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Review

The reciprocal link between EVI1 and miRNAs in human malignancies

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ABSTRACT

Ecotropic virus integration site-1 (EVI1) is an oncogenic transcription factor which locus on chromosome 3(3q26.2). Alterations in EVI1 functions correspond with poor prognosis in different cancers, underscoring their status for the clinical cancer phenotype. MicroRNAs(MiR)are a class of small non-coding RNA sequences. They post-transcriptionally influence mRNA sequence through imperfect pairing with the 3′-UTR. Moreover, a growing body of studies showed that miRNAs could regulate initiation and progression of human malignancies. Current studies have been described that identifies numerous microRNAs that can be modulated by EVI1. Interestingly, the expression level of EVI1 can also be regulated by microRNAs, thus forming a reciprocal link. Recent understanding of the functional roles of EVI1, microRNAs, and their interactions in human cancers are summarized. This review will help to define a relationship between EVI1 and microRNAs in human malignancies and develop novel therapeutic strategies.

1. Introduction

The occurrence of cancer is a multi-step process. It is known that the causes of human malignancies are through gene-gene interaction. Gene expression is modulated by activation or repression of transcription factors at transcriptional level in general. Previous studies have shown that proto-oncogenes could be initiated aberrantly by transcription factors which leads to malignancies occurrence and development.

Ecotropic virus integration site-1 (EVI1) gene was first found in a mice model of acute myeloid leukemia (AML) twenty years ago (Mucenski et al., 1988, Nucifora et al., 2006). EVI1 is an oncogenic transcription factor which locus on chromosome 3(3q26.2). EVI1 encode a zinc finger protein of 145 kDa which could bind with DNA. And some human solid cancers as well as hemopoietic diseases were found closely related to the overexpression of EVI1 (Balgobind et al., 2010; Jazaeri et al., 2010; Koos et al., 2011). In prostate cancer, the enhanced expression of EVI1 is associated with tumor progression, suggesting EVI1 overexpression as a novel factor in prostate cancer biology (Queisser et al., 2017). In human breast cancer, researchers found EVI1 as a potent oncoprotein in ER- and HER2-negative subsets of breast cancer (Wang et al., 2017). Recently, some genome-wide studies for EVI1 have been published (Noordermeer et al., 2012) (Sayadi et al., 2016). Researchers who target on EVI1 always be limited to protein-coding genes (Glass et al., 2013). However, the non-coding targets genes deserve further investigation.

MicroRNAs(MiRs) are one class of non-coding RNAs. MicroRNAs regulate gene expression post-transcriptionally through imperfect pairing with their target mRNAs. This process induces translational repression or degradation of the target mRNAs (Krol et al., 2010). Importantly, MicroRNAs are thought to play critical roles in cell biological processes, including metastasis, apoptosis, and proliferation. Numerous human malignancies are linked with them (Lujambio and Lowe, 2012), which first identified in B cell chromic lymphocytic leukemia (Calin et al., 2002). In cancer pathogenesis, alterations of microRNAs can play a role as either tumor suppressors or oncogenes named “OncomiRs”. For instance, miR-16-1 and miR15a function as tumor suppressors in

Abbreviations: EVI1, ecotropic virus integration site-1; MiR, microRNA; 3′-UTR, 3′-untranslated regions; AML, acute myeloid leukemia; DNA, deoxyribonucleic acid; RNA, ribonucleic acid; NF-κβ, nuclear factor kappa β; CHIP, Chromatin Immunoprecipitation; c-Myb, c-myeloblastosis; TGF-β, transforming growth factor-β; GATA2, GATA binding protein 2; Pbx1, pre-B-cell leukemia transcription factor 1; Map3k14, mitogen-activated protein kinase kinase kinase 14; AP1, activator protein; Bcl-2, B-cell lymphoma 2; MM, multiple myeloma; CLL, chronic lymphoid leukemia; FOXO3, forkhead box O3; ETS-1, E-twenty-six 1; HL, Hodgkin's lymphoma; HCC cell, hepatocellular carcinoma cell; CDH1, cadherin-1; PPARA, peroxisome proliferator-activated receptor alpha; ALL, acute lymphoblastic leukemia; PTPN9, tyrosine-protein phosphatase non-receptor type 9; RECK, reversion-inducing-cysteine-rich protein with kazal motifs; NSCLC, non-small-cell lung carcinoma; SAMD9, sterile alpha motif domain-containing protein 9; ASPP, apoptosis-stimulating of p53 protein; STAT3, signal transducer and activator of transcription 3; ERK, Esignal–regulated kinases; SOS1, son of sevenless homolog 1; HDAC1, histone deacetylase 1; Bmi1, B lymphoma Mo-MLV insertion region 1 homolog; VEGF, vascular endothelial growth factor; ERK5/MAPK7, mitogen-activated protein kinase 7; Akt/PKB, protein kinase B; Cdk6, cyclin-dependent kinases 6; Cdc25A, cell division cycle 25 homolog A; MECOM, MDS1 and EVI1 complex locus protein EVI1; NOTCH1, notch homolog 1; TTP, tristetraprolin; VEGFR2, vascular endothelial growth factor receptor 2; TCL1A, cell leukemia/lymphoma protein 1A; pRb, retinoblastoma protein; SIRT1, sirtuin 1; ERα, estrogen receptor alpha; HBV, hepatitis B virus; PI3K/AKT, phosphatidylinositide 3-kinases/protein kinase B; GATA1, GATA-binding factor 1

