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Review Article

What role do long-noncoding RNAs play in the pathogenesis of endometriosis-associated ovarian carcinoma (EAOC)?

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Abstract

This literature review examines evidence regarding pathogenesis of endometriosis-associated adenocarcinoma and focuses on the potential role of long, non-coding RNA molecules.

The role of long non-coding RNA species is an area of active research and represents an opportunity for novel biomarker Identification to aid early diagnosis, risk stratification and post-operative disease monitoring.

Keywords: Endometriosis, Ovarian endometrioid adenocarcinoma, Ovarian clear cell adenocarcinoma, Long non-coding RNA, Pathogenesis, Carcinogenesis, Atypical endometriosis

Introduction

Ovarian endometriosis is a common medical condition affecting up to 10% of women in the reproductive age group [1] and has an increased lifetime risk of progressing to malignancy [2-4]. There are genetic, immunohistochemical and histopathological features of endometriosis-associated ovarian carcinomas (EAOCs) to suggest that malignancy occurs through an intermediate non-invasive dysplastic stage called atypical endometriosis [2,5-8]. Literature is emerging about the role of non-coding RNA molecules in the development of both endometriosis [9,10] and also ovarian cancer [11,12]. Many of the articles relating to ovarian cancer pathogenesis and the role of non-coding RNAs discuss ovarian cancer with reference to high-grade serous carcinoma, the most common form of ovarian epithelial malignancy that has the worst prognosis [13]. High-grade serous carcinoma is histologically and biochemically distinct from EAOCs, namely endometrioid and clear cell subtypes of adenocarcinoma [13]. There is a paucity of literature regarding the role of non-coding RNA molecules in the development of EAOC [14]. RNA molecules can be detected and sequenced using massive parallel methods which generates large data sets that require computational analysis for interpretation [15,16]. This review will describe pathogenetic mechanisms of endometriosis, atypical endometriosis with respect to genomics.

Endometriosis

Endometriosis is defined as the presence of endometrial glands and stroma outside of the uterine cavity [17]. Eutopic endometrium refers to glandular epithelium lining the endometrial cavity within the uterus of endometriosis sufferers [17]. Endometriosis often involves the ovary and peritoneum but can be found in deep soft tissues, lymph nodes, and distant sites including breast, lung, urinary tract, gastrointestinal tract, umbilicus, inguinal region, pelvic nerves, as well as abdominal scars [18,19]. Endometriosis can therefore be classified as ovarian, superficial peritoneal or deep infiltrating in type [20].

Endometriosis is considered a benign condition by many authors [7,18] but actually shows many of the defining features of malignancy [21,22], for example, the ability to invade and metastasise. Some have suggested that it may be more appropriate, therefore, to reclassify usual-type endometriosis as an indolent form of malignancy with excellent survival rates [21].

Atypical endometriosis is characterised by either cytological or architecturally abnormal features within endometriosis [23]. Architectural abnormalities within atypical endometriosis generally refer to hyperplasia, defined as an increased in the number of cells and or glands in relation to the amount of background supporting connective tissue stroma. [24,25]. Cytological atypia refers to an abnormal cell phenotype characterised by an increased nuclear to cytoplasmic ratio, prominent nucleoli and pleomorphism; these are recognised features of dysplasia and are seen in both pre-invasive and invasive malignancies [7,23].

Ovarian carcinomas are subtyped based on histological features, the most common being high-grade serous carcinoma which makes up around 70% of ovarian carcinomas[13,26]. Up to 10% of ovarian carcinomas are endometrioid sub-type, having phenotypic and molecular resemblances to endometroid adenocarcinomas that arise in the endometrial cavity [27,28]. Clear cell carcinoma and endometrioid carcinoma of the ovary are the types most commonly occurring on a background of ovarian endometriosis [29,30] and clear cell carcinoma is equally as common as endometroid type, perhaps reflecting this shared cell of origin. Mucinous carcinoma is less common than endometriosis-related carcinomas at around 3% of ovarian carcinomas [13]. Mucinous carcinoma of the ovary is seen more frequently than this but is often a result of metastases from the gastrointestinal tract and true primary ovarian mucinous carcinoma is rare [31] and thought to arise from Walthard rests, nest of epithelium that occur as embryonic remnants at the junction of distal fallopian tube epithelium continuity with pelvic peritoneal mesothelium [26]. Low-grade serous carcinoma occurs in less than 5% of ovarian carcinoma cases and has a distinct molecular origin from high-grade serous carcinoma and should be regarded as entirely separate entities despite the similarity in their name [13,26,32]. High-grade serous carcinomas develop mutations in *TP53* early in pathogenesis within ciliated columnar epithelium lining the fallopian tubes [33,34]. In contrast, low grade serous carcinomas are characterised by mutations in *KRAS* and *BRAF* genes and develop in a sequential manner from benign serous cyst adenoma to serous borderline tumour to low grade serous carcinoma when invasion of ovarian stroma occurs [35,36] (**Table 1**). Other ovarian carcinoma types are even rarer and include carcinosarcoma and Brenner tumours for example [27,37].

