Long Non-Coding RNA Signature in Cervical Cancer

Dlouhé nekódující molekuly RNA u cervikálních nádorů

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Summary

Background: Cervical cancer as a common urogenital cancer among women has caused significant health problems. Efforts have been made to identify its pathogenic process in order to find targeted therapies. Long non-coding ribonucleic acids (lncRNAs) have been shown to regulate several cancer-related pathways and genes that contribute to pathogenesis of human malignancies, including cervical cancer. In the present review, we searched PubMed, Google scholar, Web of Science and Scopus databases for key words "cervical cancer" or "cervical neoplasm" and "long non-coding RNA" or "lncRNA" (up to December 2017). ***Aim:*** To elaborate the role of lncRNAs in cervical cancer. ***Conclusions:*** LncRNAs affect cervical cancer pathogenesis through numerous mechanisms, such as making scaffolds for assembly of protein complexes, serving as directors to recruit proteins, functioning as transcriptional enhancers through chromatin remodeling, serving as decoys to free up proteins from chromatin, or reversing the effects of other regulatory non-coding RNAs, such as microRNAs. Pathway-based analysis showed that several lncRNAs modulate PI3K/Akt/mTOR, Wnt-β catenin and Notch pathways in the process of cervical cancer pathogenesis. In addition, expression of a handful of lncRNAs has been associated with human papilloma virus infection. Identification of lncRNAs that alter cancer-related signaling pathways and subsequent expression analysis of these lncRNAs in patients' samples would help to design effective targeted therapies.

Key words

lncRNA – cervical cancer – oncogene – tumor suppressor gene

Souhrn

Východiska: Rakovina děložního čípku jako běžný urogenitální nádor způsobuje u žen značné zdravotní problémy. Byla vynaložena snaha o identifikaci patogeneze za účelem nalezení cílených terapií. Bylo prokázáno, že dlouhé nekódující ribonukleové kyseliny (lncRNA) regulují několik signálních drah a genů souvisejících s nádory, což přispívá k patogenezi lidských malignit vč. rakoviny děložního čípku. V rámci prezentovaného článku jsme do prosince 2017 vyhledávali klíčová slova „cervical cancer" (rakovina děložního čípku) nebo „cervical neoplasm" (cervikální novotvar) a „long non-coding RNA" (dlouhá nekódující RNA) nebo „lncRNA", publikovaná v databázi PubMed, Google scholar, Web of Science a Scopus. ***Cíl:*** Zjistit, jakou roli hrají lncRNA v rakovině děložního čípku. ***Závěry:*** LncRNA ovlivňují patogenezi rakoviny děložního čípku prostřednictvím četných mechanismů, jako je vytváření tzv. scaffolds pro sestavení proteinových komplexů, sloužící jako tzv. directors pro získávání proteinů, fungujících jako transkripční zesilovače pomocí remodelování chromatinu, sloužící jako tzv. návnady k uvolnění proteinů z chromatinu nebo zvrácení účinků jiné regulační nekódující RNA jako jsou mikroRNA. Analýza signálních drah ukázala, že v procesu patogeneze rakoviny děložního čípku několik lncRNA reguluje dráhy PI3K/Akt/mTOR, Wnt-β catenin a Notch signální dráhy. Navíc exprese několika lncRNA byla spojena s infekcí virem lidského papilomu. Identifikace lncRNA, které mění signální dráhy související s nádory, a následná expresní analýza těchto lncRNA ve vzorcích pacientů by mohly pomoci získat efektivní cílené terapie.

Klíčová slova

lncRNA – nádor děložního čípku – onkogen – tumor supresorový gen

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Introduction

In recent years, progress in genome analyses has led to recognition of an evolving class of non-coding ribonucleic acids (ncRNAs) that participate in the modulation of gene expression and epigenetic reprogramming [1]. A significant number of these ncRNAs are longer than 200 nucleotides and instead of being transcriptional "noise", they use various routes to control gene expression [1]. These so-called long non-coding RNA (lncRNAs) have tissue specific expression pattern [2] but are less conserved than protein coding RNAs [3]. They are involved in almost every aspect of physiological processes, such as preservation of DNA integrity [4], telomere biology [5], immune cell homeostasis [6], regulation of hormone receptors [7] as well as differentiation and homeostasis of metabolic tissues [8]. The differential expression of lncRNAs in malignant tissues compared with normal tissues of the same origin has been demonstrated in several studies [3,9–14] what implies their role in pathogenesis of different cancers. Such speculation has been further supported by the presence of distinct single nucleotide polymorphisms within lncRNA coding genes which alter the risk of cancer development [15,16].

