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Review

Functional roles of enhancer of zeste homolog 2 in gliomas

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ABSTRACT

Gliomas are the most common and lethal type of primary malignant brain tumor. Due to the infiltrative nature and high resistance to standard first line treatment with combinations of radiation and chemotherapy, the prognosis of patient is very poor. Recently, accumulated evidence suggests that enhancer of zeste homolog 2 (EZH2) serves as an oncogene and is involved in multiple glioma cell processes, including cell cycle, invasion, glioma stem cell maintenance, drug and radiotherapy resistance and so on. In this review, we will focus on updating current knowledge of EZH2 in gliomas. Moreover, the regulation of EZH2 by microRNAs and long non-coding RNAs and the therapeutic strategies targeting EZH2 for gliomas will also be discussed.

Contents

Abbreviations: 3′ UTRs, 3′ untranslated regions; 4E-BP1, 4E binding protein 1; BCRP, breast cancer resistance protein; BMP, bone morphogenetic protein; CNTF, ciliary neurotrophic factor; CIITA, Class II Transactivator; CPEB1, cytoplasmic polyadenylation element-binding protein 1; DZNep, 3-deazaneplanocin A; EED, Embryonic Ectoderm Development; ES, embryonic stem; EZH2, enhancer of zeste homolog 2; GBM, glioblastoma multiforme; GSCs, glioma stem cells; GSK3a/b, glycogen synthase kinase 3A and B; H3K27, methylating lysine 27 of histone 3; H3K27me3, trimethylation of lysine 27 of histone H3; H2AK119ub1, lysine 119 of histone H2A; HOTAIR, Hox transcript antisense intergenic RNA; LncRNAs, long non-coding RNAs; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; MDR, multi-drug resistance; MEG3, Maternally Expressed Gene 3; MHC II, Major Histocompatibility Class II; miRNAs, microRNA; MRP, multi-drug resistance associated protein; mTOR, mammalian target of the rapamycin; p70s6k, p70 ribosomal protein S6 kinase; P-gp, P-glycoprotein; PRC2, Polycomb repressive complexes 2; shRNA, short hairpin RNA; SUZ12, Suppressor of Zeste 12; TCGA, The Cancer Genome Atlas; TMZ, temozolomide; WHO, the World Health Organization.

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1. Introduction

Gliomas are the most common and malignant type of primary brain tumor (Hamza and Gilbert, 2014). According to histopathology, the World Health Organization (WHO) has classified the gliomas into grades I–IV, of which the glioblastoma multiforme (GBM) is classified as grade IV, the most aggressive group (Louis et al., 2007). The origin of gliomas is largely unknown but recently it is thought to be derived from a small population of glioma stem cells (GSCs) (Cheng et al., 2010; Vermeulen et al., 2012). Previous study estimated that gliomas represent approximately 28% of all primary brain tumors and 80% of malignant tumors and an annual age-adjusted incidence of 3.19 per 100 000 population, or 52,751 new cases of GBM diagnosed per year in the United States (Ostrom et al., 2014). While in China, for the youngest (aged from 0–19) strata of the population, glioma appeared to occur more than other subtypes of primary brain tumors, accounting for 55.56% of all of cases and in those aged from 20 to 59 years, gliomas still accounts for 31.1% (Jiang et al., 2011). Now combined surgery with focal fractionated radiotherapy and adjuvant temozolomide (TMZ) has become the standard first line treatment for newly diagnosed GBM (Stupp et al., 2008). Nevertheless, the median survival of GBM patients is less than 15 months despite optimal treatment (Stupp et al., 2005). This is due to the infiltrative nature of GBM and the resistance to radiation and chemotherapy (Masui et al., 2012). Thus, understanding the molecular pathways mediating cellular survival and drug resistance will enable us to find the potential therapeutic targets in GBM.

Enhancer of zeste homolog 2 (EZH2) is the core catalytic subunit of Polycomb repressive complexes 2 (PRC2) which is a multiprotein complex composed of three core subunits including EZH2, Suppressor of Zeste 12 (SUZ12), and Embryonic Ectoderm Development (EED) (Margueron and Reinberg, 2011). EZH2 can induce the tumor suppressor genes to silence by methylating lysine 27 of histone 3 (H3K27). Recent studies have found that EZH2 is overexpressed in a wide range of cancer, including those of the prostate, breast and glioma, etc. (Chinaranagari et al., 2014; Mu et al., 2013; Zhang et al., 2015a; Yoo and Hennighausen, 2012). In this review, we will focus on EZH2-related studies in glioma that have been published over the past decade, particularly those articles pertaining to its upstream regulation and roles in glioma cell cycle, invasion, GSC maintenance, drug and radiotherapy resistance, prognosis and prospects as a form of glioma treatment.