Low grade serous, seromucinous and mucinous carcinomas have also reported in association with endometriosis but rarely [47,48]. For the purposes of this literature review, EAOC will refer to endometrioid and clear cell carcinomas only.

Clinical Features

Endometriosis can cause multiple symptoms including painful periods, cyclical pelvic pain, sometimes irregular or heavy periods, painful intercourse, bowel and bladder pain, female sub-fertility, and chronic fatigue [49,50]. Endometriosis symptoms such as severe dysmenorrhea, inter-menstrual pain, dyspareunia, painful defecation, dysuria, back pain, fatigue, and infertility have a profound negative impact on quality of life. [51] Laparoscopic removal of peritoneal lesions can provide tissue for diagnosis and relief from pain, but three quarters of patients relapse within 2 years of surgery [52-54]. Subfertility is a major cause of psychological morbidity in women with endometriosis [55-58]. Some authors suggest that eutopic endometrium in women with endometriosis is abnormal and the cause of infertility [17,56]. The abnormal state of eutopic endometrium in these women may in part be responsible for the development of endometriosis [20]. Endometriosis of the peritoneum appears as purple/brown blebs just under the peritoneal surface often with inflammatory adhesions at diagnostic laparoscopy. The appearances would be the same for both typical and atypical endometriosis as atypia can only be diagnosed by a histopathologist during microscopic examination of tissue [17,18,59].

Table 1. Characteristics of Epithelial Ovarian Carcinoma subtypes [38].

Characteristic	High-grade serous [37,39-42]	Endometrioid [13,29,38,42,43]	Clear cell [43]	Mucinous [13,38,42]	Low-grade serous [36,37,44-46]
Average age at diagnosis	63	56	51	54	47
Gene mutations	TP53 BRCA1/2 RAD51C/D BRIP1 MSI genes	ARID1A, PTEN, CTNNB1, PIK3CA PPP2R1A	ARID1A PIK3CA PPP2R1A ZNF217	KRAS, HER2 ampl. TP53 c-myc	KRAS NRAS BRAF
Positive IHC	CK7, ER, WT1, p16, p53, PAX8	Vimentin, ER, PR, PAX8	CK7, napsinA	CK7, CK20, cdx2	CK7, ER, WT1, PAX8
FIGO Stage at diagnosis	51% stage III 29% stage IV	58-64% stage I	58-64% stage I	58-64% stage I	78% stage I
Platinum-based chemotherapy response	More than 70%	60%	22-56%	20-60%	4-40%
Five-year survival	10-26.9%	82%	66%	71%	88%

FIGO: International Federation of Gynecology and Obstetrics; IHC: Immunohistochemistry

Pathogenesis of endometriosis

Even though endometriosis has been recognized for around 150 years [17] there have only recently been advances in the understanding of its molecular pathogenesis [60]. There are several theories of pathogenesis as outlined below:

Retrograde or "reflux" menstruation: Retrograde menstruation has been a longstanding hypothesis of endometriosis [61,62] and is said to occur in most menstruating women [17]. It is postulated that abnormal eutopic endometrium confers a survival advantage for endometrial cells when they reach peritoneum [49,63]. A large number of differentially expressed genes (72 in total; 66 up-regulated and 6 down-regulated) were identified in eutopic endometrium samples from women with endometriosis and the mRNA products identified were associated with angiogenesis, extracellular matrix remodelling, cell proliferation and differentiation [63]. In particular matrix metalloproteinases (MMP) 3,10,11 and 27 were over expressed and these proteins are thought to aid attachment and invasion of retrograde menstrual endometrial cells on the peritoneal and ovarian surface [64,65]. Suda *et al.* provide genomic evidence in support of this hypothesis by demonstrating an overlap in somatic mutations in eutopic endometrium compared with that in corresponding ovarian endometriomas [66].

