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Targeting Long Non-Coding RNAs Binding to EZH2 for Reduced Cancer or Associated Diseases

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ABSTRACT

Enhancer of Zeste Homolog 2 (EZH2) is a polycomb group protein that tri-methylates its target genes at histone 3 position thereby leading to their transcriptional silencing. Acting as a global repressor, EZH2 has major implications in tumorigenesis and other ailments. Indispensable role of EZH2 in epigenetics has led the researchers to identify various ways that may be used to regulate it. Among these strategies, microRNA, small-interfering RNA and short-hairpin RNA has been successfully applied to regulate the expression of EZH2. In recent years, after genetic and epigenetic regulation, role of long non-coding RNA (lncRNA) has emerged as a new level of biological regulation. Recently, lncRNAs have been found to be function through EZH2 and its downstream target genes. In the present review, we discuss the mechanistic insights into the potential role of LncRNA-EZH2 axis in disease pathogenesis as reported and indexed in PubMed in the current year. Including various types of human cancer, we also analyzed other disorders where LncRNA-EZH2 axis plays defining role in disease progression.

Keywords: EZH2, LncRNAs, Oncogenes, Tumor suppressor genes, Cancer

INTRODUCTION

EZH2 is the catalytic subunit of polycomb repressive complex 2 (PRC2) that have multifaceted role normal as well as cancerous cell development. Predominantly, EZH2 functions as an oncogene and regulates several genes that have tumor suppressive role. By tri-methylating the promoter elements at histone H3 at position lysine 27, EZH2 act as an epigenetic regulator that have multiple cellular functions [1-4]. Highly expressed in human malignancies, EZH2 stimulates transformation of normal cells into cancerous [5-8]. Owing to its critical role in cellular functions, various levels of regul [ation has been studied that regulate epigenetic modifications performed by EZH2 specially H3K27me3. These regulations include microRNA [9-14], small-interfering RNA [15-17], short-hairpin RNA [18-20] and long non-coding RNAs [21]. Long non-coding RNAs are more than 200 nucleotides long that are transcribed by RNA polymerase II and do not code for any protein. These non-coding RNAs play variety of roles to regulate gene expression and modulate phenotype of cells. They act as chromatin modifiers and have essential role in epigenetic inheritance. Having modulatory role in cardiovascular diseases and multiple human malignancies, lncRNAs demonstrate a complex layer of gene regulation both transcriptional and posttranscriptional [22]. Based on their position in genomes and in relation to well known-protein coding genes, lncRNAs have been broadly categorized in five major types [23]. First among these are stand-alone lncRNAs that include large intergenic ncRNAs or lincRNAs and do no overlap protein-coding genes such as HOTAIR, Xist and MALAT1. Second category is natural antisense transcripts, which are transcribed opposite to the sense strand of known gene-coding transcripts and overlap to some extent to form sense-antisense pairs, examples of this kind are Xist/Tsix and Kcnq1/Kcnq1ot1. Other three lncRNAs include psuedogenes, long intronic ncRNAs and promoter-associated transcripts and enhancer RNAs [22, 23].

Here we discuss the category of lncRNAs that exhibit their functions by regulating polycomb group protein EZH2 and its upstream or downstream targets. Recent studies report a

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large number of lncRNA that regulate EZH2 in different cancers and other disease conditions. In the following section, we review the regulation of EZH2 by several lncRNAs that play influential role in pathophysiology of diseases/ disorders that include all cancer types such as breast, prostate, NSCLC (non-small cell lung cancer), osteosarcoma, ovarian, endometrial, colorectal, gastric, pancreatic, uveal melanoma, esophageal squamous cell carcinoma, colon cancer, anaplastic thyroid carcinoma, glioma, hepatocellular carcinoma and others. Role of lncRNAs in other disease conditions such as preeclamsia, hypoxia, sepsis, vascularization, Allergic rhinitis and atherosclerosis were also analyzed. Based on their function, lncRNA can be oncogenic or tumor suppressive.

ONCOGENIC LNCRNAS

Upregulated expression of LncRNA HOTAIR leads to EZH2-mediated down-regulation of miRNA-106 in preeclampsia placental tissue [24]. In another study, down-regulation of HOTAIR results into increased expression of miR-138-5p which in turn reduced the expression of EZH2 leading to chemosensitivity of Cisplatin resistant ovarian cancer cells [25]. Moreover, HOTAIR induced EZH2 expression leads to enhanced expression of collagen and α-SMA and at the same time reduced miR-34a expression plays influential role on myofibroblast phenotype and thus in Systemic Sclerosis (SSc) [26]. In NSCLC, down-regulation of anti-differentiation non-coding RNA (ANCR) leads to reduced expression of EZH2 and increased expression of tumor suppressor p21 and p27 [27]. HIF-1α plays major role in hypoxia, a well-known feature of tumor microenvironment. LncRNA HIF-1α inhibitor at translation level (HITT) inhibits the expression of HIF-1α by stimulating increased recruitment of EZH2 on its promoter affecting hypoxia-induced apoptosis in tumor microenvironment [28]. In breast cancer cells, LncRNA named differentiation antagonizing non-protein coding RNA (DANCR) regulates the EZH2-mediated epigenetic silencing of suppressor of cytokine signaling 3 (SOCS3) [29]. Increased tissue and plasma level of LncRNA PCAT (Prostate-cancer-associated ncRNA transcript 1) in endometrial carcinoma is associated with EZH2 intervened expression of E-cadherin [30]. Interfering LncRNA Zeb-anti-sense (AS) 1 in combination with EZH2 leads to reduced osteosarcoma cell proliferation, migration and enhanced apoptosis [31] similar to colorectal carcinoma (CRC) [32] where, in association with EZH2, LncRNA CACNA1G-AS1 regulated the expression of p53 to induce increased proliferative and invasive properties [33]. In osteosarcoma, LncRNA human homeobox A transcript at the distal tip (HOTTIP) play important role. HOTTIP are potentially upregulated in osteosarcoma tissues as well as cell lines and induces xenograft growth and lung metastasis. By recruiting EZH2 and lysine specific demethylase (LSD1) on LATS2 promoter, HOTTIP activates YAP/β-catenin signaling leading to increased osteosarcoma growth [34].

