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Review

Long non-coding RNAs and cervical cancer

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ABSTRACT

Cervical cancer is determined as the second highest number of deaths factor in female cancers. Here is a need to find new biomarkers for detection and preliminary prognosis, metastasis. To find new treatment to enhance the survival of cervical cancer patients, pivotal actions are necessitated to be implemented. Long non-coding RNAs (lncRNAs) appear to be the crucial modulators in various processes and critically influence the oncogenesis. The commencement and general review actions of the following lncRNAs *HOTAIR*, *H19*, *XIST*, *CCHE1*, *EBIC*, *MALAT1*, *ANRIL*, *LET*, *NEAT1*, *BLACAT1*, *UFC1*, *SNHG16* and *SNHG20* are focused in this review article. Roles of the lncRNAs in cervical cancer in terms of prognosis and tumor progression, invasion and metastasis, apoptosis, and radio-resistance are pointed out. In this review the utilization of lncRNAs as biomarkers in cervical cancer prognosis for metastasis is discussed. An overview of this review will be useful for selection of biomarkers in diagnosis, prognosis, and targeted therapy of cervical cancer in the future.

1. Introduction

Cervical cancer is known as one of the most prevalent malignant gynecological tumors which is accounted for 10–15% of female cancer-relevant deaths around the world, leading to the second highest number of deaths in female cancers (Ojesina et al., 2014). Roughly 80% of the patients are recognized with malignant cancer. Many studies demonstrate that, cervical cancer still carries high risks of morbidity and mortality which originates from metastasis and recurrence (Wang et al., 2014a). An immense requirement and urgent biomarker investigation of preliminary prognosis and metastasis as well as novel found treatment purposes are needed to enhance the cervical cancer survival. Despite Pap smear screening application and its result in lessening of the cervical cancer occurrence considerably, cervical cancer is still ranked as the third most common diagnosed cancer worldwide. As it has been observed in many studies, the somatic mutations, including single nucleotide polymorphisms (SNPs) in tumor suppressor genes and oncogenes play an essential role in the genetic susceptibility of cervical cancer (Yang et al., 2016). Recent studies have shown that, hormone replacement therapy usage, high-risk human papilloma viruses (HPVs), genetic factors and smoking habits have been implicated in the pathogenesis of cervical cancer (Gadducci et al., 2011). In accordance with the aggregated evidences, the survival and treatment rate for cervical cancer in the early stages (stage I–II) is up to 80–90% and 60% in stage III, but the prognosis is negligible after cancer development to an advanced stage or relapse. Many lncRNAs are discovered and play the novel regulatory role of molecular biology in many cancers including cervical cancer. It has been strived to abbreviate the provenance and conspectus function of lncRNAs, and accentuate their actions in cervical cancer, and simultaneously summarize the molecular mechanisms of lncRNAs in cervical cancer through this review. The lncRNAs application as biomarkers in prognosis of cervical cancer and a predictor for metastasis is discussed as well. The mechanisms of cervical cancer are vague, roughly more than 520,000 cervical cancer cases are diagnosed and reported annually, of which more than 80% of them are diagnosed in the developing countries (Jemal et al., 2011). The studies have suggested that lncRNAs (long non coding RNAs) have pivotal roles in commencement and advancement of human cancers (Wu et al., 2014a). Many lncRNAs repress metastasis, and assist in the prognosis of metastasis via their expression levels in cervical cancer (Chen et al., 2015a). LncRNAs are aberrantly expressed in cancer and their expression levels are correlated with relapse, prognosis, metastasis, and prediction of response to cure (Serviss et al., 2014). Diverse lncRNAs act as both oncogenes and tumor suppressors, and play a vigorous role in modifying cancer development (Sun et al., 2014a).

2. Biogenesis and functions of non-coding RNA

Protein-coding genes have the responsibility of producing just 2% of the human transcriptions. However, the bulk of transcripts are non-coding RNAs (ncRNAs) encompassing microRNAs (miRNAs) and long ncRNAs (lncRNAs) (Ma et al., 2015a). Noncoding RNAs are protected

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and have clearly defined roles (Hu et al., 2016). MicroRNAs (miRNAs) are category of small noncoding RNAs consisting of 19 to 23 nucleotides in length and substantially studied type of ncRNAs (noncoding RNAs) (Awan et al., 2018). It is appraised that miRNAs embody 0.02% of entire cellular RNA, and post transcriptionally, modulate more than 60% of coding genes areas (Tang et al., 2015). Every miRNA commonly modulates the target genes expression by connecting to their 3′ untranslated region (UTR), as a result of that suppresses gene expression by mRNA depreciation and translation prohibition (Awan et al., 2018; Djuranovic et al., 2012). MicroRNAs play dispensable roles in the modulation of the cell cycle program of normal and cancer cells (Yang et al., 2013a). Several studies have shown that 76% of the human genome transcribed to produce a series of lncRNAs, which it is what precisely the ENCODE plan has been insinuated (Zhao et al., 2013). LncRNAs are RNAs with 200 nucleotides (nt) in length, which are often transcribed by RNA polymerase II, having abundant structural characteristics of the mRNAs, consisting of a poly (A) tail, a 5′-cap, and a promoter structure and are in need of the conservative open reading domain (He et al., 2014a; Rashid et al., 2016). Several investigators have shown that, lncRNAs have no protein coding capacity and are capable to be restricted to the nucleus and cytoplasm (Ip & Nakagawa, 2012). lncRNAs act as regulators of cellular processes in diverse ways: (a) signaling lncRNAs act as molecular signals in cellular processes for instance, the inactivation of X chromosome by lncRNA-*XIST* and cellular conditions results in the activation of gene transcription by enhancer RNAs (eRNAs); (b) enticing lncRNAs interconnect to their targets and prohibit their actions in the nucleus or cytoplasm; (c) guide lncRNAs first connect to specific proteins, then guide the ribonucleoprotein complexes to specific locations; (d) scaffold lncRNAs have varied parts, which are capable to recruit various effectors (Chen et al., 2018a). By the application of the huge throughput sequencing and other research technologies, the bio-functions of lncRNAs were systematically getting to be perceived (Ye et al., 2014). In spite of lncRNAs function in wide range of cellular processes, including cell growth, survival, migration, invasion, differentiation, and so forth (Sun et al., 2013), the bio-functions and molecular mechanisms of lncRNAs in human diseases and cancers stayed significantly unsolved (Ling et al., 2015). The recent development in sequencing technique in recent years, the prevalent existence of lncRNAs in eukaryotic organisms has been corroborated, and also their action mechanisms and essential biological functions have gradually been illuminated. It is not quite apparent for the attribution of the lncRNAs. Gene mutations, chromatin's rearrangement, retro-transposition, tandem duplication events, and insertion of a transposable element are the various feasible approaches for the origination of lncRNAs as Ponting et al. declared (Ponting et al., 2009). According to their genomic vicinity among neighboring transcripts, the synthesis of lncRNAs is organized into five categories: (1) sense-strand synthesis, (2) antisense-strand synthesis, (3) bi-directional synthesis, (4) intronic synthesis, or (5) intergenic synthesis (known as lincRNAs as well) (He et al., 2014b). According to accumulated evidences, lncRNAs are essential in the physiological events such as gene imprinting, dosage compensation, and gametogenesis (Chen et al., 2018a; Quinn & Chang, 2016). They have the capability of adjusting gene expression at chromatin modification, transcription, and post-transcriptional level (Fig. 1, A-G). They display their critical roles particularly in cancer initiation and development (Wierzbicki, 2012). Long non-coding RNAs (lncRNAs) are conceivable to be as beneficial diagnostic biomarkers (Lee et al., 2011), found in the body fluids of humans (Koh et al., 2014).

