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Abstract

With 240,000 new cases and 152 000 deaths per year, ovarian cancer is the leading cause of death from gynecologic malignancies. Late diagnosis because of asymptomatic development in early stages and resistance to existing treatments are the major causes of therapeutic failure in ovarian cancer. The recent discovery of tens of thousands of long non-coding RNAs and their action as oncogenes or tumor suppressors in pathways matching all the hallmarks of cancer in most – if not all – malignancies have attracted attention of the scientific community. A growing number of studies have implicated lncRNAs in diverse aspects of ovarian carcinoma biology. We present lncRNAs which have been involved in response to the different drugs currently used for the treatment of ovarian cancers, from first-line platinum salts and taxanes to the newly available PARP inhibitors. The data already available supports the potential use of several lncRNAs, alone or in combination with other molecules, as potential biomarkers for the prediction of response to treatment. Understanding the determinants of their action might reveal new potential therapeutic targets.

Introduction

Ovarian cancer (OC) is the leading cause of death from gynecologic malignancies. It represents around 240,000 new cases and 152,000 deaths per year worldwide[1]. The majority of patients are diagnosed in advanced stages (75% in stage III/IV FIGO). The 5 years overall survival is less than 40% for advanced stages[1]. The standard treatment for advanced epithelial OCs consists of a debulking surgery followed by an adjuvant reference treatment combining platinum agents and paclitaxel for 6 cycles +/- bevacizumab. Since residual disease after surgery constitutes the strongest prognosis factor available[2], when complete resection does not seem likely to be readily achievable, a neoadjuvant treatment comprising 3 to 4 cycles of carboplatin and paclitaxel is applied before surgery, in order to increase the likeliness of complete surgical resection. In that scenario another 3 to 4 cycles of carboplatin and paclitaxel +/- bevacizumab are given post-surgery.

Despite a good response of around 75% of patients to this usual first-line combination therapy, recurrence occurs in most cases together with resistance to treatment[3], which is the major cause of therapeutic failure. Second or third line therapy combines carboplatin and another drug such as paclitaxel, liposomal doxorubicin or gemcitabine, or platinum-free monochemotherapy depending on patient's characteristics[3].

In recent years, new approaches and numerous clinical trials have been implemented to improve patient's care. However, the implementation of targeted therapies in the treatment of ovarian cancer has lagged behind when compared with other malignancies.

However, the anti-angiogenic Bevacizumab[3] has received approval in the United States from the FDA "Food and Drug Administration" and in the European Union from the EMA "European Medicines Agency" as a first-line treatment for the advanced stages (III B, III C and IV) in combination with carboplatin and paclitaxel, or as a maintenance treatment

(clinical trials: ICON7, GOG0218)[4]. A moderate improvement in progression-free survival (PFS) was observed, but no long term overall survival (OS) gains have been achieved with anti-angiogenic molecules in OC.

More recently, several PARP inhibitors (PARPi) have been approved by EMA and/or FDA for the treatment of OC. The firstly approved molecule was Olaparib in 2014 as a maintenance treatment for 'platinum-sensitive' patients bearing BRCA1/2 mutations[5] followed by Rucaparib and Niraparib for patients who are sensitive to platinum-based chemotherapy, irrespective of BRCA1/2 status[5]. These newly approved treatment options have shown impressive improvements on the PFS[5], and while the results regarding OS are not yet available they hold great promise for the improvement of therapeutic care of OC.

A better understanding of the mechanisms involved in the response or resistance to treatment is necessary for the development of new therapeutic strategies to predict and/or counter resistance. Resistance of ovarian tumors to various chemotherapeutic agents is a multifactorial process, including but not limited to: increased drug efflux, tolerance to oxidative stress, alterations of DNA repair mechanisms or resistance to apoptosis. Both genetic and epigenetic alterations have been implicated in the alteration of biological pathways related to resistance mechanisms[2].

The recent advances of high-throughput transcriptomic studies have led to the identification of tens of thousands of non-protein coding RNA transcripts[6] and these non-coding RNAs (ncRNAs) have been demonstrated to regulate gene expression through many mechanisms[6]. Among these ncRNAs, the long non-coding RNA (lncRNA) are defined by the absence of an open reading frame (ORF) and a length above 200 nucleotides[6].

