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Gene Section
Review

EZH2 (enhancer of zeste homolog 2 (Drosophila))

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Abstract

Review on EZH2, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: ENX-1, ENX1, EZH1, EZH2b, KMT6, KMT6A, WVS, WVS2

HGNC (Hugo): EZH2

Location: 7q36.1

Local order

Based on MapViewer, gene flanking EZH2 oriented on 7q35-q36 are:
- CUL1 (cullin 1); 7q36.1
- RNU7-20P (RNA, U7 small nuclear 20 pseudogene); 7q36.1
- **EZH2**; 7q35-q36.

DNA/RNA

Description

The EZH2 gene is located on chromosome 7, starting from 148504464 and ends at 148581441 bp. This gene encodes a member of the Polycomb-group (PcG) family. PcG family members form multimeric protein complexes, which are involved in maintaining the transcriptional repressive state of genes.

Transcription

Multiple alternatively spliced transcript variants have been identified for this gene. These include 5 histone-lysine N-methyltransferase EZH2 isoforms (-a/-b/-c/-d/-e). The first variant (a) has the longest isoform of histone-lysine N-methyltransferase EZH2.

The second variant (b) does not have an in-frame exon and an in-frame segment in the coding region, while (c) and (d) variants lack an in-frame segment in the coding region and two in-frame segments in the coding region, respectively, as compared to (a) variant. The last variant (e) has an alternate 5' UTR exon and lacks an in-frame exon and two in-frame segments in the coding region, as compared to (a) variant.

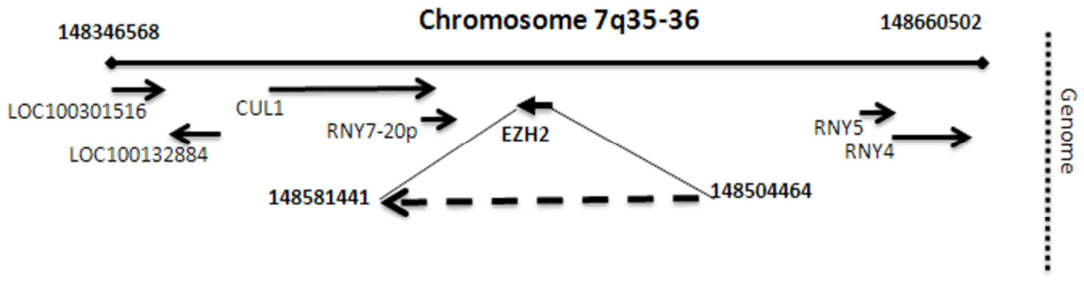

Figure 1. Location of EZH2 in chromosome 7, q35-36, which is located within 148504464 and 148581441 bp.