3. Deregulated circulating lncRNAs in cervical cancer

Cervical cancer is a complex illness, many elements are involved in its occurrence. Several investigators have proposed that lncRNAs can be utilized for diagnosing and prediction of prognostication tumor (Tong et al., 2015). Since their expression is a preferred symptom of cancer state, using lncRNAs as biomarkers will be an edge, compared to protein-coding RNAs (Hauptman & Glavač, 2013). The deregulated expression of lncRNAs, observed in tumor tissues and biological fluids vigorously corresponds to the cellular functions explained as the hallmark processes of cancer (Hirata et al., 2015). Pursuant to many studies, lncRNAs play pivotal roles in the progression of cervical cancer. Mainly, the development of non-coding RNA (ncRNA) biomarkers belongs to the assessment of their expression levels in tumor tissues. Despite of the logical association between ncRNA expression and patient diagnosis, this procedure is restricted by essential invasive processes for tissue collection. This restriction will bear the stimulation of cell-free ncRNAs analysis, which are existent in different bodily fluids or confined in extracellular vesicles discharged by cells. The circulating ncRNAs are found to be appropriate biomarkers for cancer diagnosis and prognosis, as they are constant and can be discovered by common techniques such as qRT-PCR. However, their total concentrations in body fluids are generally low, which influences their definite quantification (Huang et al., 2013). Recent studies have shown that the dysregulation of lncRNAs is led to various illnesses consisting of cancer (Hajjari & Salavaty, 2015). The expression of diverse lncRNAs in variety of tumors was inspected by Du et al. (Du et al., 2013).They distinguished clinical scenario of lncRNAs and their connection with various cancers. Dysregulation of lncRNAs is linked to prognosis, metastasis, and recurrence in varied cancer types. Studies have shown that the dysregulation of certain lncRNAs influence different processes associated to oncogenesis, embracing cell growth and proliferation. (Martens-Uzunova et al., 2014). Tumor growth enhancement and matrix invasion of cancer cells originate from over-expression of some lncRNAs with proto-oncogenic function in normal cells (Qiu et al., 2013). On the other hand, over-expression of oncogenic lncRNAs leads to tumor-cell proliferation and metastasis through chromatin looping and some other processes as well (Walsh et al., 2014).

4. LncRNA-*HOTAIR*

LncRNA-*HOTAIR* as a carefully deliberated long non-coding RNA (lncRNA), is found by Howard Chang et al. in 2007 (Rinn et al., 2007). It is on human chromosome 12q13 and settles at the mammalian HOXC gene cluster with transcription of 2158 nucleotides (Rinn et al., 2007). LncRNA-*HOTAIR* is practically in correlation with the polycomb repressive complex2 (PRC2) and LSD1/CoREST/REST complexes and harmonizes targeting of PRC2 and LSD1 to chromatin for histone H3K27 methylation and K4 demethylation (Tsai et al., 2010). The overexpression of lncRNA-*HOTAIR* has been announced in many human malignancies such as breast cancer, lung cancer, gastric carcinoma, pancreatic cancer, and hepatocellular carcinoma, which is corresponded with tumor invasion, metastasis, and poor prognosis (Ishibashi et al., 2013). Studies have shown that over-expression of lncRNA-*HOTAIR* is responsible for advancement of cellular proliferation and cell cycle progression, and elevates migration and invasion, as well as suppresses cell death. On the other hand, under-expression of lncRNA-*HOTAIR* slows down cellular proliferation and arrests cell cycle, decreases migration and invasion, and increases much needed cell death. Under-expression of lncRNA-*HOTAIR* represses growth and boosts the radio-sensitivity of cervical cancer in vivo. LncRNA-*HOTAIR* acts as an oncogene in cervical cancer, which prompts tumor invasion and metastasis by developing diverse belligerent biological behaviors. In addition, according to its prevalent impacts on tumor invasion and metastasis, it is illustrated that lncRNA-*HOTAIR* prompts the proliferation of cervical cancer. LncRNA-*HOTAIR* applies pro-oncogenic recreations and promotes invasion and metastasis, which possibly leads to the cancer in various species (Kim et al., 2013). LncRNA-*HOTAIR* is in association with lymphatic vascular space invasion and lymphatic node metastasis. The higher expression of lncRNA-*HOTAIR* in cervical cancer has been reported. The circulating lncRNA-*HOTAIR* is reported to be upregulated in cervical cancer and is remarkably increased with