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chronic lymphocytic leukemia and prostate cancer. Transcription factors regulate expression of miRNAs through predominantly binding to sites around the pre-miRNA start site. For example, miR-34a was regulated by NF-κβ through binding to a site −149 bp upstream of the miRNA start site (Li et al., 2012). MicroRNAs expressions are under control of transcriptional factors in a tissue-specific or development-specific way. Recently, microRNAs have been found to be regulated by EVI1. Evidences provided by CHIP sequencing data have shown that EVI1 can regulate several microRNAs transcription by binding to these promoters (Gomez-Benito et al., 2010; Senyuk et al., 2013). Individual microRNAs can mediate multiplex target mRNAs, while a single mRNA can be controlled by several microRNAs (Chaudhuri and Chatterjee, 2007). Considering this trait, it is not unexpected that microRNAs can act with their target genes in regulatory networks through feedback loops directly or indirectly. Then, the molecular network clarifies these bi-directional circuits one after another, such as p53/miR200, Notch/miR-326, and c-MYb/miR15a (Bracken et al., 2008, Kefas et al., 2009, Zhao et al., 2009, Pulikkan et al., 2010, Jing et al., 2015, Wu et al. 2016a). Interestingly, recent findings indicated that the relationship between EVI1 and microRNAs seems to be feedback loops. For example, miR133, which is under EVI-1 control, directly targets EVI-1 to increase drug sensitivity in AML cells (Yamamoto et al., 2016). In view of the high speed of research into EVI1 as well as microRNAs in human cancers, this review is for a better understanding of the mutual link between EVI-1 and microRNAs.

1.1. Function and expression of EVI-1 in human malignancies

EVI1 gene, locus on chromosome 3q26, is overexpressed in numerous human cancers including hematological diseases and several solid cancers (Ogami, 1996; Balgobind et al., 2010; Jazaeri et al., 2010; Koos et al., 2011; Glass et al., 2014; Queisser et al., 2017). More and more evidence has shown that EVI1 acts as an oncogene regulates a wiring of signaling pathways that leads to increasing tumor cells proliferation and suppressing their apoptosis (Yoshimi and Kurokawa, 2011; Zhou et al., 2014). For example, EVI1 suppresses c-jun phosphorylation which exerts anti-apoptotic functions in MOLM-1 cells, a human megakaryoblastoid cell line (Kurokawa et al., 2000). EVI1 promotes cellular proliferation through repressing Smad3 function and negatively regulating TGF-β signaling (Kurokawa et al., 1998; Izutsu et al., 2001). By recognizing a sequence consisting of GA(C/T)AAGA(T/C)AAGATAA-like or GACAAGATA-like motifs, EVI1 binds its target genes directly through its zinc finger domain and regulates those genes expressions (Yatsula et al., 2005; Yuasa et al., 2005). Recent studies have reported that EVI1 regulates MS4A3 (Heller et al., 2015) GATA2 (Yuasa et al., 2005), Pbx1 (Shimabe et al., 2009), Map3k14 (Yatsula et al., 2005) transcription. In human ovarian cancer, global EVI1 target genes were identified through genome-wide CHIP-Seq. From this study, more than 25% of EVI1-targeted genes were also occupied by activator protein(AP1), which providing clues for synergistic effects between EVI1 and AP1 (Bard-Chapeau et al., 2012). In a separate study, EVI1 deregulated of several reported EVI1 downstream target genes in murine myeloid leukemic cell lines (Glass et al., 2013). This study also identified some novel EVI1 gene targets involved in EVI1-induced leukemogenesis including Cebpε, Serpinb2 and several genes involved in apoptotic mechanisms mediated by ATP-dependent purinoreceptors. Some researchers found EVI1 was associated with epigenetic modifications which lead to cancer formation. More recently, accumulating evidence indicated that epigenetic aberrations related with EVI1 resulted in leukemia (Vazquez et al., 2011; White et al., 2013).