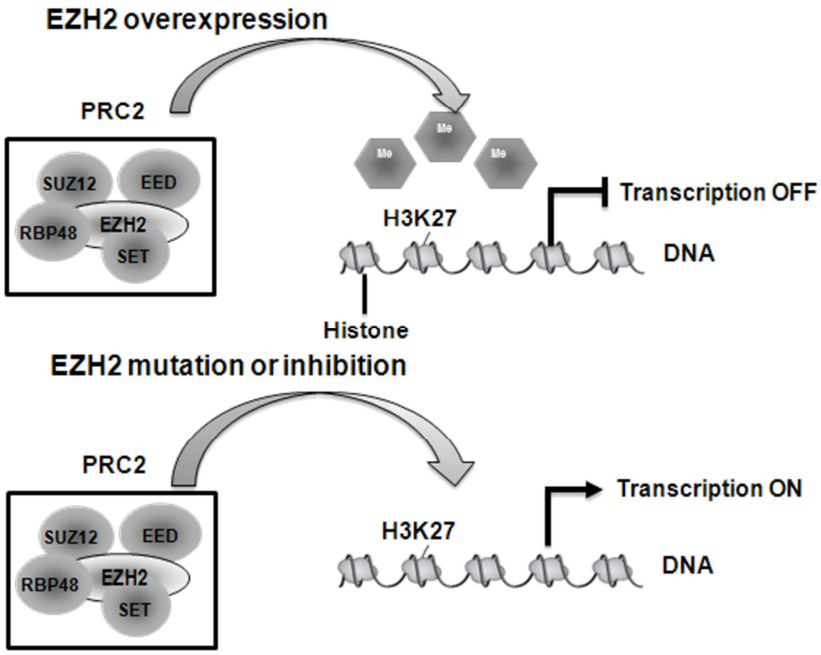

Figure 2. The interaction and effect of EZH2 in regulation of transcriptional repression. Polycomb complex 2 (PRC2) exerts methyltransferase activity to H3K27 via the SET domain of the EZH2 subunit.

Protein

Description

EZH2 protein is the catalytic subunit of Polycomb Repressive Complex 2, one of the two-multimeric repressive complexes in the organization of the PcG.

Function

PcG proteins act as an important epigenetic mediator that can repress gene expression by forming multiple complexes leading to trimethylation at lysine 27 of histone H3 (H3K27me3; Cao et al., 2002; Viré et al., 2006). On the one hand, EZH2 is a histone methyltransferase, which plays an important role in tumor development (Santos-Rosa and Caldas, 2005). Moreover, this protein might also play essential roles in the control of central nervous systems by regulating the dopamine receptor D4 (Unland et al., 2014).

Homology

The EZH2 gene is conserved in chimpanzee, Rhesus monkey, dog, cow, mouse, rat, chicken, zebrafish, fruit fly, and mosquito.

Mutations

Note

Several mutations have been reported in EZH2 gene, which has been shown to be associated with different human diseases (e.g., Weaver syndrome, lymphoma and myeloid neoplasms). In particular, Morin and collaborators, found that the mutation of EZH2 Y641, within the SET domain, is correlated with poor prognosis in myeloid neoplasms. They observed various heterozygous mutations at Y641 in 7% of follicular lymphomas and 22% of diffuse large cell B-cell lymphomas of germinal center origin (Morin et al., 2010), which increased the level of H3K27me3 (Chase and Cross, 2011). Furthermore EZH2 mutations have not yet been reported in several other human diseases such as pancreatic ductal adenocarcinoma, but we cannot exclude that such somatic alterations might occur.
Moreover, more than 4941 single nucleotide variations (SNPs) have been reported in the EZH2 gene (31th of January 2014, dbSNP), such as rs193921147, rs193921148, rs397515547, rs397515548, rs734004, rs12670401, rs6950683 etc.

Implicated in

Human diseases

Note

EZH2 is a histone methyltransferase, which is involved in the regulation of cell fate, and maintaining the balance between self-renewal and differentiation (Chang et al., 2011; Cao et al., 2002; Lund et al., 2014). This protein acts as an epigenetic mediator that can suppress gene expression by histones methylation at H3k27 (Cao et al., 2002; Viré et al., 2006). EZH2 is up-regulated in many tumors, such as breast and prostate cancer, which has been shown to be associated with tumor growth, invasion, and

metastasis as well as poor prognosis (Santos-Rosa and Caldas, 2005; Chang and Hung, 2012).

Pancreatic cancer

Note

EZH2 is found to be overexpressed in a variety of carcinomas including pancreatic adenocarcinoma (PAC), and has been shown to be associated with decreased E-cadherin expression and poor prognosis in PAC patients (Toll et al., 2010). In particular, Toll and collaborators, evaluated the correlation of EZH2 with E-cadherin expression in 54 pancreatic adenocarcinomas, 13 intraductal papillary mucinous neoplasms (IPMN), and 6 chronic pancreatitis cases, and assessed response to gemcitabine in relation to EZH2 expression in tumor cells. This study showed that high EZH2 expression in pancreatic adenocarcinoma was significantly associated with decreased E-cadherin expression and more aggressive disease. Moreover, they also observed high EZH2 expression in IPMN tissue with moderate to severe dysplasia, but not in chronic pancreatitis.