Coelomic metaplasia: An alternative theory of pathogenesis of endometriosis is in-situ metaplasia of peritoneal surface serous epithelium (coelomic epithelium). Metaplasia is the transformation from one fully differentiated epithelial type into another [67].

Metastasis: Metastasis of endometrial tissue via lymphatics and blood vessels to sites distant from their origin has long been considered a cause of endometriosis [68]. This pathogenetic mechanism may be restricted to deep, infiltrating types of endometriosis [20]. There is evidence to support this idea as it has been shown that deep infiltrating endometriosis shows different epithelial cell genetic mutations compared with peritoneal endometriosis [22,69-71].

Heredity: There is a 2 to15% risk of developing endometriosis if a first-degree relative is affected [72] and around 50% of women with endometriosis have a family history [73,74]. Genome wide association studies (GWAS) have been carried out to try to delineate which genes may be involved [72,75]. A meta-analysis by Sapkota *et al.* [74] describes 14 gene loci that have are thought associated with a risk of developing endometriosis. There is a concentration of loci on chromosomes 2, 6 and 7 involving *GREB1, ETAA1, FN1* and *IL1A* on chromosome 2, *CCDC170, ID4* and *SYNE1* on chromosome 6 and two loci located within intergenic regions on the short arm of chromosome 7; one 99kb upstream of miRNA148a at locus 7p15.2 and the other 290kb upstream of *NFEL2L3*. These findings are based on high-throughput sequencing from a large cohort of people; 17,045 endometriosis cases and 191,596 controls using robust methods. How these genes determine heritability is a complex question which is, as yet, unanswered.

Environmental factors: High-levels of environmental dioxin, oestrogen and oestrogen-like compounds have been suggested by some as a potential contributor to developing endometriosis, but it is difficult to attribute risks to a single chemical [17,76]. There are also case reports of tamoxifen causing a proliferative, architectural atypia within endometriosis of the ovary [77].

Somatic genetic events in endometriosis, atypical endometriosis and EAOC

Scott was one of the first people to recognize the association between endometriosis and malignancy [78]. The risk of malignant transformation from usual type endometriosis is estimated to be between 0.3% and 2% [2,3]. Atypical features of endometriosis in the absence of a co-existing malignancy is rare and estimated to be present in only 1.7% of cases of ovarian endometriosis [79]. Some authors suggest that severe atypia is a precursor for malignant change [80-82].

The malignant transformation of endometriosis appears to occur on a background of oxidative stress and inflammation induced by cycling endometrial glands that produce reactive oxygen species and free iron from breakdown products of haemoglobin [83-85]. These background features result in clear cell carcinoma which is estrogen receptor negative by immunohistochemistry (IHC) and HNF1beta positive as a result of up regulation of gene expression stimulated by hypoxia [86,87]. In contrast, endometrioid ovarian adenocarcinomas tend to be ER positive and HNF1beta negative due to background hyper-estrogenism [50,87,88].

HNF1beta has also been shown to be upregulated by nuclear positivity by IHC and to have a hypomethylated gene promotor in clear cell renal cell carcinomas [89]. Integrative bioinformatics links HNF1B with clear cell carcinoma and tumor-associated thrombosis. Both renal and gynaecological origin clear cell carcinomas clinically show a tendency towards thrombosis and an explanation for this observation may lie in the finding that HNF1B transcriptional targets include molecules that govern the blood clotting pathways [90]. Developments in this area may lead to tumor agnostic oncological therapies in the future [91].

Table 2 summarizes this data from a total of 987 samples in comparative form between these diagnostic groups as a percentage of the number of samples tested. No data is recorded for endometriosis in this cancer database due to its current classification as a benign entity. The COSMIC database also describes the type of mutation most commonly seen in EAOC as separate groups, clear cell and endometrioid–type adenocarcinoma. Missense mutations are by far the most common type of somatic mutation as can be seen in **Table 3**. The Catalogue of Somatic Mutations in Cancer (COSMIC) database records point mutations in somatic genes of ovarian neoplasms associated with endometriosis (histological type not otherwise specified, from ovarian clear cell carcinomas and ovarian endometrioid carcinoma [92].