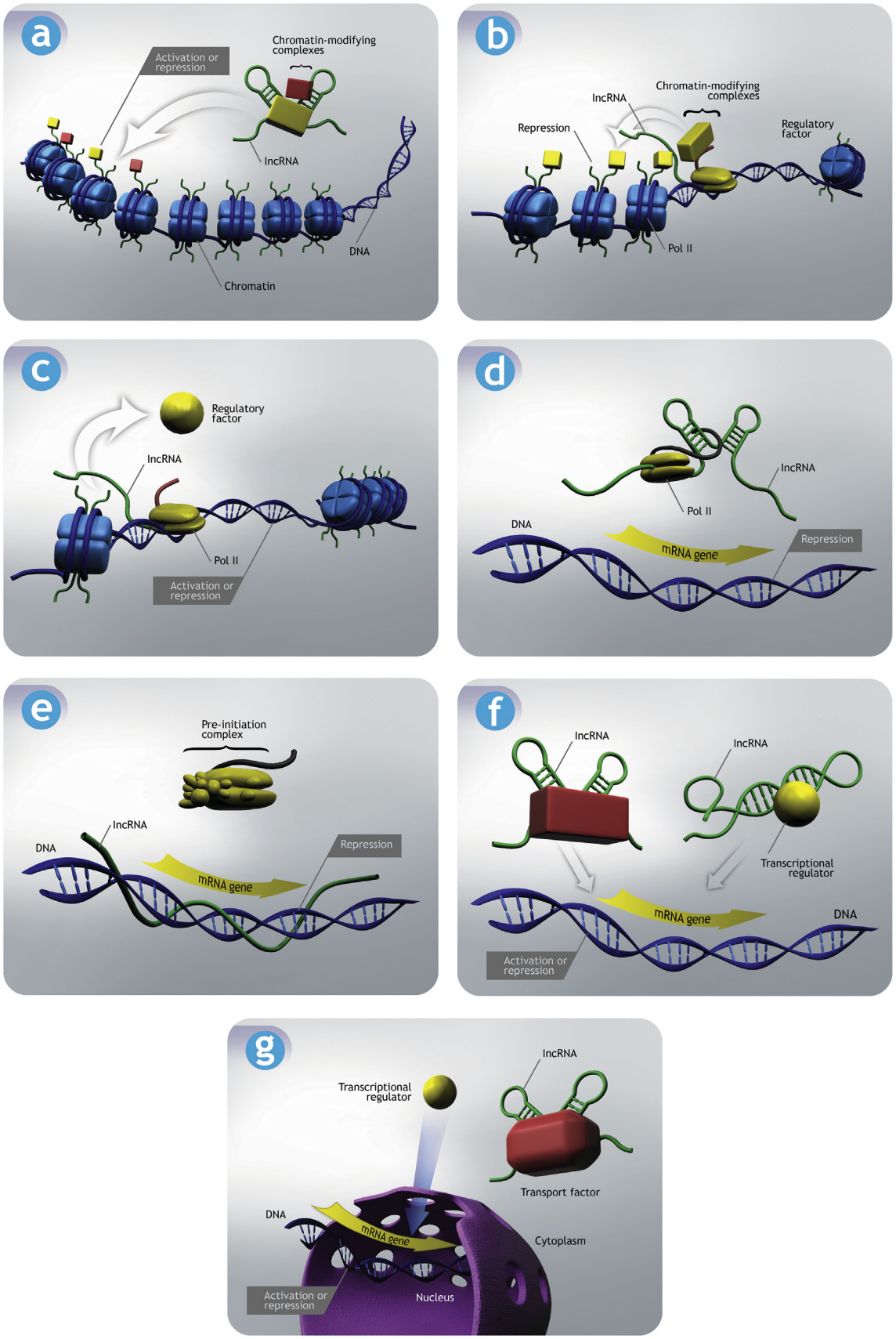

Fig. 1. A schematic diagram of the roles of lncRNAs in regulating transcription.
(a, b, c). lncRNAs playing critical roles in chromatin-modification through interaction with chromatin-modifying complexes and RNA polymerase II (Pol II) carboxy-terminal domain during the transcription process.
(d, e,f). lncRNAs can act on both the usual transcription machinery and the specific regulatory factor, which were led in the activated or repressed gene expression.
(g). lncRNAs can further manage gene expression through binding to the specific transporter agents to control the nuclear localization of special transcription factors.

tumor stage development, adenocarcinoma, lymphatic node metastasis, and deep myometrial invasion. Enhanced lncRNA-*HOTAIR* expression is correlated with tumor recurrence and decreased survival rate as well, thus it presents as a prognostic marker for cervical cancer. (Li et al., 2015a). Kim et al., (Kim et al., 2015) showed that the up-regulation of VEGF and MMP-9 and EMT-related genes in along with lncRNA-*HOTAIR* enhances tumor aggressiveness in cervical cancers. However, lncRNA-*HOTAIR* may act as a ceRNA, for miR-193a, which results in the regulation of c-KIT in acute myeloid leukemia (AML) cells (C-Y et al., 2015). In addition, lncRNA-*HOTAIR* attaches miR-331-3p to regulate HER2 expression in gastric cancer as well (Liu et al., 2014a). Many lncRNAs are discovered to be aberrantly expressed in cervical cancer. The lncRNA-*HOTAIR*, as a long intergenic ncRNA (lincRNA), based on previous reports, has crucial impacts on the most biological processes of cancer and might be utilized as probable target in tumor treatment (Wu et al., 2014b). As regards to many researches reports, lncRNA-*HOTAIR* is elevated in cervical cancer tissues and associated with FIGO stage, lymphatic metastasis, size of the tumor as well as deep invasion, that shows its collaboration in cervical cancer progression. So there would be a possibility of using lncRNA-*HOTAIR* as a probable target for the diagnosis and also as an independent predictor of overall survival (Huang et al., 2014). There is additional possibility of hastening neoplasm aggressiveness by lncRNA-*HOTAIR* through the upregulation of VEGF, MMP-9, and epithelial-mesenchymal transition (EMT)-relevant genes via decreasing the expression of E-cadherin while augmenting the expression of β-catenin, Vimentin (VIM), Snail, and Twist (Kim et al., 2015). Studies have shown that lncRNA-*HOTAIR* inhibits tumor suppressors (phosphatase and tensin homolog [PTEN] and RNA binding motif protein 38 [RBM38]), (Ding et al., 2014; Li et al., 2013). Inhibition prompts the operation of oncogenes (HER2 and MMP3), and crucial signaling pathways (Wnt/β-catenin, STAT3, and PI3K/AKT). (Liu et al., 2014b) Furthermore, the miR-17-5p action was directly targeted lncRNA-*HOTAIR* 3'-UTR. (Ji et al., 2018) When lncRNA-*HOTAIR* is repressed, miR-17-5p showed the role of tumor enhancing. Various studies have shown that lncRNA-*HOTAIR* may be applied as a novel marker for assessing recurrence and prognosis, also supplies a noteworthy aim for targeted therapy in cervical cancer.