In the study by Ougolkov and colleagues, EZH2 was identified as an important factor in pancreatic ductal adenocarcinoma (PDAC) cell chemoresistance. In particular, they showed that EZH2 depletion by RNA-interference sensitized PDAC cells to gemcitabine (Ougolkov et al., 2008). Furthermore, in our recent study, we showed that inhibition of EZH2 by EZH2 inhibitor DZNeP synergistically increased the antiproliferative activity of gemcitabine (first line agent in treatment of PDAC) through inhibition of cell proliferation and migration, and increasing apoptosis (Avan et al., 2012).

Chronic pancreatitis

Note

Mallen-St Clair and colleagues published an elegant study illustrating that the EZH2 connects pancreatitis to acinar cell regeneration, by providing a mechanism of protection against progression to cancerous lesions (Mallen-St Clair et al., 2012). In this study they showed that EZH2 is overexpressed in patients suffering from chronic pancreatitis. In particular, their findings revealed that EZH2 is constraining neoplastic progression through homeostatic mechanisms that control pancreatic regeneration (Mallen-St Clair et al., 2012).

Prostate cancer

Note

Varambally and collaborators, in 2002, demonstrated that EZH2 is up-regulated in hormone-refractory, metastatic prostate cancer. They found that small interfering RNA against EZH2 reduced the EZH2 protein expression in prostate cells and inhibited cell proliferation in vitro, while ectopic expression of EZH2 in prostate cells induces transcriptional repression of a specific cohort of genes. They also showed that EZH2 up-regulation was significantly associated with the progression of prostate cancer and poor clinical outcome (Varambally et al., 2002). Moreover, deletions of microRNA-101 in prostate cancer resulted as a negative regulator of EZH2 expression, providing a possible mechanism for EZH2 overexpression (Cao et al., 2010).

Breast cancer

Note

Kleer and collaborators explored the functional role of EZH2 in cancer cell invasion and breast cancer progression, and evaluated the expression of EZH2 in 280 patients. They showed that EZH2 transcript and protein were consistently elevated in invasive breast carcinoma compared to normal breast epithelia. Moreover, tissue microarray analysis illustrated that the levels of EZH2 expression were strongly associated with breast cancer aggressiveness. In particular, EZH2 overexpression in immortalized human mammary epithelial cell lines stimulated anchorage-independent growth and cell invasion in the cells. In this study they identified EZH2 as a marker of aggressive breast cancer, which promotes neoplastic transformation of breast epithelial cells (Kleer et al., 2003).

Bladder carcinoma

Note

Several studies have been shown the role of EZH2 in bladder carcinomas (Weikert et al., 2005; Raman et al., 2005; Arisan et al., 2005). In particular, Weikert and collaborators, evaluated the EZH2 expression in 37 bladder carcinomas using real-time reverse transcription-polymerase chain reaction (RT-PCR) and correlated the data with clinicopathological findings. They found that the mRNA levels of EZH2 were significantly higher in invasive bladder carcinomas (median value, 38.92) compared to non-invasive tumors (median value, 15.51). Moreover, the level of EZH2 expression was significantly higher in grade-3, with respect to grade-1/2 lesions, suggesting its role in the progression of bladder tumors. In addition, increased EZH2 expression correlated with oncogenesis of the bladder (Arisan et al., 2005; Weikert et al., 2005).

Gastric cancer

Note

Despite the complexity of stomach carcinogenesis, a number of markers identified as prognostic factors, including EZH2. Matsukawa and colleagues determined the expression of EZH2 in 83 surgically removed human gastric cancer tissues and analyzed its association with the

clinicopathological features of human gastric cancers. Immunohistochemical analysis of the tissue samples and corresponding non-cancerous gastric mucosa demonstrated that EZH2 was more highly expressed in the cancerous than in the non-cancerous tissues, and the expression levels of EZH2 were markedly associated with tumor size, depth of invasion, vessel invasion, lymph node metastasis and clinical stages. Furthermore, gastric cancer patients with high-level EZH2 expression had poorer prognosis, compared to those expressing low levels of EZH2 (Matsukawa et al., 2006).

