Gene Section
Review

BMI1 (BMI1 polycomb ring finger oncogene)

Lina Han, Szabolcs Fatrai, Jan Jacob Schuringa

Department of Hematology, University Medical Center Groningen, Hanzeplein 1, 9700 RB, The Netherlands (LH, SF, JJS)

Identity

Other names: MGC12685; PCGF4; RNF51;flvi-2/bmi-1

HGNC (Hugo): BMI1

Location: 10p12.31
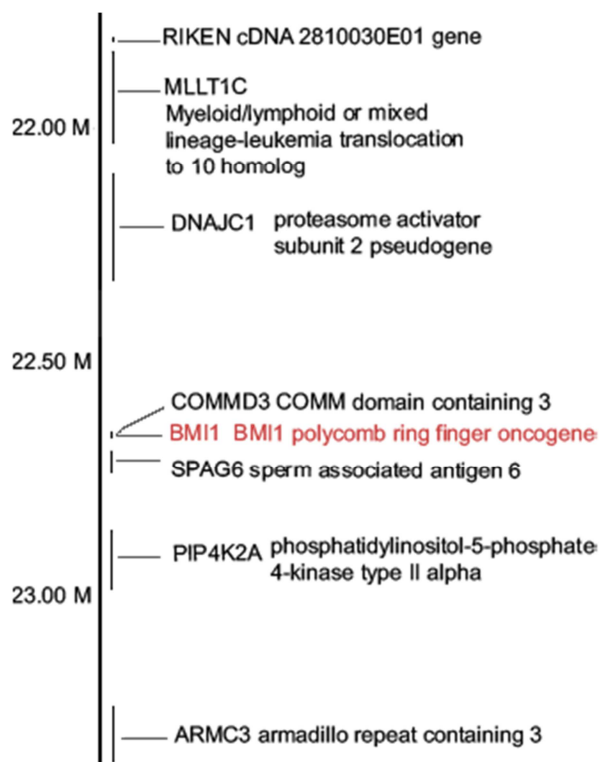
Local order: MLLT10 gene is one of the neighboring genes of BMI1. It locates 786566 base

pairs downstream from the start site of BMI1. MLLT10 or AF10 is a transcription factor which is also one of the fusion proteins of ALL. ALL-AF10 can result in the development of T-cell ALL, AML FAB 0, AML FAB 1, AML FAB 5 and AML FAB 7. PIP4K2A is the gene for Phosphatidylinositol-4-phosphate 5-kinase. The protein transcribed from this gene is catalyzing the phosphorylation of phosphatidylinositol-5-phosphate on the fourth hydroxyl of the myo-inositol ring to form phosphatidylinositol-5,4-bisphosphate.
Phosphatidylinositol-5,4-bisphosphate is a precursor to second messengers in the phosphoinositide signal trans-duction pathways and it is involved in the regulation of secretion, cell proliferation, differentiation and motility.

DNA/RNA

Description

DNA size: 10.04 kb with 10 exons.
The BMI1 gene is a highly conserved gene. The cDNA shows 86% identity to the mouse sequence.
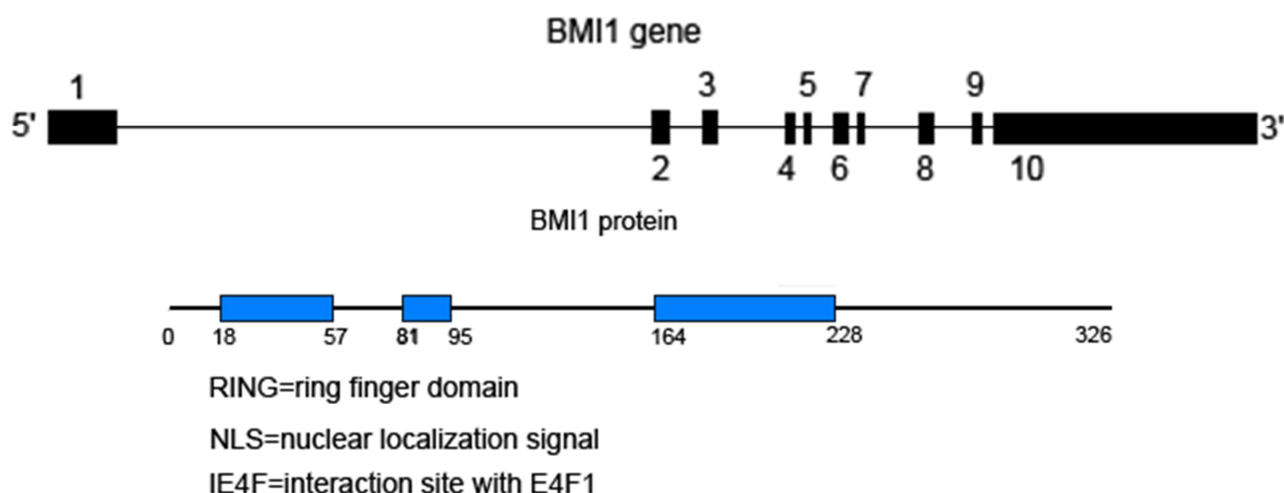
Transcription

mRNA size: 3199 bp.