LncRNAs exert their functions through various mechanisms[7] (**Figure 1**). They can bind RNA and DNA by sequence complementarity, or proteins via their secondary structures. In the cytoplasmic compartment, lncRNAs mainly bind to mRNAs or miRNAs. Binding to

mRNAs by sequence complementarity the 5'UTR can upregulate translation, whereas 3'UTR complementarity with ALU repeats destabilizes mRNAs and decreases expression levels of the corresponding protein[7]. Another mode of action is the widely described binding to miRNAs by sequence complementarity with their seed regions, efficiently sequestering miRNAs away from their mRNA targets, thereby derepressing their expression. LncRNAs sequestering miRNAs have been termed "Competing Endogenous RNAs (ceRNAs). Interestingly, some lncRNAs can also act as precursors of miRNAs[8].

In the nucleus, lncRNAs functions rely on three main modes of action, as guides, decoys or scaffolds. Guide lncRNAs address protein complexes such as Trithorax (MLL) or Polycomb (PRC1, PRC2) to specific loci in the genome, where they deposit histone post-translational modifications to epigenetically enhance or inhibit gene expression[8]. Decoy lncRNAs associate with proteins such as transcription factors, and prevent them to act on their target sequences in the genome[7]. Scaffold lncRNAs also associate with proteins complexes through their secondary structures, thus enabling assembly of larger complexes and allowing the coordinated action of several complexes in the same loci in the genome.

It is important to note that these multiple modes of action are not mutually exclusive, and a single lncRNAs can act through several different mechanisms. For example, H19 act as a scaffold for PRC2 complex, as a ceRNA by sponging miR-29a[9], and as a precursor of miR-675[10].

LncRNAs regulate many biological processes such as imprinting, differentiation, development or cell cycle[8]. They also have functions in many cancers, if not all, where they can act as oncogenes or tumor suppressors[11]. Several studies have demonstrated the essential roles of several lncRNAs such as PVT1, HOTAIR, UCA1 or MEG3 in the resistance of various tumors to chemotherapeutic agents[12] including in OC.

The objective of this review is to present the lncRNAs involved in resistance or response to the chemotherapeutic agents and targeted therapies used in the treatment of OC. The study of lncRNAs could help to better understand the determinants of the response to these

treatments, should help to define new, tools useable for the prognosis and/ or predictive of the response to treatment, and might lead to the proposal of new innovative therapies.

LncRNAs involved in the response to first-line chemotherapy

The deregulation of numerous lncRNAs in OC and their involvement in mechanisms modulating the response of OC cells to the action of taxanes and platinum salts has now been acknowledged in many studies[13,14].

Initially cisplatin (cis-diamine dichloroplatinum(II)) was the first platinum compound to be used in the treatment of OC[13]. Carboplatin (cis-diamine cyclobutane-1,1-dicarboxylate-O,O′ platinum(II)) is the second platinum complex used in OC treatment. It is known to have the same ability to form DNA adducts as cisplatin, but with lower side effects, less toxicity and a slower reactivity[15]. Paclitaxel (Taxol) is used in OC first-line therapy and exerts its action through preventing microtubules de-polymerization and therefore blocking cancer cells in the G2/M phase [16].

Out of the several lncRNAs which have been associated with the response to first line treatment in ovarian cancer cells, we chose to present only the ones for which data regarding their mechanisms of action have been made available.

UCA1 (Urothelial carcinoma-associated 1) is located on human chromosome 19p13.12, is composed of three exons and two introns and presents three isoforms. These isoforms are different by their sizes: 1.4Kb, 2.2Kb and 2.7Kb. The 1.4Kb isoform is the most studied isoform and is involved in the development of several cancers[17]. UCA1 is an oncofetal lncRNA expressed mainly in embryonic tissues, and physiologically only at apparently low levels in cardiac tissue in adults[18]. It has been proven that UCA1 is re-expressed and has

an oncogenic role in hepatocellular carcinoma, gastric, bladder, breast, colorectal and OC. UCA1 is able to promote proliferation, metastasis, and invasion[19]. Moreover, UCA1 has been shown to contribute to the development of resistance to many chemotherapeutic treatments including cisplatin or paclitaxel in OC[17,20].

It has been demonstrated that UCA1 expression is upregulated in OC and this overexpression promotes cell migration, invasion and cisplatin resistance[21]. UCA1 promotes upregulation of SRPK1 (Serine/threonine-protein kinase 1) and Bcl-2 (an anti-apoptotic protein) expression and decreases expression of many pro-apoptotic factors such as Bax, Caspase 3 and Caspase 9. SRPK1 belongs to the SR kinase family and is able to regulate gene expression by acting on pre-mRNA splicing. It has been previously shown that SRPK1 increases cisplatin resistance in OC[22].