Lung cancer

Note

Several studies have investigated the biological role and prognostic value of EZH2 in lung cancer. Recently, Xia and colleagues demonstrated that inhibition of EZH2 by RNAi enhanced irradiation-induced inhibition of human lung cancer growth in vitro and in vivo. They showed that irradiation in combination with the inhibition of EZH2 arrested A549 cells in the G1-S boundary, inhibited cell proliferation, increased the percentage of apoptotic cells in vitro, and reduced tumor size and increased survival in tumor xenograft (Xia et al., 2012). Another study evaluated the EZH2 expression in 106 patients classified as stage I non-small cell lung cancer (NSCLC). They found that patients with positive EZH2 expression had a larger tumor size and survived significantly shorter, compared to the patients with low EZH2 expression. Moreover, in vitro studies showed that knockdown of EZH2 expression in the NSCLC cell lines reduced the tumor growth rate and invasive activity, indicating that EZH2 promotes progression and invasion of NSCLC, and its expression can be considered as a novel prognostic biomarker in NSCLC (Huqun et al., 2012).

Moreover, Lv and collaborators, in 2012 evaluated the expression of EZH2 in lung adenocarcinoma tissues and cell lines. They observed that EZH2 overexpression in tumor tissue significantly correlated with histological differentiation, pathological tumor-node-metastasis stage and smoking history. Moreover, overexpression of EZH2 was also detected in cisplatin-resistant cancer cells with respect to cisplatin-sensitive cells, while inhibition of EZH2 inhibited cell proliferation and migration, and induced apoptosis in both cisplatin-resistant and cisplatin-sensitive cell lines. These data suggested that EZH2 contributed to the progression of lung adenocarcinoma, and the suppression of EZH2 inhibited cell growth and sensitized cells to cisplatin in lung adenocarcinoma (Lv et al., 2012). Furthermore, Xu and collaborators, found a positive correlation between high EZH2 expression with pathologic stage, nodal involvement in lung cancer patients. In particular, they showed that overexpression of EZH2 was associated with reduced tissue inhibitor of metalloproteinase-3 expression, which was shown to be negatively associated with tumor metastasis in lung cancer (Xu et al., 2013).

Hepatocellular carcinoma

Note

Sudo and collaborators investigated the expression of EZH2 in 66 patients with hepatocellular carcinoma (HCC), using RT-PCR, and correlated its expression with clinicopathological parameters. They observed that the expression levels of EZH2 in tumor tissue specimens were significantly higher, compared to the non-tumor tissue specimens. Moreover, these analyses demonstrated that the incidence of cancer cell invasion into the portal vein was markedly increased in the group of patients with high EZH2 expression with respect to the patients with low EZH2 expression, while there was no difference in the disease-free survival rate between the two groups of patients (Sudo et al., 2005).

Hematological malignancies

Note

The role of EZH2 in hematological malignancies is still unclear. Several point mutations, resulting in gain-of-function, or inactivating mutations (loss-of-function), have been observed in lymphoma and leukemia, suggesting its role as an oncogene or tumor-suppressor gene. Visser and collaborators, evaluated the expression of both multimeric PcG protein complexes (EZH2-EED- and a BMI1-RING1- containing complex) in six cases of mantle cell lymphoma (MCL). They showed that MCL cells expressed BMI1-RING1, but not EZH2-EED, like normal mantle cells. Moreover, they showed that the up-regulation of EZH2 was associated with higher proliferation rate of haematopoietic cells (Visser et al., 2001).