One can see from the data that the overall majority of mutations for both types of cancer are missense, which means a single nucleotide change resulting in a different codon that incorporates an alternative amino acid into the protein sequence. COSMIC also records the presence of copy number variation, gains and losses, for approximately 150 other genes in clear cell carcinoma and around 60 genes in endometrioid carcinoma.

Copy number variants have also been described in endometriosis alone and are said to contribute to its development [93]. This includes gains in sub-telomeric regions of chromosomes 1p, 16p, 19p, and 20p and losses in 17q and 20q [93]. The inter-genic locus 19q13.1 was also noted to have a particular association with endometriosis in this study [93].

Table 2: Somatic genes recorded as mutated in the COSMIC database for endometriosis-associated ovarian cancers (EAOC). Source: https://cancer.sanger.ac.uk, accessed 18th July 2019 [92].

Gene	Ovarian EAOC, not otherwise specified	Ovarian Clear Cell Carcinoma	Ovarian Endometrioid carcinoma
PIK3CA	21	33	23
ARID1A	50	50	25
TERT	0	17	0
KRAS	4	8	14
PPP2R1A	0	8	6
TP53	0	11	51
CKDN2A	0	6	8
CTNNB1	34	3	27
PTEN	31	4	18
FBXW7	0	6	7
BRAF	0	1	3
SMARCA4	0	10	0
BRCA2	0	9	11
KEAP1	0	9	0
SPOP	0	12	10
NRAS	0	3	0.047
FGFR2	0	3	3
ATM	0	3	0.026
KDM5C	0	6	0
ARID1B	0	9	0
POLE	0	0.02	18
APC	0	0	9
BRCA1	0	0	8
ATR	0	0.27	26
BRIP1	0	0.	29
PIK3R1	0	0.029	11
FGFR2	0	0.033	3
ERBB2	0	0.031	3
CTCF	2	0	0
CARD11	2	0	0
Total samples tested	**62**	**491**	**434**

Table 3. Somatic gene mutational type as recorded in COSMIC online database for endometriosis-associated ovarian cancers: endometrioid and clear cell carcinomas. Source: https://cancer.sanger.ac.uk, accessed 18th July 2019 [92].

Mutation Type	Clear Cell Carcinoma: Number	Clear Cell Carcinoma: Percentage	Endometrioid Carcinoma: Number	Endometrioid Carcinoma: Percentage
Nonsense	57	11.61	33	7.60
Missense	336	68.43	358	82.49
Synonymous	1	0.2	22	5.07
In-frame insertion	4	0.81	1	0.23
Frame-shift insertion	34	6.92	10	2.30
In-frame deletion	4	0.81	6	1.38
Frame-shift deletion	59	12.02	26	5.99
Complex	3	0.61	1	0.23
Other	15	3.05	17	3.92
Total	**491**	**100**	**434**	**100**

One of the most common and well-studied somatic gene mutations in clear cell and endometrioid adenocarcinoma of the ovary is in the *ARID1A* (AT-rich interaction domain containing protein 1A) gene [94]. Authors suggest that this gene acts as a tumor suppressor in normal cells and mutation results in malignant transformation as an early event in the process [95-98]. *ARID1A* is mutated in 42-61% of clear cell carcinomas and 21-33% of endometrioid carcinomas [20]. The normal protein product of *ARID1A*, BAF250a, forms part of the SWI/SNF chromatin remodeling complex [99] and may therefore have interactions with non-coding RNAs as part of normal cell transcription control mechanisms. *ARID1A* has been shown to interact with the long non-coding RNA molecule *MVIH* and alterations of this interaction as a result of *ARID1A* gene mutations have been implicated in the pathogenesis of hepatocellular carcinoma [100]. *HOTAIR* is another lncRNA molecule that has been shown to interact with chromatin remodeling complex proteins such as BAF250a in cancers that metastasize [101,102] and this pathway has recently been shown to have potential for developing new treatments in renal cell carcinoma [103]. The most common form of renal cell carcinoma has a clear cell phenotype similar to that of clear cell carcinoma of the ovary. It may be that similar molecular events in these cancers yield a similar phenotype. The COSMIC database of mutations illustrates that the majority of mutations in the *ARID1A* gene are nonsense type and therefore likely result in a truncated for of protein if its corresponding messenger RNA is translated (https://cancer.sanger.ac.uk). This process results in loss of expression of the BAF250a protein, which can be detected by immunohistochemistry in tissue sections in normal tissues [104]. Some authors suggest loss of this protein in atypical endometriosis without neoplasia is a useful indicator of high risk to progression to cancer [104,105]. However, there is no clear evidence to date that BAF250a can predict prognosis in EAOC or highlight treatment options [94,106].