Cervical cancer as a common urogenital cancer among women is mostly associated with human papilloma virus (HPV) infection. However, as its incidence is much lower than the prevalence of HPV infection, other factors are thought to have synergic effects with HPV infection to induce cervical cancer [17]. Dysregulation of Wnt/β-catenin signaling as well as PI3K/Akt/mTOR signaling pathway have also been implicated in the pathogenesis of cervical cancer [18]. Considering the role of lncRNAs in the regulation of these pathways, we searched the literature to identify lncRNAs that modulate cervical cancer risk especially through alteration of these pathways or through modulation of HPV infection process.

Search strategy

We searched PubMed, Google scholar, Web of Science and Scopus databases with the key words "cervical cancer" or "cervical neoplasm" AND "long non-coding RNA" or "lncRNA". Original articles were chosen if they were written in English and had enough number of samples for expression analysis (at least 20 patients' samples from exclusive clinical studies) and described the mechanism of lncRNA involvement in cervical cancer (for *in vitro* studies). Other types of papers were excluded from the study. Papers, which focused on analysis of lncRNAs at genomic level, were also excluded.

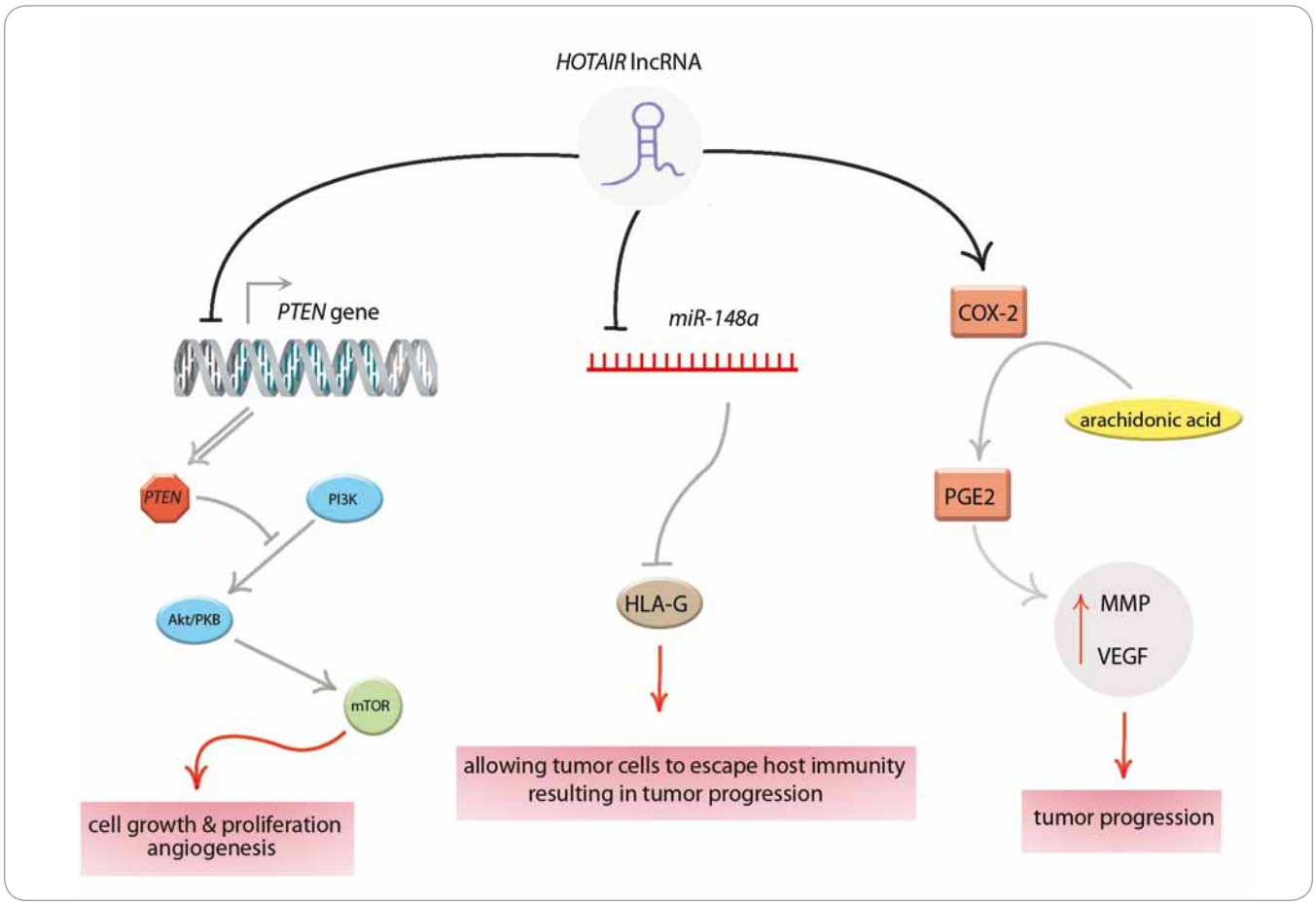
LncRNA involvement in cervical cancer

A recent study aimed at identification of expression profiles of lncRNAs, circular RNAs, microRNA (miRNA), and messenger RNA (mRNA) in HPV16 mediated cervical squamous cell carcinoma have found 19 lncRNAs that are frequently differentially expressed in cervical cancer samples compared to normal samples. Such differentially expressed lncRNAs have been shown to participate in cervical cancer pathogenesis as revealed by the co-expression network and function prediction [19]. In addition to this high throughput studies, several studies have assessed the significance of lncRNAs in cervical cancer pathogenesis. Based on the importance of HPV infection and dysregulation of signaling pathways in the pathogenesis of cervical cancer, we subsequently analyzed lncRNAs based on their involvement in one of these mechanisms.

LncRNAs and HPV infection

HPVs as double-stranded circular DNA viruses encode several proteins, which participate in their DNA replication, gene transcription and cellular transformation. E6 and E7 proteins coded by high-risk HPV viruses participate in the pathogenesis of HPV-associated carcinomas [20]. Degradation of p53 and retinoblastoma protein (Rb) as two important tumor suppressor proteins is induced by the HPV oncogenic proteins E6 and E7, respectively. E6 also participates in carcinogenesis through induction of telomerase activation, while E7 alters the expression of synthesis phase genes by directly disturbing pRb/E2F complex and enhances cell survival by inducing expression of interleukin-648 and antiapoptotic Mcl-126 and triggering the Akt/PKB pathway [20]. The cooperation of HPV oncogenes and lncRNAs in cervical cancer context has been first revealed for *metastasis-associated lung adenocarcinoma transcript 1 (MALAT1)*. This lncRNA has been over-expressed in cervical cancer cell lines compared with normal cervical squamous cell samples. However, its expression has been decreased following the E6/E7 knockdown in CaSki cells. Further assessment of clinical samples has confirmed exclusive expression of *MALAT1* in HPV-positive cervical squamous cells, but not in HPV-negative normal cervical squamous cells [21]. The positive association between *MALAT1* expression levels and HPV infection has also been documented in cervical epithelial tissues by microarray analysis [22].