It has been also described that UCA1 is overexpressed in paclitaxel-resistant OC cells and promotes the acquisition of resistance to this agent by its role of ceRNA on miR-129, therefore upregulating ABCB1 protein, a direct target of miR-129[20]. MiR-129 is known to be involved in drug sensitivity in many cancers such as breast cancer[23]. ABCB1/Pglycoprotein (P-gp) is an efflux pump and plays a role in the elimination of chemotherapeutic agents and therefore participates in resistance mechanisms in OC cells[24].

In oral squamous cell carcinoma, UCA1 is also involved in the resistance to cisplatin, through sponging miR-184[25]. Interestingly, it has been shown that high miR-184 levels in OC cells represses proliferation and induces apoptosis, suggesting a possible induction of chemoresistance by sponging miR-184[26].

HOTAIR (HOX Transcript Antisense RNA) is one of the most studied lncRNAs. It is an antisense RNA transcribed from the mammalian HOXC gene cluster[27]. This oncogenic lncRNA is involved in many cancers such as gastric, colorectal, breast or OCs[27], mainly through its guide and scaffolding functions. HOTAIR has been shown to be involved in the development of resistance to various chemotherapeutic agents such as cisplatin.

It was demonstrated that the overexpression of HOTAIR promotes cisplatin resistance in OC by the activation of Wnt/β-catenin pathway[27]. HOTAIR is able to modulate the expression of cyclin D1, its ligand CDK4 and β-catenin, thus activating the Wnt/β-catenin signaling pathway, which is often deregulated in OC[28].

HOTAIR was identified as playing a role in cisplatin chemoresistance in gastric cancer by activation of PI3K/AKT/MRP1 pathway *via* its inhibiting role on miR-126[29], which could be relevant in OC because of the prominent role of PI3K/AKT pathways in chemoresistance of OC cells.

In lung adenocarcinoma HOTAIR downregulates p21 and therefore promotes resistance to cisplatin[30]. A similar mechanism could promote OC chemoresistance as well, since p21 downregulation triggers resistance to cisplatin in OC cells[31].

PVT1 (plasmacytoma variant translocation 1) is a long non-coding RNA located on chromosome 8q24 near the MYC locus[32]. It is known to have an oncogenic role with involvement in various pathways that promote tumor growth, proliferation, invasion, and metastasis, and also represses apoptosis in various cancers[33].

PVT1 is also known for its involvement in the resistance to cisplatin in OC, and it has been described as a regulator of the apoptotic pathway of OC cells leading to cisplatin chemoresistance[32]. The expression of PVT1 is increased in tumor tissues of cisplatin-resistant patients and in OC cells and its inhibition allowed sensitizing to cisplatin action, most likely through the upregulation of Caspase 3 expression. The mechanisms of action by which PVT1 mediates its effects remain to be elucidated.

PVT1 has also been identified as being involved in the response of OC cells to treatment combining carboplatin and docetaxel[34]. In this study PVT1 has been described as a tumor suppressor, promoting the anticancer action of these chemotherapeutic agents by an upregulation of P53 and TIMP1 expression. P53 is the best known tumor suppressor, but it is inactivated in more than 95% of high-grade serous OCs, thus the action of PVT1 through P53 is most likely minor in OC. TIMP1 (TIMP Metallopeptidase Inhibitor 1) is an inhibitor of

matrix metalloproteinase, and has therefore tumor suppressor activities in many cancers including ovarian[35].

Whether PVT1 in OC is acting as an oncogene or tumor suppressor is most likely context dependent and further studies will be needed for a better understanding of its functions.

XIST (X-inactive specific transcript) originates from the XIST gene on X chromosome and is a major player of the X inactivation in women by interaction with PRC2. XIST expression is present in all normal female cells but can be decreased or absent in female cancer cell lines, such as breast, cervical and OCs[8]. XIST functions in cancer depends on the context: it is known to act as a tumor suppressor in OC with an inhibitory role on many tumor processes such as proliferation, invasion and resistance to cisplatin[36], whereas XIST acts as an oncogene in non-small cell lung cancer[37].

It has been shown in epithelial OC (EOC) cells (CAOV3/OVCAR3) that XIST is lowly expressed and that the upregulation of its expression promotes anticancer effects through its sponging of miR-214-3p by direct interaction with this miRNA[36]. XIST then competes with mir-214-3p and prevent it to act on its targets, such as PTEN, and therefore prevents this miRNA to exert induce cisplatin resistance in EOC[38].

H19 is an imprinted oncofetal gene located on the human chromosome 11p15.5, which is known to play an essential role in embryonic development and cancer progression. It is deregulated in many cancers such as bladder, breast, colorectal, esophageal and OCs[8]. This lncRNA acts as an oncogene by promoting tumor development, metastasis, epithelial-mesenchymal transition, or by allowing the acquisition of chemoresistance to multiple chemotherapeutic drugs including cisplatin in OC.