Another frequent mutation in ovarian clear cell carcinoma arises in *TERT* (Telomerase reverse transcriptase) and confers a poor prognosis when present [107,108]. A study of 525 gynecological cancers showed that longer telomeres were a particular feature of clear cell carcinoma and that this mutation tended to be mutually exclusive with loss of ARID1A protein expression [109]. This is of particular relevance as non-coding RNA is involved in the regulation of telomerase [110] and the Telomerase RNA Component (TERC) gene is overexpressed in several human cancers [111-113].

PIKC3A (Phosphatidylinositol 3-kinase, catalytic, alpha) somatic gene mutations are more common than *TERT* in both clear cell and endometrioid types of ovarian adenocarcinoma. *PIKC3A* mutations have been shown to be an early event in the neoplastic transformation of endometriosis of the most common genes to be mutated in both clear cell and endometrioid types [114,115]. *PIKC3A* mutations are often seen in conjunction with *CTNNB1* (Catenin, beta1) mutations [116] but *CTNNB1* mutations are much more common in endometrioid type ovarian carcinoma than clear cell carcinomas. Both these mutations have also been found together in cells of atypical endometriosis in a context of synchronous carcinoma [117]. Mutations in *CTNNB1* are also frequently seen in endometrioid carcinoma of the uterine cavity and catenin mutations are seen at around the same rate [118]. Microsatellite instability and *PTEN* mutations are seen less frequently in endometrioid ovarian EAOC than compared with endometrial primaries [118] but given there are some overlaps between the somatic genetic mutations in ovarian and endometrial endometrioid-type adenocarcinomas it is likely that there are also overlaps in the genetic expression profile, otherwise known as transcriptomics.

Transcriptomics

An expression microarray study of eutopic endometrium from patients with endometriosis found potential candidate genes that predispose to developing endometriosis included FOXO1A, MIG6 and CYP26A1 [119].

There are differences with respect to carcinogenesis. However, Fridley *et al.* found that 32 protein-coding genes were expressed

in a mixed group of endometrioid and clear cell carcinomas of the ovary and these included MAP2K6, KIAA1324, CDH1, ENTPD5, LAMB1, and DRAM1 [120]. Tassi *et al.* have shown that FOXM1 expression is associated with a worse prognosis in non-serous types of ovarian cancer [121]. Clear cell and endometrioid types of ovarian malignancy are said to have an expression profile similar to that of normal endometrium according to findings of microarray studies [122]. The expression profiles appear different between clear cell and endometroid adenocarcinoma groups when compared with normal surface ovarian epithelial cells. It has been found that the greatest difference in gene expression in endometrioid carcinomas lies between SERPINA1, MT1G, and CXCL14 genes compared with clear cell carcinoma where there are differences in PROM1 ABP1 and RBP4 [122]. It is interesting to note there is no overlap between the genes expressed in these EAOC tumours and those listed as somatically mutated genes in the COSMIC database; it may be that functional expression of RNA and protein is more important in pathogenesis of EAOC than the mere presence of a somatic gene mutation which is not transcriptionally active.

Non-coding RNA

Non-coding RNA is transcribed from DNA but does not encode protein and accounts for around 70% of the human genome [123-125]. Many thousands of non-coding RNA molecules are known, and they take different forms [126,127]. They can be classified according to where in the genome they are coded and by the size and shape of the molecules, as seen in diagram 1 [10]. Long non-coding RNAs (lncRNAs) are more than 200 nucleotides long and linear according to this scheme [10].

The function of LncRNAs is diverse and predominantly regulatory in nature [16]. They are involved in epigenetics and interact with polycomb repressive proteins to acetylate or methylate histone proteins in chromatin to regulate DNA activation or repression [128,129]. They are also involved in imprinting, for example the lncRNA molecule XIST is responsible for suppression of transcription of one of the X-chromosomes in female humans [130,131].