5. LncRNA-*H19*

LncRNA-*H19* was discovered in 1984, and its function still remained to be vague. LncRNA-*H19* expression can be find either in embryonic and extra-embryonic cell lineages (Li et al., 2015b). LncRNA-*H19* is located at chromosome 11p15.5 and it encodes a 2.3 kb lncRNA (Kanduri, 2016). LncRNA-*H19* deregulation is found often in tumors, and results in cancer initiation and progression (Matouk et al., 2016). Thus, lncRNA-*H19* would possibly play a significant role in the pathogenesis of cancers. Researchers using cell culture systems and mouse models have highlighted that lncRNA-*H19* can function either as oncogenes (Tsang et al., 2009) or as a tumor suppressor. (Zhu et al., 2014). LncRNA-*H19* RNA transcripts have been discovered in a majority of patient-derived malignant lesions of cervical cancer within the past few years. (Feigenberg et al., 2013) The mechanism, lncRNA-*H19* influences the progression of cervical cancer and how it functions is enigmatic. Up-regulation of LncRNA-*H19* has been stated in many cancers. (Matouk et al., 2014; Li et al., 2014). Chen et al.; detected lncRNA- *H19* as a poor prognosis and lymph node metastasis marker in their studies (Chen et al., 2016a). However, there are several studies that show lncRNA-*H19* can be used as a diagnostic biomarker and a poor prognosis would be seen through its up-regulation in gastric cancer (Chen et al., 2016b). A paternally imprinted and maternally expressed gene called lncRNA-*H19* encodes a RNA, which functions as a "riboregulator," producing no protein (Erdmann et al., 2001). LncRNA-*H19* expression can be illustrated in many human tumor types with significant levels (Cui et al., 2002). However, it is present in minimal amounts in some of the normal adult tissues (Ariel et al., 1995). Recent evidence recommends that the lncRNA-*H19* to have a pivotal role in cancer development, angiogenesis, and metastasis though the action of lncRNA-*H19* gene is not understood completely (Matouk et al., 2007). The human lncRNA-*H19* gene is situated within 200 kb downstream of the paternally expressed IGF2 gene at chromosome 11p.15.5 (Leighton et al., 1995). Aberrant expression of lncRNA-*H19* is mentioned in various studies, such as in various cancers including breast, liver, lung, cervical, esophageal, and bladder tumors (Luo et al., 2013). It is understood that the LncRNA-*H19* has an oncogenic function and responsible for proliferation in cancer cells.

6. LncRNA-*XIST*

The X inactivation center (XIC) is where exactly, lncRNA-*XIST* settles in, and inactive X chromosome transcribes lncRNA-*XIST* production (Brown et al., 1991). Then outspreads along the X chromosome. Indispensable role of lncRNA-*XIST* gene in the commencement of X inactivation in female cells is considerable, in which attains dosage equilibration with males. The mechanisms whereby lncRNA-*XIST* begins X inactivation are still undetected. Noticeable proofs derived from the investigations indicate that lncRNA-*XIST* is involved in some other crucial roles consist of differentiation, proliferation, and genome maintenance of human cells. Dysfunctional expression of lncRNA-*XIST* particularly, may have a pathologic role in cancer, which possibly is correlated to the modifications of gene expression originating from the changes in stability of heterochromatin. There is possibility of special factors in cancer cells that permits for X inactivation outside of the embryonic progression context as well. Although there is a loss in the expression of lncRNA-*XIST* gene in the female breast, ovarian, and cervical cancer cell lines, lncRNA-*XIST* expression is seen in all female somatic cells (Benoît et al., 2007). The lncRNA-*XIST* gene and the eminent regulator of X inactivation in mammals, produce lncRNA *XIST* (Lee & Bartolomei, 2013). The relevancy between lncRNA-*XIST* expression and cervical cancer development has not been proved yet. The function of lncRNA-*XIST* and its impact on cervical cancer still needs to be identified. Considering the report released by Sun et al.; it has been clarified that, lncRNA-*XIST* plays the role of an oncogene in cervical cancer. Knocking down of lncRNA-*XIST* in cervical cancer resulted in repression of cell proliferation, invasion, and migration by EMT via Wnt/β-catenin signaling pathway. Thus, the studies suggest that lncRNA-*XIST* expression can be used as a new therapeutic strategy for cervical cancer (Sun et al., 2017a). Yao et al. suggested that the knockdown of lncRNA-*XIST* through up-regulating miR-152 applies tumor-suppressive actions in human glioblastoma stem cells (Yao et al., 2015). Fang et al. illustrate lncRNA-*XIST* function as an oncogene in non-small cell lung cancer by suppressing KLF2 expression epigenetically (Fang et al., 2016). Noticeable proofs derived from Zhou et al. investigations illustrate that lncRNA-*XIST* functions as a molecular sponge of miR-101 to regulate EZH2 expression in gastric cancer (Chen D-L, Ju, et al., 2016). It has been suggested that lncRNA-*XIST* is correlated with the OS and could be used as a potential biomarker in the prognosis of cervical squamous cell carcinoma (SCC) patients after chemo-radiotherapy. (Kobayashi et al., 2016) Though the mechanisms of lncRNA-*XIST* action in consistent with prognosis are still enigmatic.

7. LncRNA-*CCHE1*

LncRNA-*CCHE1* (Cervical carcinoma high-expressed1) is detected to be over-expressed in cervical cancer tissues, that as a specific area of excellence it enhances cervical cancer cell proliferation through increasing the PCNA (Proliferating cell nuclear antigen) level (Yang et al., 2015a). So as to promote the expression of PCNA in cervical cancer, lncRNA-*CCHE1* physically enhances proliferation which is in connection with PCNA (Yang et al., 2015a). LncRNA-*CCHE1* produces an LncRNA which delineates to chromosome 1019 (Ota et al., 2004). Studies by Meng et al. suggest prominent role for lncRNA-*CCHE1* in the

proliferation of cervical cancer and its function as a potential prognostic biomarker and therapeutic purpose in cervical cancer (Yang et al., 2015a). The Peng et al., study exhibit the lncRNA-*CCHE1* over-expression in hepatocellular carcinoma tissues which is in connection with tumor number, tumor size, and TNM stage (Peng & Fan, 2016). LncRNA-*CCHE1* is upregulated in cervical cancer tissues compared to normal tissues pursuant to Yang et al. findings (Yang et al., 2015a). Gain-of-function and loss-of-function experiments disclose that up-regulation of lncRNA-*CCHE1* advances the proliferation of cervical cancer. On the other hand, lncRNA-*CCHE1* down-regulation hampers the proliferation of cervical cancer. The most interesting point in this study is that, Kaplan-Meier analysis is done simultaneously by mentioned researchers above and as result shorter overall survival is perceived in patients with over-expression of the lncRNA-*CCHE1*. Although, the univariate and multivariate analysis, to authenticate the lncRNA-*CCHE1* prognosis impact in cervical cancer is not carried out. In the following review, considering the former analysis lncRNA-*CCHE1* overexpression is perceived in cervical cancer (Yang et al., 2015a). Furthermore, up-regulation of lncRNA-*CCHE1* is recognized to be in correlation with the progressed FIGO stage, tumor size, lymph node metastasis and positive HPV. Moreover, lncRNA-*CCHE1* over-expression is discovered in cervical cancer tissues. LncRNA-*CCHE1* over-expression is corresponds with large tumor size, progressed Federation of Gynecology and Obstetrics stage, uterine corpus invasion, and poor survival. Biochemical RNA extraction technique experiments acknowledged physically correlation of lncRNA-*CCHE1* with proliferating cell nuclear antigen (PCNA), in which as a consequence it increases the PCNA expression. The lncRNA-*CCHE1* and PCNA expression is remarkably associated in cervical cancer tissues. Taken together, the studies show that, lncRNA-*CCHE1* as a prognosis factor in cervical cancer, which has the capability of physically correlating with PCNA mRNA and enhancing PCNA expression, and at the time of over-expression, results in enhancement of the cervical cancer cells proliferation. In conclusion, lncRNA-*CCHE1* is a pivotal cervical cancer biomarker for prognosis and a potent goal for cervical cancer therapy. (Yang et al., 2015a)