A recent study performed a comparative microarray analysis of gene expression in primary adult T-cell leukemia/lymphoma samples. This study found the higher levels of EZH2, RING1 and YY1 binding protein transcripts with enhanced levels of H3K27m3 in adult T-cell leukemia/lymphoma cells, compared with those in normal CD4 (+) T cells. They also showed that patients with high EZH2 expression had a significantly poorer prognosis, indicating a possible role of this gene in the oncogenesis and progression of this disease (Sasaki et al., 2011). Another gene expression profiling of Polycomb, Hox and Meis genes in 126 patients with acute myeloid leukemia showed that the expression levels of EZH2 and MEL18 were significantly higher in patients with complex karyotype and lower in CBF-mutated patients. Moreover, comparisons between the PcG and PcG-

regulated genes and clinical data demonstrated the correlations of genes involved in DNA methylation with apoptosis (BAX, Caspase 3) and multidrug-resistance (MDR1, MRP), suggesting the role of PcG and PcG-regulated genes in leukaemogenesis (Grubach et al., 2008). Moreover, Xu and collaborators examined a heterogeneous myelodysplastic syndrome (MDS)/AML population known to harbor DNA methylation of tumor-suppressor genes, such as p15INK4B. They observed that patients with p15INK4B gene methylation had a significantly higher expression of EZH2 with respect to the non-methylated counterparts, and the level of EZH2 expression correlated with poor clinical outcome (Xu et al., 2011).

Conversely, Nikoloski and collaborators demonstrated the role of EZH2 as tumor suppressor gene in myelodysplastic syndromes (MDS). In this study, they sequenced the EZH2 gene in 126 patients with MDS. These analyses revealed that EZH2 gene was frequently mutated in MDS patients. Similarly, another recent study demonstrated that inhibition of EZH2 increased the tumorigenic potential and mortality of T cell acute lymphoblastic leukemia cells transplanted into NOD-SCID mice, suggesting the tumor suppressor role of PRC2 in human leukemia (Ntziachristos et al., 2012).

Qi and collaborators recently developed an EZH2-selective small-molecule inhibitor EI1 that binds to the S-adenosylmethionine of EZH2. They observed that inhibition of EZH2 by EI1 in diffused large B-cell lymphomas cells carrying the Y641 mutations decreased the cell proliferation, cell cycle arrest, and enhanced apoptosis (Qi et al., 2012). Two other recent studies have demonstrated further advances in the therapeutic potential of EZH2 inhibition to treat lymphoma. Among the compounds, which have been developed so far, EPZ005687 and GSK126 have been found to induce apoptosis in lymphoma cell lines harboring Tyr641 mutations with minimal effect on WT cells, in vitro (Knutson et al., 2012) and in vivo (McCabe et al., 2012). In particular, McCabe and collaborators, showed that GSK126 molecule inhibited tumor growth and significantly increased survival of the mice carrying lymphoma cells (McCabe et al., 2012; Lund et al., 2014).

In aggregate, considering the dual function of EZH2, which has been shown to act as oncogene or tumor-suppressor gene in hematological malignancies, the therapeutic potential of EZH2 inhibitors should be evaluated carefully, to ensure achievement of beneficial effect, rather than tumorigenic effect (Lund et al., 2014).

Pediatric tumors of the central nervous system

Note

The dopamine receptor D4 (DRD4) is a G-protein-coupled receptor widely expressed throughout the central nervous system (CNS). Disruption of dopamine signaling is implied in diseases including schizophrenia, Parkinson's and Huntington's disease (Oak et al., 2000). Recently Unland and colleagues identified DRD4 as a methylated candidate in pediatric CNS tumors, using a genome-wide methylation approach. Their analyses suggested DRD4 as a direct target of EZH2. In particular, they showed that depletion of EZH2 is sufficient to induce re-expression of DRD4, suggesting the role of EZH2 for DNA hypermethylation in the epigenetic inhibition of DRD4 (Unland et al., 2014).

Glioblastoma multiforme

Note

Overexpression of the EZH2 has been observed in different malignancies, including glioblastoma multiforme (GBM) (Venneti et al., 2013). Suvà and collaborators demonstrated that disruption of EZH2 by DZNep, or its specific down-regulation by short hairpin RNA, strongly impairs GBM cancer stem cell self-renewal in vitro and tumor-initiating capacity in vivo. They also showed the direct transcriptional regulation of c-myc by EZH2, using genome-wide expression analysis of DZNep-treated GBM, suggesting its role as a valuable new therapeutic target for management of patients with GBM (Suvà et al., 2009).

To be noted

Note

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