LncRNA molecules are key regulators of pre- and post-transcriptional control of gene expression [16]. In pre-transcriptional control they can act in *cis* by regulating transcription factors adjacent to or overlapping their site of coding and, due to both their length and ability to form 2- and 3-dimensional structures, they can act in *trans* to regulate transcription factors at sites distant to their location [16,132,133]. They can also regulate mRNA splicing within the nucleus [134]. In post-transcriptional control of gene expression, lncRNAs can interact with microRNA molecules that target messenger RNA for degradation before translation into protein [132].

Long non-coding RNAs are known to have oncogenic and tumour suppressor activity in a variety of human cancers [132,135,136]. Hanahan and Weinberg described six key defining features of malignancy and lncRNA molecules have been found to be involved in cell pathways for all these features; they include sustaining proliferative signalling, evading growth suppressors, enabling replicative immortality, activating invasion and metastasis, inducing angiogenesis and resisting cell death [132,137]. These findings are summarized in **Table 4**.

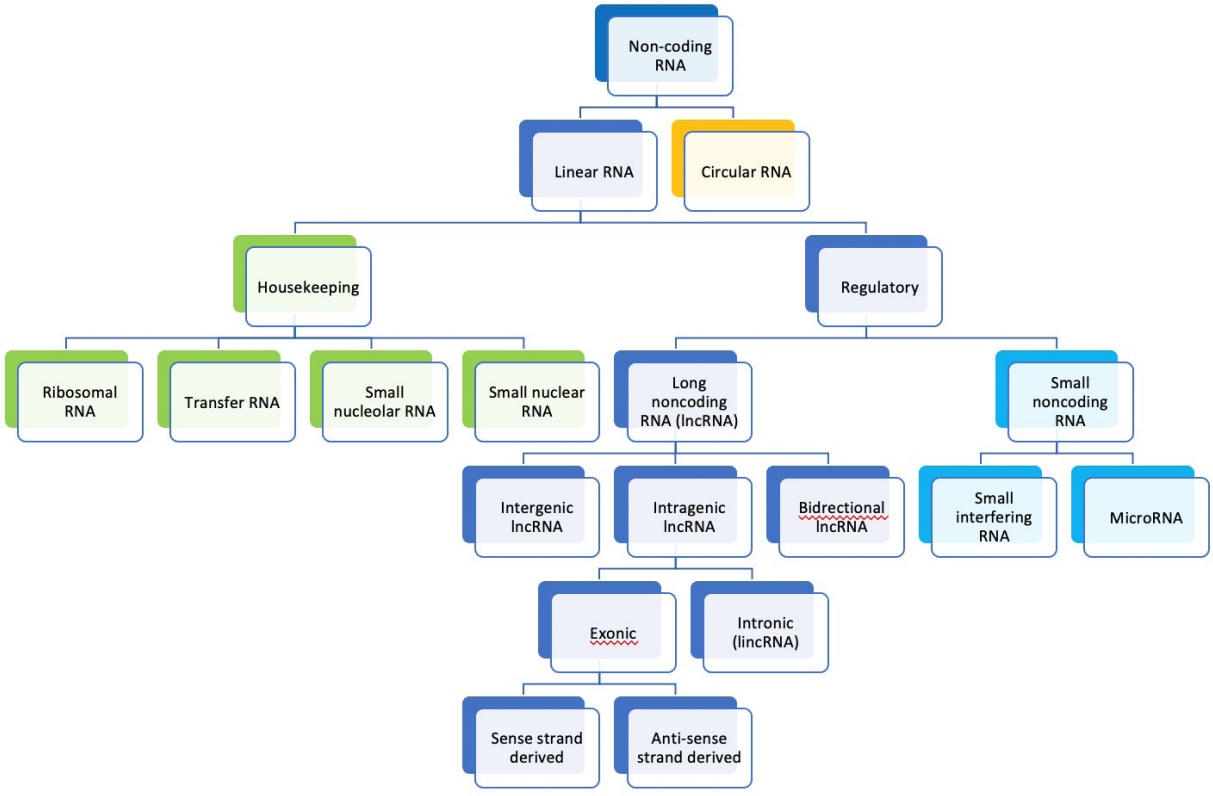

Figure 1. Classification of RNA molecules according to size and cellular function [10].

Table 4. Long non-coding RNA molecules in the pathogenesis of cancer [132].