8. LncRNA-*EBIC*

LncRNA-*EBIC* has the potential to hinder E-cadherin through correlation with EZH2, and function as a promoter to enlist EZH2 to the promoter area of E-cadherin. LncRNA-*EBIC* and EZH2 might be two unified segments of the H3K27me3 procedure. Enhancement in expression levels of lncRNA-*EBIC* (EZH2-binding lncRNA in cervical cancer) is notably reported in cervical cancer tissues and cell lines. TI17313 is a noncoding RNA (1201 bp nucleotide long) that is transcribed from a processed pseudogene present in chromosome 16q and encodes RP11-144N1.1 (Sun et al., 2014b). LncRNATI17313 is known as lncRNA-*EBIC*. As many reports have that claimed, the action of this lncRNA has been discovered. The physical interplay of lncRNA-*EBIC* with EZH2 is also demonstrated by Repeat-induced point mutation. In vitro, according to assessments obtained from loss-of-function, down-regulation of lncRNA-*EBIC* prevents cervical cancer cell migration and invasion. Studies recommend that lncRNA-*EBIC* may function as an oncogene via collaborating with EZH2. Additionally, the correlation of lncRNA-*EBIC* with EZH2 supplies an indication to the elaborated regulation mechanism of EZH2 as well. Cervical cancer habitually leads to dwindled expression of E-cadherin and is connected with the HPV oncoproteins E6 and E7 (D'Costa et al., 2012). The studies have shown that the up-regulation of EZH2 lessens the level of E-cadherin gene expression via H3K27me3 (Cao et al., 2008). In contrast, lncRNA-*EBIC* knockdown enhances E-cadherin expression levels. In addition, down-regulation of EZH2 and unaltered form of lncRNA-*EBIC* can advance E-cadherin expression as well. There is not much evidence about the transcription initiation/terminal sites and full-length sequence of lncRNA-*EBIC*. There is not much evidence to show the gain-of-function of lncRNA-*EBIC* and thus, the probable mechanism is not yet determined. While, the correlation between lncRNA-*EBIC* and EZH2 proposes the point that lncRNA-*EBIC* has a dispensable role in the epigenetic control of gene expression. LncRNA-*EBIC* can result in invasion development of cervical cancer cells through correlating with EZH2 and then suppress E-cadherin expression afterward. These findings recommend that lncRNA-*EBIC* may function as an assistant in enlisting EZH2 to the target genes. Therefore, the obtained results propose an essential role for epigenetic mechanisms in cervical cancer pathogenesis. Outstanding comprehension of lncRNAs role in the epigenetic activity regulation will supply more targets for anticancer therapy, so is favorable for the individualized treatment of cervical cancer. (Sun et al., 2014b)

9. LncRNA-*MALAT1*

LncRNA-*MALAT1* (Metastasis-associated lung adenocarcinoma transcript 1), or popular as nuclear-enriched transcript 2 as well (*NEAT2*), is detected as a prognosis biomarker for lung cancer metastasis and even is in connection with other solid tumors (Gutschner et al., 2013b). LncRNA-*MALAT1* is known as a fascinating target in anti-metastatic therapy of cancer. Guo et al. claim that down-regulation of lncRNA-*MALAT1* diminishes the capability of cell migration and results in reduction of cervical cancer tumor growth in vivo, which it exhibits that lncRNA-*MALAT1* plays a crucial role in cervical cancer metastasis (Guo et al., 2010). LncRNA-*MALAT1* is reported to be up-regulated in tumor tissues compared to adjacent which is correlated with the size, FIGO stage, vessel invasion, and lymphatic dissemination (Yang et al., 2015b). It develops cellular movement to a certain extent through the lncRNA-*MALAT1*/miR-124/RBG2 signaling (Liu et al., 2016). Guo et al. have also suggested that the lncRNA-*MALAT1* enhances invasion and metastasis through hastening EMT by over-expression of 'Snail' in cervical cancer and the participation of lncRNA-MALAT1 in cell apoptosis is via affecting the expression of caspase-3, caspase-8, Bax, Bcl-2, and Bcl-xL in cervical cancer, which it illuminates the significant role of *MALAT1* in cervical cancer biology (Guo et al., 2010). On the one hand, lncRNA-*MALAT1* leads to cell colony formation enhancement and cell cycle regulation while represses cell apoptosis via sponging miR-145 in cervical cancer (Lu et al., 2016). On the other hand, lncRNA-*MALAT1* accelerates proliferation and invasion partially via the lncRNA-*MALAT1*/miR-124/RBG2 signaling (Liu et al., 2016). Taken together above studies illustrate a proof on the lncRNA-miRNA interplay in cervical cancer carcinogenesis. In vitro, evidence obtained from discoveries expose that lncRNA-*MALAT1*develops proliferation and invasion in cervical cancer (Yang et al., 2015b). Another research announces that lncRNA-*MALAT1* expression in cervical epithelial tissues positively connects with HPV infection (Sun et al., 2016). There is a thought that the lncRNA-*MALAT1* modifies (EMT) via regulation of the expression of proteins participate in EMT, embracing E-cadherin, ZO-1, b-catenin, vimentin, and snail (Sun et al., 2016). LncRNA-*MALAT1* is an extensively protected lncRNA with a length of 8708 nucleotide (Ji et al., 2003). LncRNA-*MALAT1* is a broadly plentiful nucleus-retained RNA that situates to nuclear speckles, a sub-nuclear domain enhanced in pre-mRNA splicing factors and influences differential splicing of pre-mRNAs via adjusting the cellular dispensation and acting of serine arginine dipeptide-containing SR splicing factors (Yang et al., 2011). Multiple researchers indicate that the over-expression of lncRNA-*MALAT1* in several cancers and assists in proliferation, apoptosis, migration and invasion. LncRNA-*MALAT1* is located at chromosome 11q13. Its expression is highly reported in lung, pancreas, and other sound organs. Based on the studies, over-expression of lncRNA-*MALAT1* is indicated in many cancers including cervical cancer, hepatocellular, colorectal, and non-small cell lung cancer (Mohamadkhani, 2014; Zheng et al., 2014). It is because of HPV infection, over-expression of lncRNA-*MALAT1* is usually detected in cervical cancer (Jiang et al., 2014). Through the information this research provides, it can be said