It has been demonstrated that in OC cells H19 expression was triggered after cisplatin treatment in sensitive cells and upregulated in cisplatin-resistant cells and its inhibition promotes sensitivity to cisplatin. H19 is thought to act by regulating glutathione (GSH)

metabolism and NRF2 targets[39]. NRF2 belongs to the GSH pathway and is a regulator of various antioxidant molecules, a pathway involved in cisplatin resistance in OC[40].

BC200 (Brain cytoplasmic 200) is involved in carboplatin resistance of OC. BC200 is a small cytoplasmic non-messenger RNA of about 200 nucleotides. This lncRNA is physiologically expressed in the human nervous system. It has been demonstrated that BC200 expression is associated with cancer cells from malignancies originating from various tissues such as breast, esophagus, lungs, cervix and ovaries.

It has been shown that the expression of BC200 is decreased in OC cells compared to normal cells, promoting cell proliferation and carboplatin resistance[41]. In addition, carboplatin-induced BC200 expression promotes the sensitivity of cancer cells, highlighting a tumor suppressor role for BC 200. The mechanism through which BC200 is induced or operates remains to be elucidated.

NEAT1 (Nuclear paraspeckle assembly transcript 1)**,** is located on human chromosome 11[42]. This lncRNA is a component of the paraspeckles, a nuclear structure whose functions are only poorly defined. NEAT1 is known for its oncogenic role in many cancers, including OC, where it promotes cell proliferation, migration and apoptosis[43].

It has been demonstrated that NEAT1 is increased in paclitaxel-resistant OC cells and tissues and an increase of its expression is involved in the acquisition of resistance. It is explained by its ability to induce ZEB1 (zinc finger E-box-binding homeobox 1) expression through sponging miR-194[42]. It has been also demonstrated that ZEB1 plays an important role in many cancers' progression including OC, and that ZEB1 is involved in the resistance to many drugs such as doxorubicin, gemcitabine and paclitaxel[44].

FER1L4 (Fer-1-like protein 4) is downregulated in various cancers and a role of FER1L4 in paclitaxel tolerance in OC cells was demonstrated[45]. Low expression of FER1L4 allows tumor growth and the development of chemoresistance by the regulation of MAPK signaling

pathway, implicated in cisplatin chemoresistance of OC[46], although the mechanisms of FER1L4 action are not precisely described.

LncRNAs involved in angiogenesis and possibly in response to Bevacizumab

The biological process of angiogenesis is one of the pivotal hallmarks of cancer where it induces tumor development through the formation of new vessels. This neovascularization will depend on a balance between pro- and anti-angiogenic factors. The key angiogenic growth factors are vascular endothelial growth factor (VEGF), platelet derivative growth factor (PDGF) and fibroblast growth factor (FGF), and their receptors. These are positively regulated in tumors, thus promoting their growth, hence the relevance of the design of targeted therapeutics to counteract tumor neo-angiogenesis. The anti-angiogenic agent currently used in the treatment of OC is bevacizumab. It is a recombinant humanized monoclonal antibody that that binds to VEGF and prevents it to promote tumoral neo-angiogenesis[3,4].

To date, no study to our knowledge has demonstrated the involvement of lncRNAs in regulating the response of cancer cells to anti-angiogenic action. To our knowledge, only one study has demonstrated a direct link between a lncRNA and angiogenesis in OC, while only a few other studies have reported such a connection in other malignancies such as bladder, breast, liver cancers and glioblastoma[47,48].

MALAT1 has been identified as being transferred by (EOC) cells to HUVECS (human umbilical vein endothelial cells) *via* exosomes. This transfer not only stimulates tumor growth but also the expression of pro-angiogenic genes such as VEGF and FGF, and increases angiogenesis in tumors *in vivo* in nude mice[48].

H19 has been shown to be overexpressed in microvessels and their associated endothelial cells in a glioma model, where it sponges miR-29a, a miRNA able to directly target vasohibin2 (VASH2). Therefore, VASH2 is upregulated, promoting angiogenesis in glioma [9]. This mode of action could add to the previously described deleterious effects of H19 regarding the response to cisplatin in OC cells. Moreover, independently of its role in angiogenesis, down regulation of miR-29a has also been shown to promote cisplatin resistance in OC cells[49].