Cancer Hallmark	LncRNA	Mode of Action
Sustaining proliferative signalling	SRA	Transcriptional co-activator
	PCAT-1	Regulates gene expression
	RN7SK	Regulated transcription
	KRASP1	miRNA sponge
Evading growth suppressors	ANRIL	Chromatin remodelling
	GAS5	Competitor
	lincRNA-p21	Transcriptional co-repressor
	E2F4 antisense	Regulates gene expression
Enabling replicative immortality	TERC	RNA primer
	TERRA	Enzymatic inhibitor
Activating invasion and metastasis	MALAT1	Modulates protein activity
	HOTAIR	Chromatin remodelling
	HULC	miRNA sponge
	BC200	Translational modulator
Inducing angiogenesis	AlphaHIF	RNA decay
	sONE	RNA decay
	tie-1AS	RNA decay
	ncR-uPAR	Regulates gene expression
Resisting cell death	PCGEM1	Regulates gene expression
	SPRY4-IT1	Unknown
	PANDA	Modulates protein activity
	LUST	RNA-splicing

Long non-coding RNA (lncRNA) in endometriosis, atypical endometriosis and endometriosis-associated ovarian cancers

Endometriosis: There is emerging evidence regarding non-coding RNA expression in endometriosis [9,10,138,139]. Cui *et al.* looked at the profile of messengers RNA transcripts and non-coding RNA sequences present in the endometrial biopsies from women with and without endometriosis. They describe a large data set and show impact on a number of cell signaling pathways involved in angiogenesis, proliferation, invasion, adhesion and migration. They discovered eighty-six lncRNAs in their data set, 22 of which were considered novel. The SNORD3A (a type of small nucleolar RNA involved in resistance to oxidative stress [140] was the most up-regulated and ABO was the most down-regulated of the known RNA molecules found in comparison with controls [9]. TCONS_00006582 and TCONs_08347373 were novel transcripts of unknown function or relevance [9]. This study is of questionable reliability given that ABO is a protein-coding gene and the authors have included a snoRNA under the lncRNA classification.

Atypical endometriosis: There are no published studies regarding the lncRNA profiles found in epithelial cells of atypical endometriosis to date. This perhaps reflects the rarity of isolated atypical endometriosis of the ovary.

Endometriosis-associated ovarian cancer: LncRNA molecules play a role in ovarian carcinogenesis by affecting a number of cell signalling pathways from cellular proliferation, apoptosis and control of the cell cycle to conferring drug resistance and propagating neoplasm to invade and metastasize [9,12,16,141]. There are no papers that describe the influence of lncRNA specifically regarding carcinogenesis of EAOC but there is evidence regarding the role of microRNAs (miRNAs) [142] and circulating blood miRNA molecules have been targeted by researchers as potential diagnostic biomarkers for endometriosis as compared with a surgical tissue biopsy [143-146]. Given that lncRNAs interact with cytoplasmic miRNA in post-transcriptional control of mRNA translation, it may be that lncRNAs also play a significant role in pathogenesis of EAOC and represent potential as biomarkers for diagnosis.

There is overlap in expression profiling seen between clear cell and endometrioid carcinomas and that seen in normal endometrium and this may be reflected in lncRNA activity also [122]. We know that *NEAT1* is overexpressed in endometrial endometroid adenocarcinoma and is thought to be a critical step in pathogenesis of this malignancy [147]. *MALAT1, HOTAIR, OVAL,* and *H19* lncRNAs are also overexpressed in endometrioid carcinoma of the endometrium [148].

MALAT1 promotes development of endometrioid carcinoma via regulation of the wnt/beta-catenin signalling pathway [149,150]. MALAT1 has also been implicated in regulation of cellular apoptosis in 'ovarian cancer' via influence on the PI3K/AKT cell signaling pathway [151]. MALAT1 may also affect functioning of microRNA molecules miR-211 and miRNA-506 resulting in tumorigenesis in the ovary according to some studies [152-155].

HOTAIR, otherwise known as homeobox transcript antisense intergenic RNA, has been found to be up-regulated in endometrial carcinoma using in-situ hybridization methods specific to this lncRNA [14]. *HOTAIR* is transcribed from intergenic regions of the cluster of Homeobox genes which are usually only expressed in embryonic development as they are responsible for overall organizational development of living organisms [156].

He *et al.* suggests that overexpression of *HOTAIR* is correlated with a poorer clinical outcome in this cancer type, but their experimental sample contained a mixture of serous and endometrioid types of endometrial cancer and therefore calls the significance of the study findings into question [14]. *HOTAIR* has also been found to be transcriptionally up-regulated in response to increased estrogen levels which may have implications for endometriosis sufferers [157,158].

