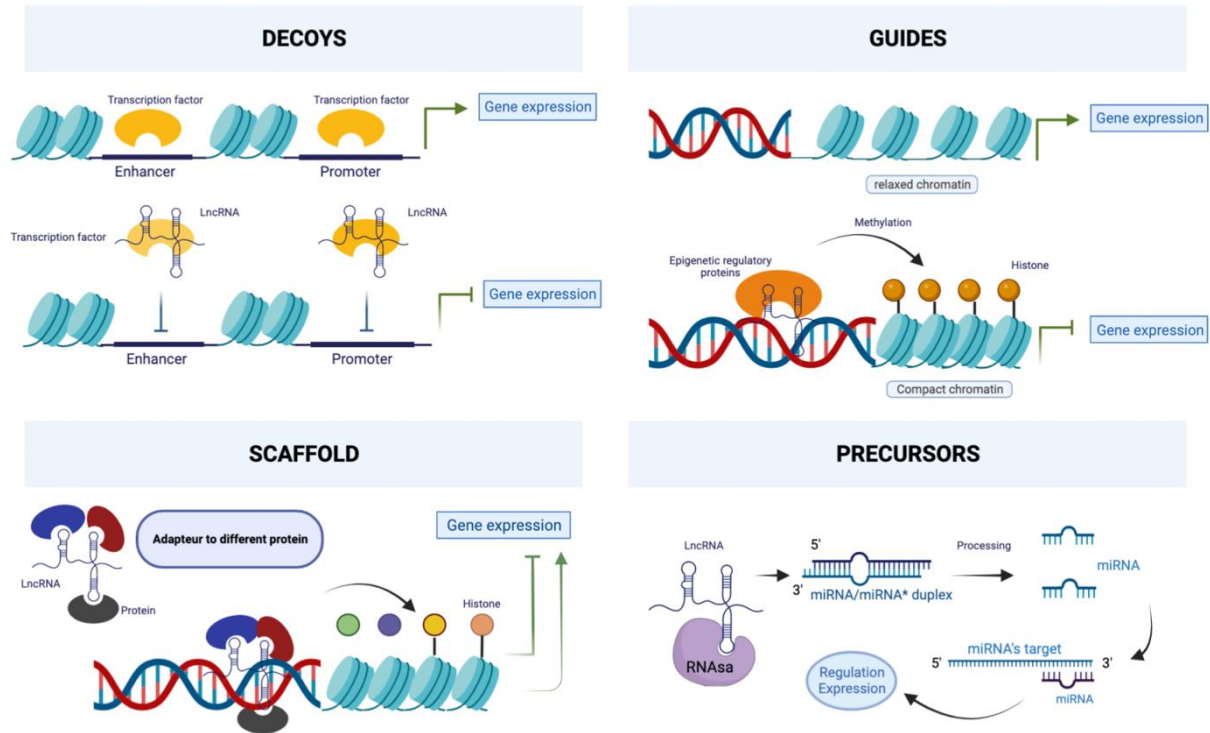
## 325 7. Long non-coding RNAs (lncRNAs)

326 lncRNAs act via various pathways to regulate gene expression at different levels  
327 [136] with a biogenesis similar to mRNAs (Figure 3) . Arbitrarily, lncRNAs are defined  
328 as composed of more than 200 nucleotides mainly between 1,000 and 10,000.

329 Four different archetypes of lncRNA functions have been described (Figure 3) [137].  
330 Since the discovery of lncRNAs, more than a thousand publications have been listed in

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PubMed in the specific setting of OC but only about one percent focused on their expression in biofluids. Numerous studies about lncRNAs, mainly based on OC tissue samples, have demonstrated an association between clinicopathological characteristics such as histological type and grade, FIGO stages, lymph node and distant metastasis and some lncRNAs [138]. In a review including 34 studies involving more than 4,000 women with OC, Hosseini and al observed an association between lncRNAs expression and PFS (HR: 1.88, 95% CI: (1.35–2.62)) and DFS (HR: 6.07, 95% CI: 1.28–28.78). However, among the 34 studies only one evaluating lncRNA in plasma [139] was included. They concluded that their work support the robust prognostic significance of altered lncRNAs in ovarian cancer but more extensive studies are required.