LncRNAs involved in DNA repair and possibly in response to PARPi

The study of DNA damage response and manipulation of this process is now recognized as an important area of research and could lead to an improvement of OC therapeutic care. PARP (Poly-ADP ribose polymerase) has an important role in the repair of single-strand DNA breaks (SSB) and the use of PARP inhibitors (PARPi) can result in double-strand breaks (DSB). DSB normally would be repaired by Homologous Recombination (HR) DNA repair pathway which is a complex process involving many proteins, notably BRCA1 and BRCA2. In HR-deficient (HRD) tumors, alternative DNA repair by non-homologous end joining (NEHJ), a low fidelity repair mechanism, eventually results in cell death[50].

PARPi have been identified as a particularly beneficial treatment for patients bearing g/s*BRCA*mt, however they represent only a small portion of high-grade serous OC cases (HGSOC)[51]. Importantly, patients with g/s*BRCA*mt achieved longer progression-free survival (PFS), although results among patients without g/sBRCAmt treated by PARPi were better than those with placebo. These evidences suggest that patients with other defects (regardless of BRCA status) in the HR DNA repair system (HRD patients), such as

alterations in ATM, CHEK2, PALB2, RAD51C, RAD51D, etc., may also benefit from PARPi[52].

Germline and somatic mutations in HR genes are present in approximately one-third of OCs and also predict a better response to primary platinum-chemotherapy. More broadly, the HRD status reflects all alterations leading to HR abnormalities and conferring sensitivity to platinum and PARPi. To date, the HRD status has been partially determined through the analysis of gene mutations *via* multigene panel testing or through different HRD assays, some of them studying genomic instability. However, the determinants of response to PARPi remain incompletely characterized, and important efforts are made to identify molecular signatures as well as functional assays able to predict the response to PARPi.

To date, lncRNAs involved in HR or NHEJ have not been documented in OC. However, given the large number of lncRNAs and their diverse functions, it is not surprising that several lncRNAs play intricate roles in genome integrity maintenance and in the DNA damage response, and more particularly in DSB repair[53].

PCAT-1 (Prostate Cancer Associated Transcript 1) is overexpressed in prostate cancer, downregulates BRCA2 and impairs HR, which, in turn, sensitize prostate cancer cells to PARP inhibitors[54]. The mechanism by which PCAT-1 down-regulates BRCA2 is at least in part by a post-transcriptional repression of the 3' UTR of BRCA2 mRNA. Interestingly, PCAT-1 levels are inversely correlated with RAD51 foci formation when prostate cancer cells are treated with PARPi. A recent study has shown that this lncRNA, overexpressed in OC cell lines and tumors, could be involved in the development and progression of OC[55]. However, no information was provided regarding the response to platinum-based chemotherapy or innovative treatments such as PARPi.

DDSR1 (DNA Damage-Sensitive RNA1) has been proposed to have a role in modulating DNA repair by HR[56]. DDSR1 expression is induced by ATM in immortalized human skin

fibroblasts. Moreover, DDSR1-depleted cells present a defective HR and show increased sensitivity to PARPi. The HR defect in the absence of DDSR1 is noticeable by aberrant accumulation of BRCA1 and RAP80 at DSB sites. In agreement with a role in regulating HR, DDSR1 interacts with BRCA1 and hnRNPUL1, an RNA-binding protein involved in DNA end resection, and thus likely acts through a scaffolding mechanism. To our knowledge, this lncRNA has never been studied in OC.

NEAT1 levels in cholangiocarcinoma (CCA), are negatively correlated with BAP1 (BRCA-1 associated protein-1) according to TCGA dataset. BAP1 is a member of the ubiquitin C-terminal hydrolase superfamily that plays a critical role in chromatin remodeling[57]. The knockdown of BAP1 by upregulating NEAT1 expression sensitizes CCA cells to chemotherapy and PARPi.

In a study in an OC model, the authors reported that NEAT1 was a ceRNA for miR-506 to promote cell proliferation and migration[58]. MiR-506 is targeting directly RAD51 mRNA, and its systemic delivery in *nude* mice improved the response to cisplatin and olaparib[59].

NORAD (non-coding RNA activated by DNA damage), is located on chromosome 20q11 and his length is 5.3 kb. NORAD is expressed abundantly, ubiquitously and is necessary to maintain genomic stability[60].

It was identified NORAD as being involved in genome stability through the interaction with RBMX, an element of the response to DNA damage. This RNP complex associates with other proteins, including TOP1, a known promoter of genomic stability. NORAD inhibition induces defects in DNA replication and chromosome segregation[60]. It has also been shown that NORAD sequesters PUMILIO proteins, which otherwise repress DNA repair and induces genomic instability. Oncogenic roles of NORAD have been shown in cancer cells from different origins, including ovarian[61].