OVAAL (ovarian adenocarcinoma amplified lncRNA) is found on chromosome 1 at locus 1q25 and has been shown to over-expressed in endometrioid and serous carcinomas of the ovary [159,160]. Its function within ovarian carcinoma cells is not yet known [148].

H19 is an imprinted gene expressed from maternally inherited chromosomes and yields a well-researched lncRNA molecule in humans [161,162]. *H19* is only expressed in embryonic tissues under normal physiological conditions but is found to be overexpressed 85% of ovarian cancers and some benign uterine neoplasms [163-165]. It is associated with the ability of neoplasms to metastasize [163,166]. *H19* is on chromosome 11 and codes for a MAP kinase protein as well as miRNA 675 and a lncRNA molecule involved in cyclicity of endometrial mucosa [167,168]. *H19* has been shown to be involved in regulation of steroid hormone synthesis [169] and this may be why it has been implicated in the pathogenesis of endometrial hyperplasia and endometrioid carcinoma [170]. *H19* levels have also been found to be inversely proportional to the degree of endometrioid adenocarcinoma differentiation and so, by inference, correlates with prognosis and survival [170,171]. Other studies suggest that *H19* promotes ovarian malignancy by interacting with cell signaling pathways promoting cell proliferation and inhibiting apoptosis [172,173]. Interestingly, there have been recent phase 1 dose-toxicity trials aimed at treatments directed at *H19* in patients with platinum resistant tubo-ovarian high-grade serous carcinoma [174].

There are many other lncRNA molecules that have been implicated as being involved in ovarian carcinoma pathogenesis and these include *SOX2OT, DGCR5, PC3A, FAL1, ABO73614, HULC, ZFAS1, HST2, LSINCT5, PVT1, TUG1, ANRIL, PVT1, HOST2, GAS5, PTAF, LINK-A, HOXA11-AS, BC200,* many of which are said to act as oncogenes [146,148,175-177]. Most of these studies refer to ovarian cancer as though it were a homogenous single entity. If a mixed collection of histological types of ovarian carcinoma were used this would generate unreliable results as discussed above [178]. Having a collection of pure tissue samples for sequencing is perhaps even more important in the context of lncRNA as these molecules are thought to be pivotal in determining cell differentiation [16,179]. Any study resulting from this literature review will use accurate histopathological classification of ovarian carcinoma to generate a robust data set regarding the presence of non-coding RNA molecules.

Conclusion

Long non-coding RNA molecules are involved in carcinogenesis through interactive networks alongside messenger RNA and microRNAs. We are just beginning to piece together the complex pathways that exist governing protein expression and it is clear that non-coding elements o the human genome are most definitely not 'junk' [131]. There is evidence that H19, MALAT1, OVAAL, HOTAIR, and possibly NEAT1, may be involved in the pathogenesis of EAOCs but, to date, much of the work has justifiably focussed on high-grade serous carcinoma due to its common occurrence [11,37,180]. There is a need to clarify the relevance of lncRNA molecule sin EAOCs, and particularly in ovarian clear cell carcinomas because of the frequency of resistance to standard platinum-based chemotherapy with consequent poor prognosis [38,181].

Future Directions

LncRNA molecules represent potential biomarkers for early diagnosis of EAOC by less invasive methods than surgery [142] and could also be used as a starting point for discovery of novel oncological drugs [182].

It remains to be seen what spatial resolution may bring to the understanding of EAOC pathology as both for protein coding gene expression and for the non-coding genome. LncRNAs are not well studied by this method but reasons for employing this technique To EAOC pathology are clear; spatial transcriptomics will allow focus on the epithelial cells forming atypical endometriosis, in the background of EAOCs and also in standalone cases, where the number of cells of interest are few [183,184]. Digital spatial profiling (DSP) holds great promise for enhanced reproducibility within the field of cancer research [184]. DSP will allow for detailed exploration of tumoral heterogeneity and focused correlation with phenotype, the cornerstone of clinical interpretation of genetics, somatic and constitutional [185-187]. Better understanding of the pathogenesis of EAOC may help inform development of lncRNAs by immunohistochemistry may open up a new angle on research in this domain and create opportunities for translation to clinical diagnostic practice as a form of companion diagnostic test that is rapid and cost effective for the NHS to administer [14,188].

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