LncRNA actin filament associated protein 1-antisense RNA1 (AFAP1-AS1) binds directly to EZH2 to regulate the expression of Kruppel-like factor 2 (KFL2) which in turn affects gastric cancer cell growth and proliferation [35]. Another LncRNA that plays important role in gastric cancer cell progression is large tumor suppressor kinase 2 antisense transcript 1 (LATS2-AS1-001). Upon binding with EZH2, LATS2-AS1-001 induces the phosphorylation of YAP thereby inhibiting gastric cancer progression [36]. LncRNA metastasis-associated lung adenocarcinoma transcript 1(MALAT1) regulates the expression of BRCA1 by recruiting EZH2 and stimulating AKT phosphorylation thereby aggravating sepsis progression [37]. Similarly, in hepatocellular carcinoma (HCC), in cooperation with EZH2, MALAT1 regulates the expression of miR-22, E-cadherin and Snail family transcriptional repressor 1 (SNAI1) elucidating the underlying mechanism of MALAT1-mediated increased HCC progression and metastasis [38]. Another LncRNA urothelial carcinoma antigen-1 (UCA1) regulates vascular smooth muscle cell growth and migration by stimulating EZH2 recruitment on promoter of matrix metalloproteinase-9 leading to its repression [39]. By increasing the interaction of CDK1, EZH2 and its downstream target nuclear factor of activated T (NFAT), lncRNA UCA1 also play influential role in arsenic-induced cell toxicity [40]. Yet another oncogenic role of lncRNA UCA1 was evident in gastric cancer where it promoted cisplatin resistance in gastric cancer cells [41]. Upregulated expression level of LncRNA NRON, a repressor of NFAT in breast cancer samples and cells is oncogenic that induces EZH2 expression leading to increase breast cancer cell growth and metastasis [42]. On the other hand, lncRNA LOXL1-AS1 interacts with EZH2 to repress miR-708-5p expression that directly regulates nuclear factor kappa B (NFkB) to induce increased breast cancer progression [43]. Bekric et al. reviewed the functional significance of lncRNAs that in association with chromatin modifying eznymes such as EZH2 play important regulatory role in biliary tract cancer [44].

Upon interaction with EZH2, LncRNA small nucleolar RNA host gene 14 (SNHG14) regulates the expression of epithelial cell marker E-cadherin to induce increased cell invasion in pancreatic carcinoma [45]. Competitive binding of LncRNA proteasome subunit α3 antisense 1 to miRNA-101, a direct negative regulator of EZH2, has been elucidated to promote esophageal squamous cell proliferation, migration and invasion in vitro [46]. LncRNA CDKN2B-AS1 (cyclin dependent kinase inhibitor 2B antisense 1) is highly expressed in atherosclerosis, a leading cause of cardiovascular diseases. CDKN2B-AS1 promotes plague formation by stimulating EZH2 recruitment on CDKN2B promoter thereby inhibiting its tumor suppressive role [47]. Increased expression of LncRNA long non-coding RNA associated with poor prognosis of colon cancer (LNAPPCC) is associated with poor survival of colon cancer

patients. Upon binding, LNAPPCC inhibits EZH2-mediated repression of protocadherin 7 (PCDH7) which in turn activates LNAPPCC via ERK/c-FOS signaling forming a positive regulatory loop [48]. DLEU2 or deleted in lymphoctic leukemia 2 is a LncRNA that is highly expressed in human hepatocellular carcinoma and is expressed in liver. It binds directly to Hepatitis B protein HBx and polycomb group protein EZH2 leading to hepatocytes transformation [49]. LncRNA associated with poor prognosis of hepatocellular carcinoma (AWPPH) plays oncogenic role in hepatocellular carcinoma by repressing tumor suppressor gene PTEN by stimulating increased occupancy of EZH2 and LSD on its promoter [50]. Yet another lncRNA lymphoid enhancer-binding factor-1 antisense RNA 1 (LEF1-AS1) induces increased hepatocellular cancer cell growth by increasing the expression of EZH2 and cell division cycle-associated 7 (CDCA7) [51]. EZH2-mediated epigenetic silencing of LINC00632 leads to silencing of lncRNA cerebellar degeneration-related 1 antisense (CDR1 AS) which in turn regulates miR-7 playing critical role in metastasis in melanoma [52].