HOX transcript antisense RNA (HOTAIR) participates in epigenetic regulation of gene expression through recruitment of chromatin remodeling polycomb repressive complex 2 (PRC2). This lncRNA has been recognized as a target of E7 in HPV16 related cervical cancers. *HOTAIR* expression has been shown to be progressively decreased in a linear manner from HPV negative controls to HPV16 positive non-malignant and cervical cancer samples. Such down-regulation was concomitant with up-regulation of *HOTAIR* target, *HOXD10*, and enhancement of cancer related pathways in most cervical cancer cases. Conversely, a minority of them had considerably higher *HOTAIR* expression, associated with high E7 expression and enhancement of metastatic pathways. The interaction between *HOTAIR* and E7 has further been supported by observation of a positive correlation between E7 expression and expressions of both *HOTAIR* and PRC2 complex members (EZH2 and SUZ12) in cervical cancer cases. In addition, both in silico analysis and RNA immunoprecipitation endorsed the functional inactivation of *HOTAIR* by direct interaction with E7. Consequently, *HOTAIR* has been



Schema 1. Different roles of *HOTAIR* in cervical cancer tumorigenesis: *HOTAIR* has a negative regulatory role on *PTEN* tumor suppressor gene. *HOTAIR* role in EMT is due to its effect on COX-2 stabilization which leads to induction of MMPs and VEGF. *HOTAIR* also enhances HLA-G associated immune escape by competitively binding to *miR-148a*.

lncRNA – long non-coding ribonucleic acid, EMT – epithelial-mesenchymal transition, MMP – matrix metallopeptidase, VEGF – vascular endothelial growth factor, HLA-G – human leukocyte antigen G, PGE2 – prostaglandin E2, COX – cyclooxygenase

identified as a downstream target of HPV16 E7 in the process of cervical cancer pathogenesis [23].

LncRNAs and PI3K/Akt/mTOR pathway

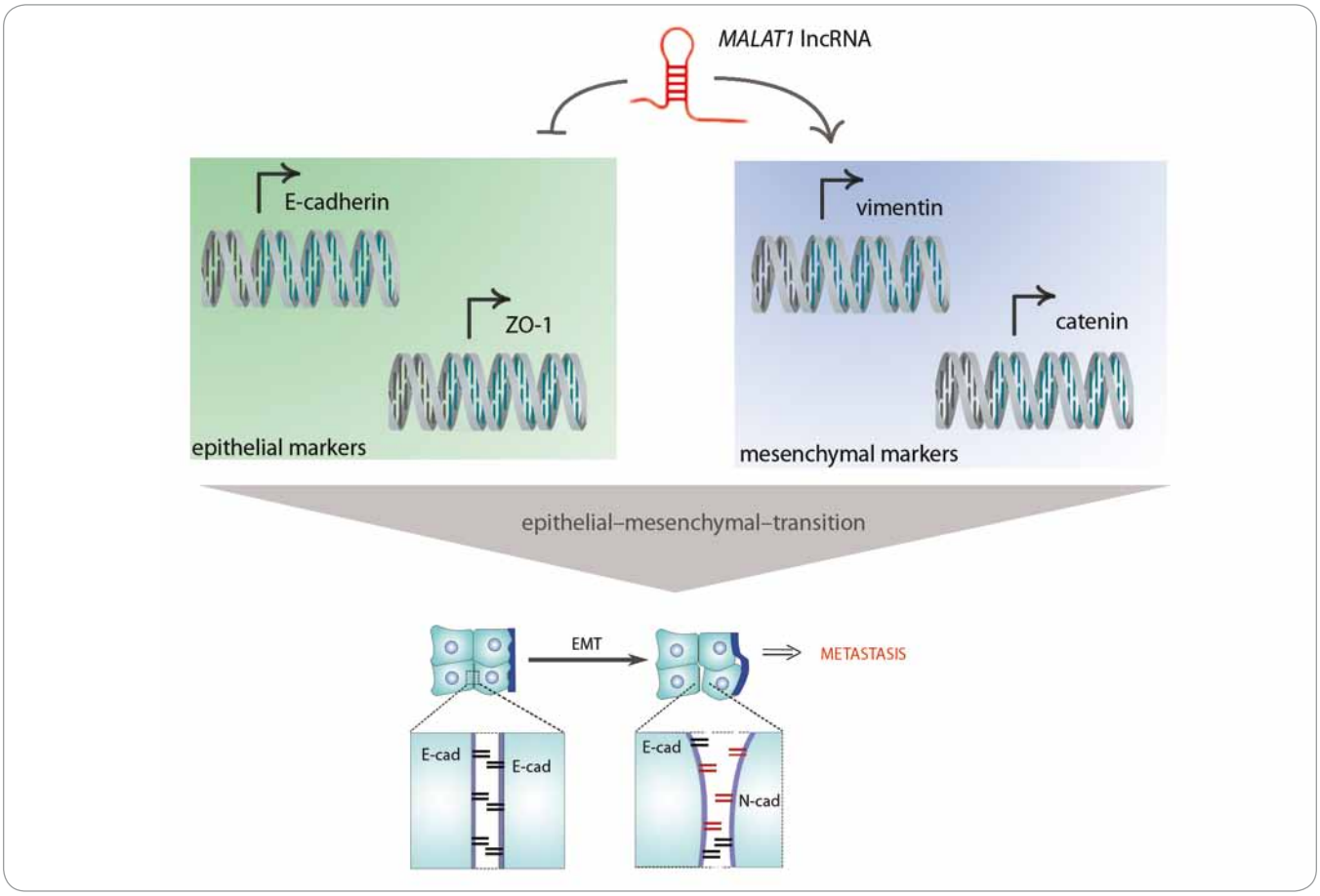
Maternally expressed 3 (MEG3) as a tumor suppressor lncRNA has been implicated in cervical cancer. Its over-expression in cervical cancer cells resulted in down-regulation of PI3K, Akt, MMP-2, MMP-9 and Bcl-2 expression while up-regulating Bax and P21 expression. Consequently, lncRNA MEG3 inhibits cervical cancer by modification of PI3K/Akt/Bcl-2/Bax/P21 and PI3K/Akt/MMP-2/9 signaling pathway [24]. *GAS5* as another tumor suppressor has been shown to modulate cellular growth and drug resistance through the *PTEN*/PI3K/Akt/mTOR pathway. The low level of *GAS5* leads to *PTEN* down-regulation by interacting with *miR-21* because *PTEN* is one of the genes in the PI3K/Akt/mTOR pathway whose expression is decreased by *GAS5*. Eventually, the low expression of *PTEN* triggers the PI3K/Akt pathway, therefore producing a circulation. Moreover, *GAS5* and *miR-21* modulate cisplatin resistance in cervical cancer cells via the PI3K/Akt pathway [25].