LncRNAs involved in response to 2nd and 3rd line treatments

Second and third line treatments upon relapse are indicated depending on the patient's response to first-line treatments. For platinum-sensitive patients, therapy combining platinum salt and paclitaxel or liposomal doxorubicin or gemcitabine is indicated. For patients refractory or resistant to platinum, platinum-free monochemotherapy is recommended, with paclitaxel, doxorubicin, topotecan or gemcitabine.

Doxorubicin (liposomal pegylated doxorubicin; Adriamycin) is a cytotoxic antibiotic belonging to the anthracycline family, whose anti-tumor effects mainly depend on the ability to inhibit the action of topoisomerase II and thus create DNA damage and apoptosis of cancer cells[62].

Gemcitabine is a pyrimidine nucleoside antimetabolite analog (20,20-Difluoro 20-deoxycytidine, dFdC) able to replace cytidine during DNA replication and therefore inhibit DNA synthesis and cause apoptosis[62].

Topotecan is a topoisomerase I (TOP1) inhibitor which binds to TOP1-DNA cleavage complex. This complex between topotecan-TOP1-DNA interferes with the replication fork and leads to apoptosis of the cells[63].

To date, no studies have identified in OC the involvement of lncRNAs in the mechanisms regulating the resistance of these drugs, which is not entirely surprising since they play a minor role compared to platinum salts in the treatment of this disease, and they are therefore less often studied in this context. However, in other malignancies, several lncRNAs have been shown to play a role in the response to these drugs. The mechanisms of action which could be relevant in OC are presented below.

UCA1 in breast cancer cells promotes doxorubicin chemoresistance through a mechanism involving the heterogeneous nuclear ribonucleoprotein I (hnRNPI) and P27 (Kip1)[64]. HnRNPI is located in the cytoplasm after doxorubicin treatment and binds to p27 (Kip1) mRNA, a known tumor suppressor, to promote its translation[65]. It has been demonstrated that hnRNPI is able to bind UCA1 creating a competition between p27 and UCA1. UCA1 overexpression therefore leads to a decrease in p27 protein levels.

PVT1 has been shown to increase the resistance of osteosarcoma cells to gemcitabine[33] where it is a ceRNA to miR-152, sponging it away from its target c-Met. In OC cells, targeting c-Met has been shown to enhance sensitivity to paclitaxel[66]. Interestingly, c-MET inhibition also prevents PARP1 phosphorylation, thereby enhancing breast cancer cells response to PARP inhibitors. In addition to other roles of PVT1 in chemoresistance of OC cells, this pathway might be of significant value to predict or potentiate OC response to the newly introduced PARP inhibitors[67].

TUG1 is upregulated in bladder urothelial carcinoma (BUC) where it is associated with a poor response to doxorubicin chemotherapy[68]. TUG1 influences doxorubicin resistance in this cancer by the regulation of Wnt/β-catenin pathway, which is known to be involved in tumorigenesis and response to treatment in OC[27]. TUG1 has also been shown to increase ovarian cancer cell proliferation and decrease apoptosis, although the involvement of Wnt/β-catenin pathway was not assessed in this study[69].

H19 is upregulated in doxorubicin resistant breast cancer cells, and plays a leading role in this resistance by increasing the expression of ABCB1/MDR1, a drug efflux factor involved in drug resistance in different context, including OC[70].

Conclusions and perspectives

In summary, the mechanisms by which lncRNAs modulate response to the drugs used for the treatment of OC are diverse and can occur at every step of the action of chemotherapeutic drugs: from drug efflux to diverse pro-survival or anti-apoptotic pathways, including the management of genome stability and the response to DNA damage.

While many studies[8], have correlated altered expression of lncRNAs with the prediction of disease-free survival and overall survival in OC, none of these candidate have been turned so far into reliable and clinically useable biomarkers able to predict patient's survival and response to available treatments.

The definition of such biomarkers will need an increased number of discovery and validation studies, preferably in cohorts of homogenous subtypes of OC. Since the different histologies and subtypes of OC constitute different diseases at the histological and molecular levels, it is expected that no common biomarker will be defined for the full range of OC subtypes. In this regard, lncRNAs for which a role in the response to treatment has been identified might constitute valuable candidates to refine the predictive value of other biomarkers. For instance, a given lncRNA with a role as ceRNA for a given miRNA might hold a predictive value only in light of the expression level of the miRNA.

The growing evidence about lncRNAs suggests that alone or in combination with other factors (protein coding genes, lncRNAs or miRNAs) lncRNAs may serve as biomarkers that are highly valuable and desirable for prognosis and prediction of the response to therapies, including the newly available and highly promising PARP inhibitors in OC.