Protein

Note

326 amino acids
Molecular weight of the protein: 36949 Da.

BMI1 gene

BMI1 protein

RING=ring finger domain
NLS=nuclear localization signal
IE4F=interaction site with E4F1

Description

The ring finger domain is a cysteine-rich domain that binds two atoms of zinc and plays a key role in the process of ubiquitination. In hematopoietic stem cells BMI1 interacts with a proliferation inhibitor E4F through the IE4F site.

Expression

Hematopoietic system: BMI1 is expressed in adult and embryonic fetal liver hematopoietic stem cells (HSC). During hematopoietic development the expression of BMI1 declines. Bmi1$^{-/-}$ mice are born with a hypocellular bone marrow, they have normal number of myeloid cells in the peripheral blood but lower number of lymphocytes. In the bone marrow of Bmi1$^{-/-}$ mice the total HSC number is decreased with 10-fold and transplanted bone marrow and fetal liver cells were able to contribute to hematopoiesis only transiently. Bmi1-depleted mice die within two months after birth. Adult HSCs from Bmi1$^{-/-}$ mice lack self-renewal potential. Further-more, expression of stem cell-associated genes, cell survival genes, transcription factors and genes modulating proliferation was altered in the bone marrow cells. BMI1 overexpression was studied in transgenic mice and human CB models. In these mouse models 14% of the mice developed lymphoma. BMI1 overexpression in CD34+ cord blood cells resulted in long term maintenance and self-renewal of human hematopoietic stem and progenitor cells. These cells engrafted more efficiently in NOD-SCID mice and gave a rise to secondary engraftment.

Nervous system: BMI1 is required for neural stem cell self-renewal but it does not influence their survival and differentiation. BMI1 is strongly expressed in proliferating cerebellar precursor cells in mice and humans. The absence of BMI1 was related to the low level of p16 Ink4 as well as to low proliferation rate of neural stem cells. BMI1-deficient mice develop balance disorders, tremor, behavior disorders and they have a severe reduction in total postnatal brain mass.

Fibroblasts: In BMI1-deficient primary mouse embryonic fibroblast cell cycle progression to S phase was impaired and cells entered early senescence.

Localisation

In nucleus and in the cytoplasm.

Function

BMI1 is a member of the Polycomb group (PcG) genes, which are transcriptional repressors that play essential roles in the maintenance of appropriate gene expression during development. Two distinct multiprotein PcG complexes have been identified, the Polycomb Repression Complex (PRC) 1 and PRC2. The PRC2 complex is involved in initiation of silencing and contains histone deacetylases and methyltransferases that can methylate H3 lysine 9 and 27 (H3K27). Deletion of PRC2 genes in mice results in embryonic lethality, emphasizing their importance in development. PRC1 is implicated in stable maintenance of gene repression and recog-nizes the methylation marks set by PRC2. Mice mutant for most PRC1 genes survive until birth as result of partial functional redundancy provided by their homologues, but developmental defects do arise thereafter as is e.g. the case in the hemato-poietic compartment after deletion of BMI1. Targeted deletion of BMI1 has shown that although the numbers of fetal liver-derived HSCs is normal in these mice, their proliferative and self-renewal capacity is severely impaired. In adult BMI1-deficient mice, the HSCs are less frequent and display an impaired competitive repopulation capacity. Gain-of-function studies demonstrated enhanced self-renewal of murine HSC and with a shift in balance towards more symmetric stem cell divisions. Constitutive expression of BMI1 in human cord blood cells results in prolonged maintenance of the stem cell pool and enhances self-renewal of human stem and progenitor cells. BMI1 is potent negative regulator of the Ink4a/Arf locus in embryonic fibroblasts. This locus encodes the cell cycle regulators and tumor suppressor p16 and p19/p14.

Increased expression of these genes was observed in the BMI1-deficient mice. However, INK4A/ARF-independent BMI1-targets must exist as well since overexpression of BMI1 in p16/p19-deficient cells still altered HSC self-renewal phenotypes.

Mutations

Note
A mutation in BMI1 that results in a cysteine into tyrosine substitution at position 18 within the RING domain has been identified, which is associated
with a decrease in BMI1 expression levels and elevated ubiquitination.

Implicated in

Hematological malignancies

Disease
BMI1 overexpression has been demonstrated in several hematological malignancies, mainly including mantle cell lymphoma, myeloid dysplastic syndrome (MDS), chronic myeloid leukemia (CML) and acute myeloid leukemia (AML).