that lncRNA-*MALAT1* is a prognosis factor for overall survival of cervical cancer. Down-regulation of it lessens the proliferation and invasion of cervical cancer cells and enhances apoptosis. Some investigations announced the fact that, lncRNA-*MALAT1* over-expression is in correlation with Cervical Cancer poor prognosis and acts to develop cancer cell growth and invasion. Accordingly, lncRNA-*MALAT1* may be detected as a prognosis marker and a probable therapeutic target in cervical cancer (Yang et al., 2015b) lncRNA-*MALAT1* is able to enhance proliferation of cervical cancer cell via diminishing cell cycle regulation molecules cyclinD1, cyclin E, and CDK6 in CaSki cells, as result repress cell cycle transition (Jiang et al., 2014). Up-regulation of lncRNA-*MALAT1* is correlated with tumorigenesis of multiple cancer, for instance, lung cancer (Gutschner et al., 2013a), colorectal cancer (Hou et al., 2014), gastric cancer (Wang et al., 2014b), and cervical cancer (Jiang et al., 2014).

10. LncRNA-*ANRIL*

LncRNA-*ANRIL* (CDKN2B antisense RNA 1) is first discovered in patients with familial melanoma, which encodes 3834 nucleotide RNA and includes 19 exons at the antisense orientation of the INK4B-ARF-INK4A gene cluster (Zhang et al., 2018a). Oncogenic role of lncRNA-*ANRIL* as lncRNA is verified in various tumors containing nasopharyngeal carcinoma (Zou et al., 2016), thyroid cancer (Zhao et al., 2016) and osteosarcoma (Wei et al., 2016). RNA polymerase II is responsible to transcribe LncRNA-*ANRIL* (antisense non-coding RNA in the INK4 locus). LncRNA-*ANRIL* has many linear isoforms that are encoded in a genetic region which displays its correlation with multiple human diseases containing various cancers (Kotake et al., 2011; Pasmant et al., 2011). Various constant researches illustrate pivotal role of lncRNA-*ANRIL* in development of tumor progression. While, lncRNA-*ANRIL* expression and the action it might play in cervical cancer is unidentified. An interface develops among lncRNA-*ANRIL* and SUZ12 (a subunit of the PRC2) that is able to conscript a suppressive complex in expression of a tumor suppressor gene, p15 (Gutschner & Diederichs, 2012). Additionally, lncRNA-*ANRIL* down-regulation with p15 over-expression prevent cellular proliferation (Kotake et al., 2011). According to obtained results, up-regulation of lncRNA-*ANRIL* is in connection with promoted FIGO stage and lymph node metastasis. Interestingly, patients with up-regulation of lncRNA-*ANRIL* in Cervical cancer indicate a poor overall survival in comparison to patients with under-expressed lncRNA-*ANRIL*. In vitro, loss-of-function assessments declare that lncRNA-*ANRIL* down-regulation represses cervical cancer cell proliferation, migration and invasion (Zhang et al., 2017a). LncRNA-*ANRIL* is targeted by miR-186. MiR-186 expression was knocked down in cervical cancer cell lines. LncRNA-*ANRIL*/miR-186 axis has a pivotal role in the tumorigenesis of cervical cancer (Zhang et al., 2018b). Based on obtained evidences, lncRNA-*ANRIL* is over-expressed in cervical cancer. In addition, under-expression of lncRNA-*ANRIL* results in PI3K/Akt pathway deactivation. So, lncRNA-*ANRIL* can be detected as a new target in diagnosis and treatment of cervical cancer (Zhang et al., 2017a).

11. LncRNA-*LET*

LncRNA-*LET* knockdown is reported in many malignancies for instance, hepatocellular, colorectal, and squamous cell lung cancers (Ma et al., 2015b). Yang et al. indicate that down-regulation of lncRNA-*LET* is an indispensable stage in the equilibrium of nuclear factor 90 protein, in which leads to hypoxia cancer cell invasion (Yang et al., 2013b). According to Ma et al. research, lncRNA-*LET* is figured out as a prognostic factor and a tumor suppressor in gallbladder cancer (Ma et al., 2015b). LncRNA-*LET* expression is connected with FIGO stage, lymph node metastasis. It highlights the fact that lncRNA-*LET* is associated with invasion and metastasis in cervical cancer. It is observed that, up-regulation of lncRNA-*LET* is in correlation with overall survival in cervical cancer. On the other hand, diminished lncRNA-*LET* leads to short survival in cervical cancer. As described in above mentioned studies, lncRNA-*LET* is reported to be utilized as a prognostic factor in other human tumors including hepatocellular and gallbladder. Multiple studies, have shown that lncRNA-*LET* is decreased in cervical cancer tissues. Therefore, lncRNA-*LET* can be identified as biomarker in prognosis of cervical cancer. The obtained information recommend that lncRNA-*LET* can be applied as a probable target in diagnosis and gene therapy of cervical cancer. However, the function of lncRNA-*LET* in cervical cancer needs to be investigated in detail (Jiang et al., 2015).