TUMOR SUPPRESSIVE LNCRNAS

By inhibiting EZH2, LncRNA Growth Arrest Specific 5 (LncGAS5) alters the balance of Th1/Th2 differentiation, which contributes to the immune response in Allergic rhinitis patients [53]. LncRNA GAS5 plays anti-tumorigenic role in melanoma cells by recruiting E2F to EZH2 promoter thereby inhibiting its occupancy on CDKN1C [54], a well-known tumor suppressor. Similar tumor suppressive role of LncRNA GAS5 was found in glioma where it was found to directly interact with EZH2 to alleviate the expression of miR-424 leading to suppressed malignant phenotypes [55]. However, in atherosclerosis, LncRNA GAS5 promotes lipid accumulation by inhibiting ATP-binding cassette transporter A1 (ABCA1) expression upon binding to EZH2 [56]. Another anti-tumor LncRNA is Prader Willi/ Angelman region RNA 5(PAR5) that reduces EZH2 expression and its binding to E-cadherin to inhibit anaplastic thyroid carcinoma progression [57]. LncRNA GATA antisense 1 (GATA-AS1) show anti-tumor activity in gastric cancer. By stimulating increased occupancy of EZH2 on promote region of Frizzled 4 protein associated with Wnt/β-catenin signaling, GATA-AS1 inhibits gastric cancer progression [58]. Reduced expression of BLACAT1 (bladder cancer associated transcript 1) is prostate cancer tissues and cell lines were observed and LncRNA (BLACAT1) inhibited prostate cancer cell proliferation by interacting with miR-361 and binding to EZH2 which in turn binds to mitogen-activated protein kinase and regulates cancer cell growth [59]. In acute myeloid leukemia (AML), lncRNA NR-104098 inhibits proliferation and induces differentiation of AML cells by recruiting E2F on promoter of EZH2 thereby repressing its transcription [60]. In uveal melanoma, low expression of LncRNA SNHG7 is associated with poor prognosis, as it inhibits malignant transformation by repressing polycomb group protein EZH2 [61]. However, in ovarian cancer, SNHG7 is activated by specificity protein 1 (SP1) and exhibits oncogenic properties by regulating EZH2-mediated KLF2 expression [62].

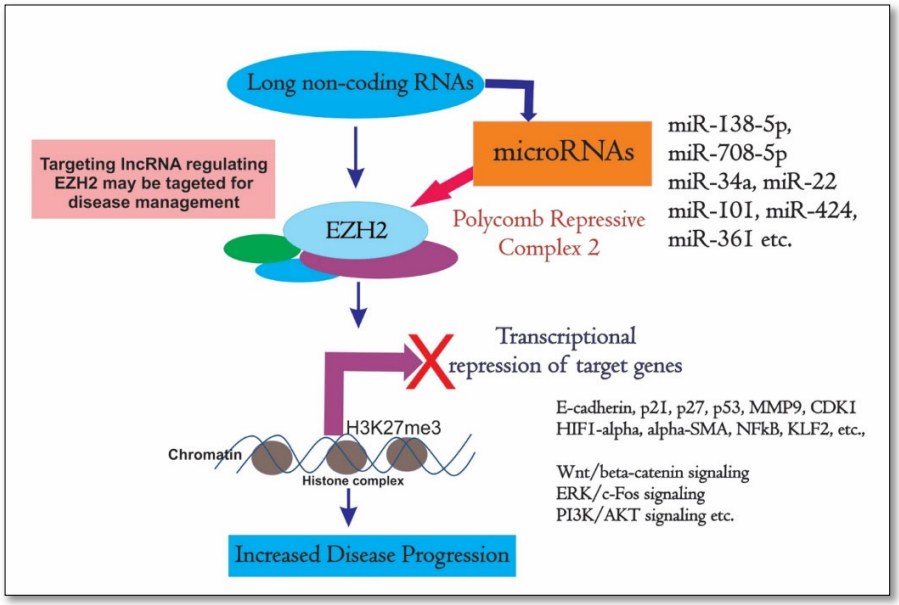

Figure 1. Intricate relation of lncRNAs and EZH2.

CONCLUSIONS

LncRNAs have emerged as important gene regulators that regulate gene transcription in nucleus and alter mRNA stability and posttranslational modifications in cytoplasm [63]. Representing to a highly heterogeneous group of transcripts, lncRNAs function by binding to transcription

factors or DNA binding proteins, histone modifying complexes or to enzymes like RNA polymerases [64-66]. LncRNAs recruit PRC2 complex to promoter elements of gene specific chromatin thereby regulating the overall cellular functions [67] as an oncogene or as a tumor suppressor. As discussed, several studies report binding of lncRNAs to EZH2, which affects its recruitment to its target genes leading to severe pathological consequences **(Figure 1)**. Thus, targeting EZH2 binding lncRNAs may prove to be beneficial for disease management.

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