

Gene Section

Review

DOT1L (DOT1 like histone H3K79 methyltransferase)

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Abstract

DOT1L is a histone lysine methyltransferase (KMT). It is the only known methyltransferase for lysine residue 79 on histone 3 (H3K79). The active site of DOT1L bears more homology to the active site in Protein Arginin Methyl Transferases (PRMTs) than the SET domain of other KMTs. DOT1L has important roles in normal development and cellular differentiation. DOT1L plays especially important roles in normal hematopoiesis and in leukemia. Initially characterized as a therapeutic target in MLL-rearranged acute leukemias, recent data suggest that DOT1L is also therapeutic target in other molecular subtypes of acute leukemia and in selected solid tumors. A phase 1 clinical trial of a small molecule inhibitor of Dot1L has been described, with encouraging responses being reported.

Keywords

DOT1L, Epigenetics, Methyltransferase, Leukemia

Identity

Other names: KMT4, DOT1

HGNC (Hugo): DOT1L

Location: 19p13.3. GRCh38.p7 NC_000019.10 (2163963..2232578)

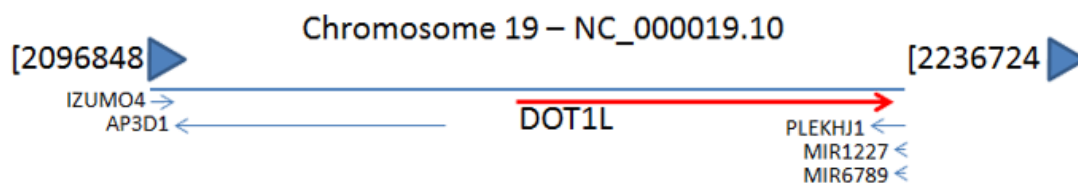
DNA/RNA

Description

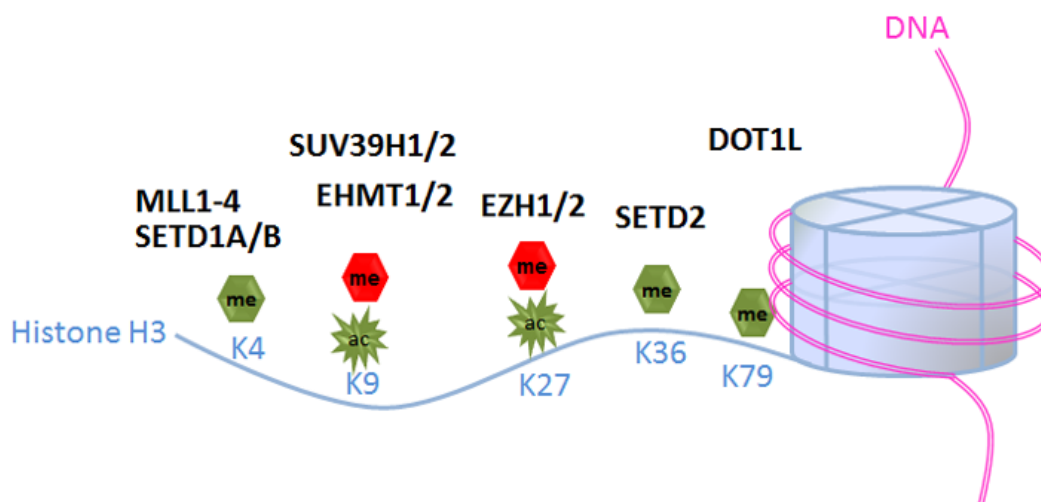
Orientation: Plus strand; 68615 bases; Exon count: 30 (NCBI Homo sapiens Annotation Release 108).

Transcription

7 transcripts for DOT1L are described in the NCBI Nucleotide database. They are predicted by computational analysis. To the best of our knowledge, the functional significance of the different transcripts is to this point unknown. In the mouse, five isoforms have been described (Zhang, W. et al., 2004).



Gene neighbours of DOT1L on chromosome 19p13.3 (NCBI Homo sapiens Annotation Release 108).



Selected methyl residues on the N-terminal tail of histone 3 modified by histone methyltransferases. A non-comprehensive list of corresponding methyl-transferases is shown. Some methyltransferases can methylate different residues. Notable points regarding DOT1L are: 1.) DOT1L does not methylate free peptides, or free histone 3 but only whole nucleosomes. 2.) K79 is located in the nucleosome core, not the N-terminal tail. 3.) The catalytic domain is homologous to arginine methyl-transferases and does not contain a SET-domain typical for most lysine methyl-transferases.