Mitogen activated protein kinases (MAPK) pathway

TCONS_00026907 as a newly identified lncRNA enhances expression of cyclin D1 and Bcl-2 *in vivo* and *in vitro*. Its knock-down inhibits growth of cervical tumors and modulates the expression of ELK1, p-ELK1, c-fos, cyclin D1 and Bcl-2 *in vivo*. Considering the role of ELK1 as a nuclear target for the Ras-Raf-MAPK signaling cascade [26], the oncogenic effect of this lncRNA in cervical cancer might be due to its effect on MAPK pathway.

LncRNAs and Wnt/β-catenin pathway

The Wnt/β-catenin signaling pathway is a quintessential survival pathway which modulates several cellular processes including proliferation, growth, survival and metabolism. *XIST* silencing in cervical cancer cells decreased the protein level of β-catenin and inhibited the protein expression of two Wnt/β-catenin downstream genes – cyclin D1 and *c-Myc* [27]. Besides, *CCAT-1* role in enhancement of proliferation and suppression of apoptosis of cervical cancer cells is also



Schema 2. *MALAT1* role in cervical cancer: *MALAT1* inhibits epithelial markers E-cadherin and ZO-1, and simultaneously enhances expression of the mesenchymal markers β-catenin and vimentin as well as the Snail transcription factor.
lncRNA – long non-coding ribonucleic acids, EMT – epithelial-mesenchymal transition, E-cad – E-cadherin

through induction of the Wnt/β-catenin pathway [28].

LncRNAs and Notch pathway

Evaluation of the essential signaling cascades regulated by Notch in *HOTAIR*-overexpressing cells has shown that *HOTAIR* overexpression in SiHa cells has led to increased NOTCH1, HES1 and p300 expression [29].