Prognosis
In general, high BMI1 expression levels are associated with a poor prognosis and increased aggressiveness of the tumors. In CML, the level of BMI1 at diagnosis correlated with time to transfor-mation to blast crisis. In MDS, patients with RA and RARS with a higher percentage of BMI1-positive cells showed disease progression to RAEB. Intriguingly, in CML post allo-SCT, high BMI1 at diagnosis predicts better overall survival, which might be ascribed to the neutralized effects against BMI1 by an immune response in donor cells.

Cytogenetics
Different chromosomal translocations involving the 10p11-13 region have also been identified in infant leukemias, occurring in children < 12 months of age and T cell lymphoproliferative disorders, including mainly adult T cell leukemia/lymphomas and occasional cutaneous T cell lymphomas. It was demonstrated that BMI1 was overexpressed with MEIS1 in 11q23 (MLL) rearrangements, suggesting that p16/p19 suppression maybe involved in MLL-associated leukemia.

Oncogenesis
See below.

Solid tumors

Disease
BMI1 overexpression was implicated in various solid tumors, including ovarian cancer, bladder cancer, squamous cell carcinoma, prostate cancer, breast carcinomas, non-small-cell lung cancer and GI cancer.

Prognosis
The oncogenic role of the BMI1 activation may contribute to progression of many types of solid tumors. The median survival is 46 months and 5-year survival is 37.5% in BMI1/EZH2-positive prostate cancer patients after radical prostatectomy (The 5-year survival is 72.4% in BMI1/EZH2-negative prostate cancer patients). But in breast cancer, increased BMI1 expression is associated with a good prognosis, which might be because BMI1 overexpression correlates with higher ER expression and lower TP53 mutations.

Oncogenesis
See below.

Neural stem cells renewal

Note
BMI1 promotes the maintenance of adult neural stem cells (NSCs) by repressing the cyclin-depen-dent kinase inhibitors, $p16^{Ink4a}$ and $p19^{ARF}$. Recent study showed that BMI1 was also important for NSCs in the embryo, using lentiviral-delivered shRNAs in vitro and in vivo. These defects caused by BMI1 downregulation were unexpectedly mediated by p21.

Oncogenesis
Gene-profiling studies show that $BMI^{-/-}$ HSC displayed altered expression of multiple genes important for stem cell fate decisions. The tumor suppressor locus $p16^{Ink4a}/p19^{ARF}$ is one of the important targets that is repressed by BMI1. The $p16^{Ink4a}$ protein blocks the cyclinD-CDK complexes by binding directly to CDK4 and CDK6, enabling CIP1 and KIP1 to associate with and inhibit cyclin E-CDK2 and cyclin A-CDK2, which results the hypophosphorylated pRb. The E2F transcription factors will be sequestered and their target genes will be repressed, ultimately leading to G1-phase cell cycle arrest, senescence, or apoptosis. $p19^{ARF}$ binds to MDM2 and inhibits its ubiquitin ligase activity, resulting in activation of p53 target genes, including Wig1 and p21, leading to cell cycle arrest and apoptosis. Furthermore, cells might undergo apoptosis as a result of down-regulated apoptosis inhibitor AI-6 in the absence of BMI1. BMI1 was also demonstrated to upregulate the human telomerase RT gene (hTERT), which might also be relevant for the self-renewal ability of HSCs or LSCs.

Deregulated Hox gene expression caused by chromosomal translocations and MLL rearrange-ments, is involved in some types of leukemia. The skeletal defects of PcG mutant mice revealed PcG genes as Hox gene regulators. Knockout of BMI1 results in alterations in Hox gene expression, with 12 Hox genes significantly upregulated (for example, HoxA7-HoxA13; HoxC10-HoxC13) and 13 downregulated (for example, HoxA1-HoxA4). This study demonstrated that BMI1 and RING1A play important roles in H2A ubiquitylation and Hox gene silencing.

Overexpression of BMI1 is involved in tumor development and is used as an important marker for predicting prognosis. The mechanisms regulating BMI1 expression are not fully elucidated yet. In AML, BMI1 was demonstrated to be a direct target gene of SALL4, a zinc-finger transcription factor, which is expressed constitutively in human leukemia cell lines and primary AML cells. High levels of H3-K4 trimethylation and H3-K79 dimethylation were observed in the SALL4 binding region of the BMI1promoter. In normal and malignant human mammary stem cells activation of hedgehog signaling increases BMI1 expression and BMI1 overexpression promotes mammary stem cell self-renewal and proliferation. In CML, it was suggested that BMI1 was positively regulated by BCR-ABL as well as by additional posttrans-criptional modification in the course of the disease progression.

Chromatin association and dissociation of BMI1 was also studied. BMI1 can be phosphorylated by 3pk (MAPKAP kinase 3), a convergence point downstream of activated ERK and p38 signaling pathways which are implicated in differentiation and developmental processes. BMI1 phosphoryla-tion results in dissociation of BMI1 from chroma-tin, followed by de-repression of target genes.

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