12. LncRNA-*NEAT1*

The nuclear paraspeckle assembly transcript 1 (*NEAT1*) is present on chromosome 11 (11q13.1). This lncRNA is defined as an essential domain of paraspeckle (Chen et al., 2018b; Sasaki et al., 2009a), and plays indispensable roles in the pathogenesis and progression of multiple cancers such as prostate, lung, and breast (Ding et al., 2017). LncRNA-*NEAT1* is transcribed by RNA polymerase II (pol II) and was found to be broadly expressed in all types of mammalian cells. LncRNA-*NEAT1* has 2 types: a »3.7 knt subtype of *NEAT1*_1 with poly (A) tail and a »23 knt subtype of *NEAT1*_2. (Yu & Shan, 2016; Sasaki et al., 2009b). Both subtypes of lncRNA-*NEAT1* are key elements of the paraspeckles as well (Sunwoo et al., 2009). Paraspeckles are remarkable subnuclear formations created from particular proteins and RNAs. It was shown to be elevated in many cancers, and enhancing expression levels are connected to poor prognosis in the mentioned cancers (Chen et al., 2015b). LncRNA-*NEAT1* is found as a transcriptional target of HIF in various breast cancer cell lines and as well as in some solid tumors, which prompts cell proliferation, and lessens cell apoptosis (Choudhry et al., 2015). Zhang et al. showed that lncRNA-*NEAT1* was intimately correlated with enhancement of breast cancer through enhancing proliferation and EMT (Zhang et al., 2017b). β-catenin and N-cad levels were diminished while *E*-cad was promoted after lncRNA-*NEAT1* was repressed (Zhang et al., 2017b). LncRNA-*NEAT1* elevation develops cell proliferation and invasion by serving as a competing endogenous RNA of miR-218 (Zhao et al., 2017). LncRNA-*NEAT1* up-regulation prohibited the miR-129-5p expression via modulating VCP/IκB, and as a consequence results in development of the hepatocellular carcinoma (HCC) cells proliferation (Fang et al., 2017). Assessment of the ChIP-seq data, Idogawa et al. revealed that lncRNA-*NEAT1* was a direct transcriptional target of p53. It is possible that lncRNA-*NEAT1* could act via different signaling pathways. For example, lncRNA-*NEAT1* led to the tumorigenesis and promotion of non-small cell lung cancer (NSCLC) by operating Wnt/β-catenin signaling pathway with enigmatic mechanisms (Sun et al., 2017b). LncRNA-*NEAT1* is reported to be elevated in the cervical cancer tissue. LncRNA-*NEAT1* up-regulation is anticipated in the poor clinical properties and a short survival time for the patients of cervical cancer. The S phase in the cell cycle was dwindled in CaSki and HeLa cells, and silencing of lncRNA-*NEAT1* led to enhancement of apoptosis. The interplay between lncRNA-*NEAT1* and miR-101 resulted in increase of the colony formation, cell migration, and invasion repression. LncRNA-*NEAT1* develops cervical cancer enhancement by targeting miR-101 (Fu et al., 2017). Thus, lncRNA-*NEAT1* can be recognized as a biomarker in prognosis of cervical cancer. The studies suggest that the lncRNA-*NEAT1* can be applied as a potential target in diagnosis and gene therapy of cervical cancer.

13. LncRNA-*BLACAT1*

The body of evidences illustrated that lncRNA-*BLACAT1*, a novel lncRNA, was involved in various cancers. LncRNA-*BLACAT1* played the role of an oncogene in varied tumors such as urothelial carcinoma, gastric cancer, and colorectal cancer according to the investigations (Droop et al., 2017; Wang et al., 2018). Shan et al. revealed that lncRNA-*BLACAT1* enhanced cell proliferation, invasion, and EMT

process in human cervical cancer (Shan et al., 2018a). Though, the lncRNA-*BLACAT1* prognostic significance in cervical cancer patients was not specified in Shan et al., investigation (Shan et al., 2018a). The clinical value of lncRNA-*BLACAT1* was identified and the probable mechanism by which lncRNA-*BLACAT1* developed cervical cancer proliferation and metastasis was broadly investigated (Wang et al., 2018). It was revealed that up-regulation of lncRNA-*BLACAT1* was efficiently consistent with promoted FIGO stage, distant metastasis, and poor histological grade. Meanwhile, information available suggests that patients with elevated lncRNA-*BLACAT1* indicated shorter OS and PFS than those with knockdown lncRNA-*BLACAT1*. Univariate and multivariate survival assessments revealed the fact that lncRNA-*BLACAT1* could be utilized as a potential prognostic biomarker for cervical cancer (Wang et al., 2018). Gao et al., have shown lncRNA-*BLACAT1* up-regulation was connected with poor prognosis of colorectal cancer patients (Gao et al., 2017). Hu et al., have shown, high lncRNA-*BLACAT1*expression level associated with lymph node metastasis, TNM stage, and poorer prognosis of patients in gastric cancer, (Hu et al., 2015). The loss-function assay indicated that Si-*BLACAT1* was utilized to lessen the lncRNA-*BLACAT1* expression. Studies utilizing MTT and trans well assays, shown that down-regulation of lncRNA-*BLACAT1* remarkably repressed the proliferation, migration, and invasion of cervical cancer cells. Shan et al., also shown that, the lncRNA-*BLACAT1* down-regulation, repressed cell proliferation and metastasis of ME180 and C33A cells (Shan et al., 2018b). LncRNA-*BLACAT1* increases cells proliferation and metastasis in non-small cell lung cancer and bladder cancer. Based on the studies indicated that lncRNA-*BLACAT1* led to the promotion of cancers. The Wnt signaling pathways are a category of signal transduction pathways which contains multiple various proteins that are necessitated for cell proliferation and differentiation in different tissues (Rudnicki & Williams, 2015). It is known that the Wnt/β-catenin pathway modulates cells proliferation, migration, and invasion in specific sorts of tumors (Stewart et al., 2014). The operation of Wnt/β-catenin pathway resulted in enhancement and promotion of different cancers, and it was revealed that many lncRNAs have the role of a modulator in the Wnt/β-catenin pathway (Christensen et al., 2016). Various studies have confirmed that lncRNA-*BLACAT1* knockdown led to an lower expression of β-catenin. The MMP-7 expression, is a main target gene of Wnt/β-catenin pathway, studies have shown that an indispensable knockdown in cervical cancer cells transfected with si-*BLACAT1 (Wang et al., 2018)*.

14. LncRNA-*UFC1*

LncRNA-*UFC1* is a recognized oncogene interplaying with the mRNA-stabilizing protein HuR enhances the level of β-catenin in liver cancer cells (Cao et al., 2015). LncRNA-*UFC1* was said to be over-expressed in colorectal cancer as well. Although lncRNA-*UFC1* prohibited apoptosis by operating phosphorylated P38 and repressing β-catenin, inhibition of apoptosis developed proliferation (Yu et al., 2017). We assessed the clinical value of lncRNA-*UFC1* expression in cervical cancer tissue through this review. The essential role of lncRNA-*UFC1* in regulation of growth and metastasis was illustrated. Accordingly, the up-regulation of lncRNA-*UFC1* was perceived in cervical cancer, and elevated lncRNA-*UFC1* was correlated with FIGO stage, tumor size, lymph node metastasis, poor prognosis, and distant metastasis. LncRNA-*UFC1* develops proliferation, migration, and invasion in cervical cancer via binding miR-34a and enhancing expression level of FOXP3. As a result, using the mentioned discoveries it was concluded that lncRNA-*UFC1* has a substantial role in growth and metastasis of cervical cancer. Thus, the oncogenic role of lncRNA-*UFC1* in cervical cancer was detected. The oncogenic role of lncRNA-*UFC1* has been identified in some other cancers, such as colorectal cancer and liver cancer (Yu et al., 2017). According to the literature survey, multiple lncRNAs act as ceRNAs via connecting with general microRNAs (Chen et al., 2017; Xi et al., 2018). While, lncRNA-*UFC1* role as a ceRNA has not been discovered yet. In this review, we indicate that lncRNA-*UFC1* contributes miR-34a response elements with FOXP3 in cancers. Furthermore, it was exhibited that the enhanced lncRNA-*UFC1* promotes FOXP3 which simultaneously assists cell proliferation, migration, and invasion. As a consequence, our review validates that lncRNA-*UFC1* up-regulation in cervical cancer tissues is associated with malignant clinical features and with poor prognosis. The lncRNA-*UFC1* played a role of oncogene in cervical cancer and its action was obtained from the regulation of FOXP3 expression via correlation of miR-34a. Taken together, our evidences recommend the encouraging value and impressive target of lncRNA-*UFC1* in cervical cancer therapies.