LncRNA involvement in epithelial-mesenchymal transition (EMT) of cervical cancer cells

HOTAIR as an oncogenic lncRNA in cervical cancer has been shown to alter the expression of several genes participated in cell migration, invasion and EMT, such as vascular endothelial growth factor, MMP-9, E-cadherin, β-catenin, vimentin, Snail and Twist [30]. EMT-related levels have also been elevated in xenografts originated from *HOTAIR*-overexpressing SiHa cells compared with the control tumors [29]. In addition, *HOTAIR* enhances migration and invasion of HeLa cervical cancer cells, at least partially, through the modulation of vimentin expression [31]. *HOTAIR* role in EMT might also due to its effect on COX-2 stabilization, which leads to induction of matrix metalloproteinases and vascular endothelial growth factor (Schema 1) [32].

MALAT1 exerts its role in cervical cancer cell invasion and metastasis by enhancement of the EMT process through increasing the expression of Snail [33]. *MALAT1* silencing suppressed the invasion and metastasis of cervical cancer cells, increased expression of the epithelial markers E-cadherin and ZO-1, and simultaneously decreased expression of mesenchymal markers β-catenin and vimentin as well as the Snail transcription factor (Schema 2) [22].

The lncRNA *taurine-upregulated gene 1* (TUG1) was also shown to increase migration and invasion of cervical cancer cells by modulating EMT-related markers such as fibronectin, vimentin and cytokeratin [34].

HOXA11-AS has also been shown to participate in EMT. *HOXA11-AS* silencing has led to increase in E-cadherin expression while decreasing levels of β-catenin, vimentin and the EMT-mediating transcription factor Snail [35].

In addition, EZH2-binding lncRNA in cervical cancer (lncRNA-EBIC) has a role in migration and invasion of cervical cancer cells through modulation of E-cadherin [36].

LncRNAs role in cervical cancer immune evasion

The human leukocyte antigen-G (HLA-G) as a member of the non-classical major histocompatibility complex family

is recruited by cancer cells to beat attentive immuno-surveillance of the host. *HOTAIR* has been shown to enhance HLA-G associated immune escape by competitively binding to *miR-148a* (Schema 1) [37].

Discussion

Consistent with diverse mechanisms of lncRNAs participation in regulation of gene expression, lncRNAs can affect cervical cancer pathogenesis through various mechanisms. Overall, the regulatory function of lncRNAs can be exerted through making scaffolds for assembly of protein complexes, serving as guides to recruit proteins, functioning as transcriptional enhancers through chromatin remodeling, serving as decoys to free up proteins from chromatin, or reversing the effects of other regulatory ncRNAs, such as miRNAs [38]. Besides, the expression of HPV oncogenes as the most important causal factor in cervical cancer has been shown to be linked to expression levels of some lncRNAs. However, functional studies to reveal the exact mechanism of this association has been performed for only two lncRNAs, namely *MALAT1* and *HOTAIR*. Moreover, expression of several lncRNAs has been shown to be dysregulated in tumor tissues as well as plasma samples from cervical cancer patients. Higher expression of certain lncRNAs in the plasma of cervical cancer patients compared to healthy subjects provides an applicable tool for screening and follow-up of patients.

More importantly, methylation pattern of the *MEG3* lncRNA has been demonstrated to be a diagnostic and prognostic marker of cervical cancer with the capability to predict high-risk HPV infection and lymph node metastasis [39]. Considering the early onset of methylation alterations during carcinogenesis, identification of such marks is valuable in early detection of cancer.

Notable, several lncRNAs have been shown to affect cancer-related pathways. Alterations in these pathways modulate response to conventional chemotherapeutic approaches as revealed for cisplatin resistance in cervical cancer [25]. On the other hand, dysregulation of numerous signaling pathways, such as Notch and mTOR pathways, has been demonstrated in cervical cancers through transcriptome analysis. Considering the therapeutic potential of these signaling pathways in at least some types of cervical cancer, targeted inhibition of Notch and mTOR pathways has been suggested as therapeutic options for cervical cancer patients [40]. Consequently, identification of lncRNAs that alter these signaling pathways and subsequent expression analysis of these lncRNAs in patients' samples would help to better select patients for recruitment in these trials.

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