Protein

Description

DOT1L includes several domains: catalytic domain (1-332), Bat3-interacting domain (361-380), K-rich patch (390-407) with a partially overlapping NLS (395-417), leucine zipper motif (576-594), CTD binding patch (618-627), three ENL/AF9 binding sites (628-653, 863-878, 877-900), and two more NLSs (1088-1111, 1164-1171) - reviewed in (Vlaming et al., 2016).

Localisation

DOT1L is thought to predominantly or entirely localize to the nucleus.

Function

DOT1L is the human ortholog of the yeast (*S. cerevisiae*) gene 'Disruptor of telomere silencing 1' (Dot1). The gene was reported to be involved in the regulation of telomeric gene silencing and position effect variegation (Singer et al., 1998). Interestingly, more recent data suggest that only select telomeric gene loci are regulated by Dot1 and that H3K79 methylation by Dot1 does not play a role in the maintenance of natural HML silencing but only silences the HM locus in the context of a reporter strain (Takahashi et al., 2011).

The biochemical function of yeast DOT1 and mammalian DOT1L is the methylation of the histone 3 core lysine 79 residue (Feng et al., 2002; Lacoste et al., 2002; Ng et al., 2002; van Leeuwen et al., 2002). DOT1 and hDOT1L methylate nucleosomal substrates, but not free histone H3. They have homology with arginine methyltransferases, but do not contain a SET-domain typical of most lysine methyl-transferases.

Lysine K79me_{2/3} is thought to be associated with expressed genes. Some evidence suggests antagonism between K79me_{2/3} and histone 3 lysine 9 methylation-mediated gene silencing mediated by SIRT1 and SUV39H1, which is compatible with prior findings in yeast (Ehrentraut et al., 2011). H3K79 methylation is thought to be linked to cell cycle regulation (Schulze et al., 2009) and to the DNA damage response (Giannattasio et al., 2005).

In bone marrow and leukemia, DOT1L is thought to be important in the regulation of, among other genes, the late HOXA cluster (Bernt et al., 2011; Riedel et al., 2016). In prostate cancer there is evidence for a link between androgen receptor signaling and DOT1L (Yang et al., 2013).

Homology

Homolog genes exist in Euteleostomi, with AA and DNA identity of approximately 65 - 99 % (see <https://www.ncbi.nlm.nih.gov/homologene/>; HomoloGene:32779). Related genes with K79 methyltransferase activity in lower species include the originally discovered yeast (*S. cerevisiae*) gene Dot1 (Disruptor of telomere silencing 1) (Lacoste et al., 2002; Singer et al., 1998) and the *Drosophila* ortholog grappa (gpp) (Shanower et al., 2005), mutants of which interestingly exhibit Pc-G phenotypes, but also display phenotypes characteristic of trithorax-group mutants.

Mutations

Note

Generally speaking, somatic and germline mutations of DOT1L have been identified, but their significance is currently unknown. One published report has suggested a link between Dot1L-mutation and Gastric Cancer (Donner et al., 2015).

Germinal

A number of germline mutations (missense and loss-of-function) are described in the Exac database (<http://exac.broadinstitute.org/gene/ENSG00000104885>). The functional significance is unknown. To the best of our knowledge, there is as yet no human phenotype or syndrome associated with germline DOT1L-mutation.

Somatic

DOT1L is mutated in a number of human cancers including hematopoietic and solid tumors. The frequency of mutations is typically <1% to the low single digit range (source: Cosmic). The functional significance of DOT1L to the best of our knowledge is unknown.

Implicated in

Acute myeloid leukaemia (AML)

DOT1L is thought to be a therapeutic target in MLL-rearranged AML with nuclear and cytoplasmic fusion partners (Bernt et al., 2011; Deshpande et al., 2013). DOT1L is thought to be a therapeutic target in t(10;11)(p13;q14-21) PICALM (CALM) / MLLT10 (AF10) leukemia (Chen, L. et al., 2012). DOT1L has also be reported to be a therapeutic target in AML with high expression of MN1 (Riedel et al., 2016), AML with IDH-mutations (Sarkaria et al., 2014), AML with DNMT3A mutations (Lu et al., 2016; Rau et al., 2016) and AML with NPM1 mutations (Kuhn et al., 2016).

Prostate Cancer

DOT1L has been linked to the regulation of androgen receptor regulated gene activation programs in prostate cancer (Yang et al., 2013). A fusion gene DOT1L/ HES6 has been described in prostate cancer (Annala et al., 2014). Of note, this fusion reportedly drives androgen independent growth of prostate cancer.

Breast Cancer

DOT1L has been suggested as a therapeutic target in breast cancer (Zhang, L. et al., 2014).

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