2. EZH2 and the Polycomb family

Human EZH2 gene is located on the long arm of chromosome7 at position 7q35 and encodes a 746 amino acid protein belonged to the Polycomb family (Cardoso et al., 2000). The Polycomb family comprises a structurally diverse set of proteins which are epigenetic regulators of transcription and function mechanistically through multiprotein complexes, called Polycomb repressive complexes (PRCs) which contain two main families of PRC1 and PRC2 in mammals (Di Croce and Helin, 2013). The core of the PRC1 complex includes one subunit of the PCGF, CBX, HPH, and RING1 paralog groups, while the core of PRC2 complexes comprises SUZ12, one of the EED isoforms and the histone methyltransferase EZH1 or EZH2, which catalyze the trimethylation of lysine 27 of histone H3 (H3K27me3) (Sauvageau and Sauvageau, 2010). When the PRC2 complex is recruited to chromatin, the histone methyltransferase EZH1/2 catalyzes the H3K27me3. Subsequent recruitment of the PRC1 complex occurs in part through affinity binding of the chromodomain of the CBX subunit to the H3K27me3 covalent mark. Then the PRC1 RING1 E3 ligase monoubiquitylates the lysine 119 of histone H2A (H2AK119ub1), which can prevent access to chromatin remodelers, inhibit RNA polymerase II-dependent transcriptional elongation and facilitate chromatin compaction (Francis et al., 2004; Zhou et al., 2008). In addition, EZH2 has also been reported to interact directly with the DNA methyltransferases DNMT1 (Ning et al., 2015), DNMT3A, and DNMT3B to allow the subsequent methylation (Vire et al., 2006) (Fig. 1).

3. Upstream regulation of noncoding RNAs

In recent years, noncoding RNAs have been recognized as major players in regulatory pathways, and many of them are deregulated in cancers. Increasing evidences indicate that EZH2 can be regulated in gliomas by various noncoding RNAs. Now we made a summary of those direct regulators of EZH2 expression or activity in gliomas (Table 1).

3.1. miRNAs

microRNA (miRNAs) are small, non-coding RNAs about 18–24 nucleotides in length that negatively regulate gene expression at the post-transcriptional and/or translational level by binding the 3′ untranslated regions (3′ UTRs) of target mRNAs (Bartel, 2004). Accumulating studies suggest that miRNAs are pivotal roles in glioma biology exhibiting tumorsuppressive functions by downregulating EZH2.

Smits et al. (2010) found that miR-101 was down-regulated in primary glioma samples of different WHO grades by quantitative PCR analysis, and upregulation of miR-101 by pre-miR-101 notably repressed EZH2 protein expression and reduced the levels of trimethylation of H3K27. miR-101 upregulation significantly reduced cellular proliferation, migration, invasion and tubule network formation in U87 GBM cells (Smits et al., 2010). Subsequently, Xiaoping et al. (2013) found that cytoplasmic polyadenylation element-binding protein 1 (CPEB1), which is hypomethylated and overexpressed in glioma cells and tissues, can be regulated directly by the tumor suppressor miR-101. Moreover downregulation of CPEB1 induced senescence in a p53-dependent manner. It's reported that miR-101 downregulated expression of CPEB1 through reversing methylation status of the CPEB1 promoter by regulating the presence on the promoter of the methylation-related histones H3K4me2, H3K27me3, H3K9me3 and H4K20me3. The epigenetic regulation of H3K27me3 on CPEB1 promoter is mediated by EZH2 and EED while the epigenetic regulation of H3K4me2 is mediated by EZH2. These results indicated that miR-101 epigenetically downregulated expression of CPEB1 by inhibiting EZH2 (Xiaoping et al., 2013). Guo et al. (2013) reported that miR-708 in GBM cell lines was decreased in comparison to that in normal brain tissue, and moreover, overexpression of miR-708 reduced EZH2 protein expression and inhibited cell proliferation and invasion and induced apoptosis in human GBM cell lines. Importantly, EZH2 plays a critical role in increasing the invasive ability of several tumor cell types (Ren et al., 2012; Rao et al., 2010). Herein, these findings suggest that regulation of EZH2 also provides support for miR-708 as a tumor suppressor that targets cell invasion (Guo et al., 2013). A study from our group demonstrated that miR-138 is reduced in both GBM clinical specimens and cell lines, and is effective to inhibit EZH2 expression (Qiu et al., 1832). What's more, upregulation of miR-138 effectively inhibits GBM cell proliferation in vitro and tumorigenicity in vivo through inducing cell cycles G1/S arrest. In mechanism investigation, we found that miRNA-138 acquires tumor inhibitory function through directly blocking the EZH2-CDK4/6-pRb-E2F1 signal loop (Qiu et al., 1832).

3.2. lncRNAs

Recently, regulation of long non-coding RNAs (lncRNAs) on global gene expression and pluripotency and differentiation of embryonic stem (ES) cells have been extensively studied (Guttman et al., 2011) and functions of lncRNAs are gradually unveiled. Different from miRNAs, lncRNAs generally comprise non-protein-coding RNAs that consist of more than 200 nucleotides (Mercer et al., 2009). The broad functions of lncRNAs involve roles in chromatin modification, transcriptional regulation and post-transcriptional regulation (Mercer et al.,