Although the study of lncRNAs is still in its infancy, this is a highly dynamic field of research and accumulation of knowledge about their roles and functions in the biology of OC will eventually lead to the identification of innovative potential therapeutic strategies. RNA interference is quite relevant to target specific lncRNAs but such strategies have failed so far to successfully enter the clinics and their use, while likely to become available in the future,

might still remain years ahead. However, a detailed knowledge of the mechanisms of action of lncRNAs, and of the genes whose expression they regulate, could enlighten relevant target which could be druggable through more commonly used drug design strategies. Altogether, the raising *corpus* of knowledge about the roles and functions of lncRNAs in the biology of OC may provide highly relevant tools to predict the response to treatments, as well as seed the definition of innovative therapeutic strategies in the years to come.

Acknowledgments

We apologize for our inability to cite all the contributing literature due to space restrictions. This work was supported by the « Ligue Contre le Cancer » (Normandy Confederation), the "Normandy Region", the French State, Inserm (National Institute for Health and Medical Research), the "Cancéropôle Nord-Ouest, the University of Caen Normandy and the Cancer Center F. Baclesse (Caen, France). A.W. is a recipient of a doctoral fellowship from the "Normandy Region". MRA.A is a recipient of a doctoral fellowship from Egyptian Ministry of Higher Education and Scientific Research. The authors wish to thank Monique N'Diaye for helpful comments on the manuscript.

Conflict of interest

The authors declare no conflict of interest

Author contribution

Anaïs Wambecke: Conceptualization, Writing – Original Draft. **Mohammad Ahmad**: Writing Review & Editing. **Bernard Lambert**: Writing – Original Draft. **Florence Joly**: Writing Review & Editing. **Laurent Poulain**: Writing Review & Editing. **Christophe Denoyelle**:

Conceptualization, Writing – Original Draft. **Matthieu Meryet-Figuiere**: Supervision, Conceptualization, Writing – Original Draft.

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Table legend

Table1: LncRNAs whose deregulation is related to first line chemotherapeutic agents in ovarian cancer.

Figure legend

Figure1: Mechanisms of action of lncRNAs. In the nucleus lncRNAs can act as (A) scaffold for several protein complexes, (B) as guide for proteins or (C) as decoy for transcription factors. In the cytoplasm lncRNAs can bind (D) in the 5'UTR region of mRNAs to upregulate translation, (E) in the 3'UTR region of mRNAs in ALU repeats to destabilize mRNAs or (F) can compete for the binding of endogenous miRNAs and keep them away from mRNA targets.

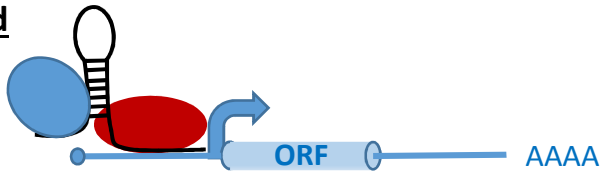
Highlights

- Ovarian cancer is the leading cause of death from gynecological malignancies
- Resistance to treatment is the major cause of therapeutic failure

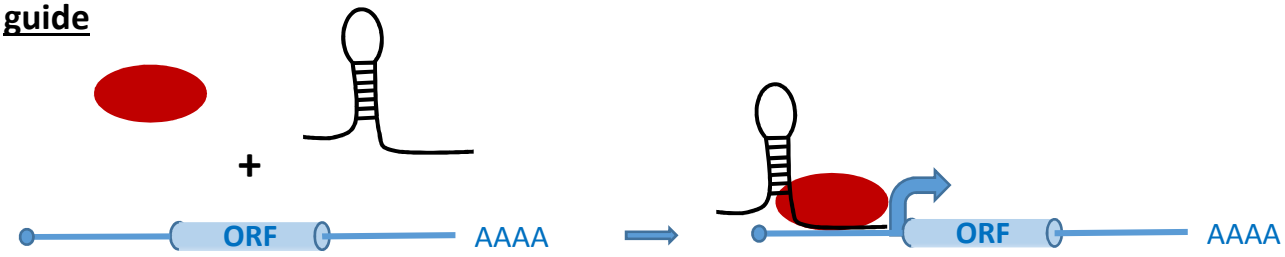
- LncRNAs act as oncogene or tumor suppressors and are involved in the response to treatment
- LncRNAs expression levels might predict response to treatment
- Understanding lncRNAs modes of action could reveal innovative therapeutic strategies