1.2. Tumor suppressor microRNA and OncomiRs

MicroRNAs can be considered as oncogenes or suppressors decided to their expressions in malignant tissues compared with the normal counterpart. MicroRNAs act as a tumor suppressor by targeting oncogene mRNA. For instance, miR-15a/16-1 genes can repress tumor development through down-regulated Bcl-2 and several oncogenes. And the expression of miR-15a/16-1 genes are decreased in multiple myeloma(MM) (Li et al., 2015), CLL (Cimmino et al., 2005), and prostate cancer (Musumeci et al., 2011). In contrast, 'oncomiR's' are a kind of microRNAs which targets expression of tumor suppressor mRNA directly. For example, miR155 was found to target tumor suppressor FOXO3 (Huang et al., 2015). And in several solid tumor tissues, miR155 was over expressed, including breast cancer (Poliseno et al., 2010; Liu et al., 2013a), cervical cancer (Wang et al., 2008), thyroid carcinoma (Nikiforova et al., 2008), and lung cancer (Yanaihara et al., 2006).

In human cancers, the peculiarity of these microRNAs function is tumor-specific. For instance, miR125b is over expressed in the leukemic translocation t(2;11)(p21;q23). In some AML subtypes, miR125b was reported to be an oncomiR (Bousquet et al., 2008; Bousquet et al., 2010). However, in breast cancer, miR125b can repress ETS-1 oncogenes and acts as a tumor suppressor (Zhang et al., 2011).

2. MicroRNA-EVI1 interactive relation

The bi-directional circuits exist in EVI1 and miRNAs have attracted more and more researchers' attention. More recently, some CHIP-seq data indicated EVI1 can occupy the promoter of target miRNAs which can regulate their expression (De Weer et al., 2011). In this section, we summarize the interactive relation between EVI1 and cancer-related miRNAs in human malignancies (Table 1) (Fig. 1A).

2.1. EVI1 acts as a microRNA transcription factor

2.1.1. miR-1-2

miR-1-2 is a class of miR-1 family, which is predominantly associated with tumor development and therapy resistance (Weiss et al., 2016). In the most of cancers, the miR-1 family members act as tumor suppressor miRs. And they are repressed in lung cancer, prostate cancer, sarcomas, breast cancer, and gastric cancer (Nasser et al., 2008; Osaka et al., 2014; Han et al., 2015; Liu et al., 2015). However, there are also a few studies provide evidence that miR-1 may act as an 'oncomiR' in some hematological cancers. MiR-1 was up-regulated in multiple myeloma(MM) (Gutierrez et al., 2010). Additionally, the expression of miR-1 was higher in several different subtypes of MM (Lionetti et al., 2009). In cytogenetic normal-AML patient, miR-1 has been found to be up-regulated (Seyyedi et al., 2016). Suppression of miR-1 precursor (miR-1-2) can repress the AML cells proliferation (Gomez-Benito et al., 2010). The expression of EVI1 and miR-1-2 has a strong positive correlation in AML patient samples and cell lines. In addition, EVI1 is found to activate miR-1-2 expression through binding to a region upstream of miR-1-2. Functional studies suggested that miR-1-2 was a central proliferation regulator in EVI1-overexpressed AML cell lines (Gomez-Benito et al., 2010).

2.1.2. miR-9

miR-9 targeting distinct downstream genes can act opposite functions in different tumor types. Overexpression of miR-9 was found in several cancers including Hodgkin's lymphoma (HL) (Nie et al., 2008), endometrial cancer (Myatt et al., 2010), and primary brain tumors (Nass et al., 2009). However, down-regulation of miR-9 was observed in different malignancies such as colorectal (Lizarbe et al., 2017), cervical (Hu et al., 2010), and ovarian cancer (Guo et al., 2009), and in hepatocellular (Tan et al., 2010) and gastric cancer (Luo et al., 2009). HCC cell invasiveness and proliferation were induced by miR-9 overexpressed targeting CDH1 and PPARA genes (Drakaki et al., 2015). In contrast, recently down-regulation of miR-9 was associated with several tumors development including cervical cancer, lung squamous cell carcinoma as well as ALL (Hildebrandt et al., 2010). And it is considered as a marker of poor survival. Despite miR-9 could be a critical regulator in different cancers, regulation about miR-9 expression is still