15. LncRNA-*SNHG16*

LncRNA-*SNHG16* (Small nucleolar RNA host gene 16) is a novel recognized lncRNA which detected as a probable oncogene in some cancers including lung cancer, breast cancer, bladder cancer and colorectal cancer (Zhu et al., 2018; Yan et al., 2017). In spite of mentioned information above, the lncRNA-*SNHG16* function and mechanism in cervical cancer is enigmatic. The major objective of our review was to discover the function and the fundamental mechanism of lncRNA-*SNHG16* in cervical cancer. It indicated that the lncRNA-*SNHG16* was elevated in cervical cancer and involved in the migration and invasion of cervical cancer through targeting miR-216-5p/ZEB1 signal pathway. Oncogenic role of lncRNA-*SNHG16* has been reported in different cancers including breast cancer and colorectal cancer (Cai et al., 2017); while, its expression pattern, biological function and basic mechanism in cervical cancer remain unknown. In our review, it was substantiated that lncRNA-*SNHG16* was up-regulated in cervical cancer tissues and cells. The lncRNA-*SNHG16* enhancement was consistent with large tumor size, promoted FIGO stage, lymph node metastasis, and lower differentiation. Thus, exhibiting that the lncRNA-*SNHG16* expression level was connected with the cervical cancer malignancy, and had impact on the tumorigenesis. Ye et al., suggested that lncRNA-*SNHG16* could act as a ceRNA through sponging miR-216-5p and modulating the target gene ZEB1. Concertedly our review proves that lncRNA-*SNHG16* was over-expressed in the cervical cancer. Cellular assays exhibited that down-regulation of lncRNA-*SNHG16* affected cell proliferation, migration and EMT pattern in cervical cancer. Molecular mechanism experiments revealed that lncRNA-*SNHG16* functioned as a molecular sponge for miR-216-5p to modulate target gene of ZEB1 which leads to tumorigenesis in cervical cancer (Ma et al., 2017). According to our review, the lncRNA-*SNHG16* can be distinguished as a prognostic biomarker in cervical cancer and could serve as a probable target in gene therapy.

16. LncRNA-*SNHG20*

LncRNA-*SNHG20* (Small nucleolar RNA host gene20) is located at 17q25.2 and it was initially recognized in hepatocellular carcinoma (HCC) and found to be elevated in two categories of HCC and TGCA dataset (Guo et al., 2018). Extended observations exhibited that lncRNA-*SNHG20* developed tumor invasion and metastasis. Meantime, over-expression of lncRNA-*SNHG20* showed poor prognosis in colorectal cancer declared by Li et al. (Li et al., 2016). Enhanced lncRNA-*SNHG20* developed ovarian cancer promotion through Wnt/β-catenin signaling as stated by He et al. (He et al., 2018). LncRNA-*SNHG20* enhanced gastric cancer promotion by prohibiting p21 expression level and modulating the GSK-3β/β-catenin signaling pathway as recommended by Liu et al. (Liu et al., 2017). Although, lncRNA-*SNHG20* role in cervical cancer tumorigeneses still is unknown. LncRNA-*SNHG20* biological function was generally studied both in vitro and in vivo, to determine the impact that lncRNA-SNHG20 implemented on cervical cancer progression. According to Guo et al. findings, lncRNA-*SNHG20* could function as a miRNA sponge in cervical cancer (Guo et al., 2018). They showed that lncRNA-*SNHG20* has binding sites for

miR-140-5p. Down-regulation of lncRNA-*SNHG20* enhanced miR-140-5p expression level in cervical cancer cells, luciferase evaluation revealed that miR-140-5p could be interconnected to lncRNA-*SNHG20* through the presumptive miRNA response element. QRT-PCR assessment exhibited that miR-140-5p expression level was diminished and negatively rectified with the expression level of lncRNA-*SNHG20* in cervical cancer tissues (Guo et al., 2018). The above studies recommended that miR-140-5p is a prohibitory target of lncRNA-*SNHG20* in cervical cancer. Their experiments demonstrated that the prohibition of lncRNA-*SNHG20* repressed the proliferation and invasion of cervical cancer cells both in vitro and in vivo, showing lncRNA-*SNHG20* could function as an oncogenic lncRNA in cervical cancer promotion (Guo et al., 2018). They also revealed that lncRNA-*SNHG20* developed the proliferation and invasion of cervical cancer cells through the lncRNA-*SNHG20*/miR-140-5p/ADAM10 axis (Guo et al., 2018). Guo et al. uncovered that lncRNA-*SNHG20* was remarkably enhanced and correlated with larger tumor size, advanced FIGO stage, and lymph node metastasis. Furthermore, up-regulation of lncRNA-*SNHG20* resulted in a poor overall survival in the patients of cervical cancer (Guo et al., 2018). These studies determined that lncRNA-*SNHG20* has a significant role in cervical cancer enhancement, and can be used as potential target and serve as a biomarker in the prognosis of cervical cancer.

17. Conclusion and prospective

In this review, the role and importance of lncRNAs were discussed in cervical cancer. In developing countries where high mortality rate is reported, the initial diagnosis and therapy for cervical cancer would be very essential. LncRNAs have made the preliminary diagnosis so practicable. According to above mentioned literature, lncRNAs have a significant role in therapy influence, prognostic elements, individual treatment, and incidence and promotive mechanisms in cervical cancer. The correlation of lncRNAs, with ncRNAs, and mRNAs is not completely obvious and need more research. The great number of articles have shown that the lncRNAs as a probable therapeutic target and prognostic marker. In future LncRNAs could be utilized as a novel therapy in various tumors and in cervical cancer. Within the past years, in developing countries women with cervical cancer have derived profits from imaging techniques, desirable therapies like chemo-radiotherapy and surgery techniques. In the places that services for radiology, chemo-radiotherapy are not obtainable, recognizing the impressive healthcare necessities and possible techniques are very essential. In the near future, the first approach to prevent mortality from cervical cancer will be to concentrate on preliminary inhibition with preventive vaccines against human papillomavirus. In conclusion, it was recognized that lncRNAs mentioned above, can be applied as biomarkers in prognosis, invasion and metastasis of cervical cancer. These lncRNAs even have the potential to be utilized as new targets for clinical therapy of cervical cancer.

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