NUCLEUS

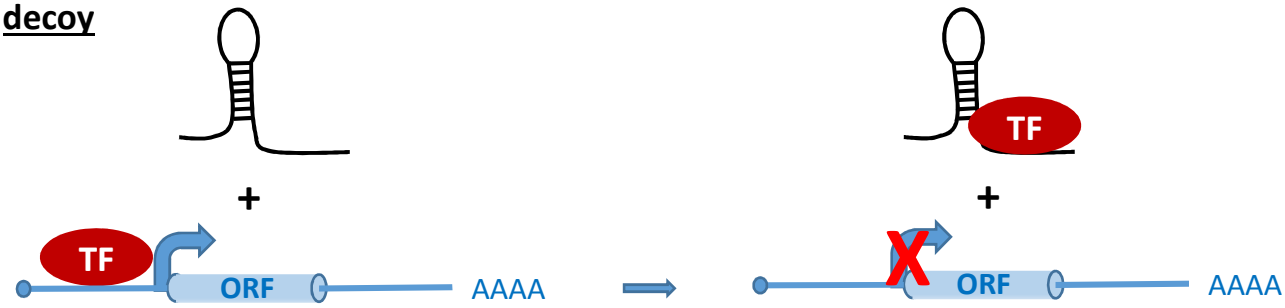
A scaffold



B guide

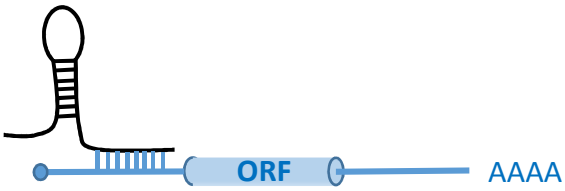


C decoy

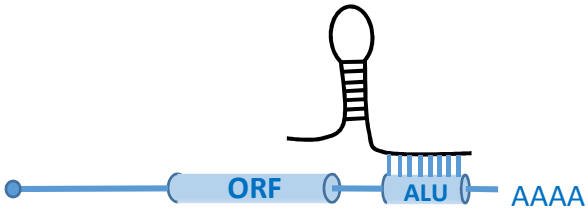


CYTOPLASM

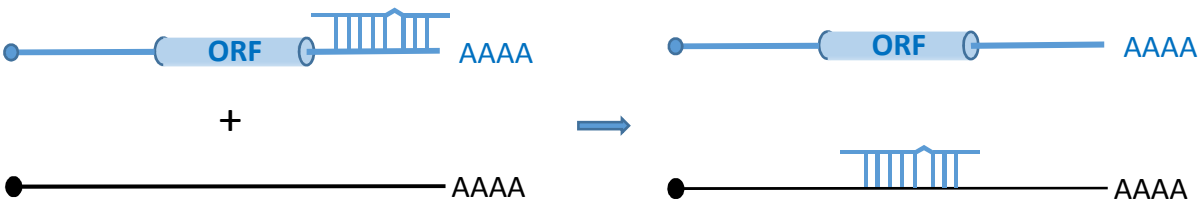
D upregulates translation



E destabilizes mRNA



F endogenous competition for miRNA binding



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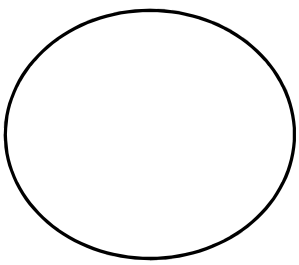

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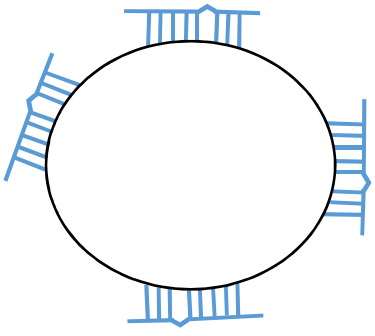

Therapeutic Molecule	LncRNA	Up- or Down-regulation promotes resistance	Mechanism of action	References
Platinum salts	UCA1	up	Upregulates SRPK1 and Bcl-2, downregulates Bax, Caspases 3 and 9. Mechanism unknown	21
	HOTAIR	up	Activates Wnt/b-Catenin pathway. Mechanism unknown	27
	PVT1	up	Downregulates Caspase 3. Mechanism unknown	32
	PVT1	down	Downregulates P53 and TIMP1. Mechanism unknown	34
	XIST	down	Downregulates PTEN by releasing miR-214-3p	36
	H19	up	Upregulates glutathione metabolism. Mechanism unknown	39
	BC200	down	Mechanism unknown	41
Taxanes	UCA1	up	Upregulates ABCB1 by sponging miR-129	20
	NEAT1	up	Upregulates ZEB1 by sponging miR-194	42
	FER1L4	down	Activates MAPK signaling pathway. Mechanism unknown	45