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**Figure 3.**: lncRNAs synthesis and functions. Four different archetypes of lncRNAs functions have been described; (i) lncRNAs can act as molecular signals occurring at a specific time and location to integrate developmental signals, interpret the cellular context, or respond to various stimuli, (ii) lncRNAs act as a molecular decoy by binding to their target proteins following transcription with mainly negative regulation, (iii) lncRNAs act as gene expression guides under a cis-form in the immediate vicinity of genes, and under trans-form for distant genes, and (iv) lncRNAs act as scaffolds.

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From the diagnostic point of view, numerous studies have reported a relation between some lncRNAs and clinicopathological characteristics using OC samples analyzed by RT-qPCR, microarray and hybridization and fluorescence in situ hybridization (FISH) from cancer tissue compared with adjacent normal tissue or samples from healthy patients (Salamini-Montemurri). In a recent review, Salamini-Montemurri et al have listed the various lncRNAs with clinicopathological value [138]. Among them, only E2F4AS [140], FLVCR1-AS1[141], LINK-A [142], MLK7-AS1 [143] and aHIF [144] were evaluated in blood serum but none of them exhibited a sufficient diagnostic value. Chun-Na Liu et al in 185 EOC patients and 43 healthy volunteers evaluated by RT-qPCR the expression of LOXL1-AS1 showing a higher expression in EOC patients with an AUC of 0.843 but a sensitivity and specificity of only 65.3% and 68.2%, respectively [145]. Using RT-qPCR, Jiezh Ma & Min Xue investigated the expression of LINK-A in the plasma of 68 patients with OC and 34 healthy females showing a higher level in OC patients. Recently, for the diagnosis of OC, Barwal and al found that blood lncRNA RP5-

363 837]1.2 had a sensitivity, specificity and AUC of 97.3%, 94.6% and 0.99, respectively but  
364 without external validation [146].

365 From the prognostic point of view, some studies have evaluated the value of  
366 lncRNAs in blood or serum to predict survival. In the meta-analysis using RT-qPCR,  
367 Chen et al evaluated plasma levels of MALAT1 in 47 patients with EOC with metastasis  
368 (EOC/DM), 47 patients without metastasis (EOC/NDM), and 47 healthy controls (HC)  
369 [147]. Plasma MALAT1 allowed to distinguish EOC/DM and HC with an AUC of 0.884  
370 (95% CI, 0.820-0.949; P<0.001) with respective sensitivity and specificity of 89.4% and  
371 72.3%. Jianming Gong et al, analyzing plasma samples from 66 patients with OC and 54  
372 healthy controls, showed that lncRNA MIR4435-2HG was higher in patients with stage  
373 I-II FIGO stages OC but a high overlap of the value between the groups [148].

374 From theragnostic point of view, Weiwei Xie et al have reviewed the contribution of  
375 lncRNAs in response to chemotherapy [149]. The main lncRNAs involved in the  
376 cisplatin resistance were HOTAIR, H19, MALAT1, MEG3, XIST, DNMT3OS and ANRIL.  
377 Other lncRNAs have been proved to be associated to drug resistance such as LSINCT5,  
378 NEAT1 for paclitaxel resistance, UCA1 for paclitaxel-cisplatin resistance, GAS5 for plat-  
379 inum resistance. So far, most of these lncRNA have been merely evaluated on very small  
380 series of plasma [150,151] not allowing to draw conclusions on their relevance.

## 381 8. Perspectives et conclusions

382 Despite an abundant literature on ncRNAs in OC mainly based on cell culture and  
383 tissue samples, relatively few data are yet available in biofluid while previous studies  
384 [79,152,153] have demonstrated the possibility to quantify ncRNAs in various biofluids  
385 such as plasma, serum, urine and saliva. Moreover, it is important to note some limits of  
386 the previous published studies such as the small sample size, the absence of external val-  
387 idation, and the use in most studies of RT-qPCR and microarrays allowing ncRNA quan-  
388 tification of a predefined set of target sequences while NGS and bioinformatics, repre-  
389 senting an unbiased biomarker discovery method, is rarely used. To improve the pre-  
390 operative diagnosis of ovarian cancer, studies evaluating the expression of ncRNAs in  
391 easily accessible biofluids should be promoted, imposing the use of new sequencing  
392 technologies. So far, to our knowledge, only two studies, the clinical trial NCT03738319  
393 focusing on ncRNA profile in exosomes of OC patients, [154] and the clinical trial NCT  
394 [155] evaluating the saliva expression of ncRNA in ovarian tumors including, benign,  
395 borderline and ovarian cancer, are ongoing.

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