Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section

Review

PRDM2 (PR domain containing 2, with ZNF domain)

Erika Di Zazzo, Bruno Moncharmont

Dipartimento di Scienze per la Salute, Università degli studi del Molise, Via Francesco De Sanctis - edificio polifunzionale III, 86170 Campobasso, Italia (ED, BM)

Published in Atlas Database: March 2008

Online updated version: http://AtlasGeneticsOncology.org/Genes/PRDM2ID41834ch1p36.html
DOI: 10.4267/2042/44381

Identity

Other names: GATA 3 binding protein; HUMHOXY1; KMT8; MTB-ZF(MTE-binding protein zinc-finger); RIZ (retinoblastoma interacting zinc-finger protein); RIZ1; RIZ2
HGNC (Hugo): PRDM2
Location: 1p36.21

DNA/RNA

Description

Spans 150 Kb; 5156 bp coding **sequence**; 13 exons.

Transcription

Two promoters localized, respectively, in exon 1 and exon 6 guide the synthesis of two transcripts: the first one encodes for the PR domain-containing product (RIZ1) and the other one for the PR domain-lacking form (RIZ2).

Protein

Description

RIZ1 (280 kDa) and RIZ2 (260 kDa) differ only for the presence in the larger form (RIZ1) of the PR domain. In the sequence of both proteins have been identified several domains:
PR domain (130 aa), endowed with histone-methyltransferase activity (Lys 9 of histone H3) and implicated in protein-protein interactions;
E1A like-domain (100 aa), contains the LXCXE sequence able to interact with the oncosupressor gene Rb;
Two zinc-finger clusters;
Proline-rich domain, containing a LXXLL motif mediating the interaction with estrogen receptor.

Expression

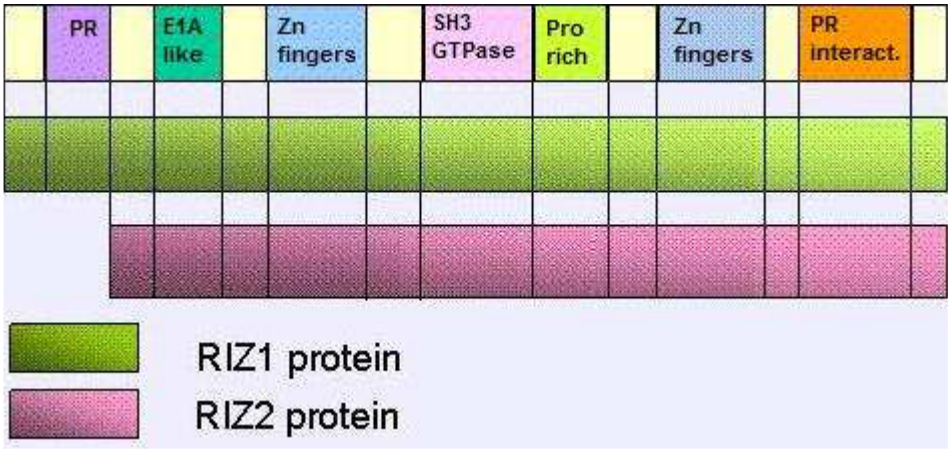
RIZ1 and RIZ2 have an ubiquitous and approxi-mately equimolar expression with higher expres-sion levels in neuroendocrine tissues.

Localisation

Nuclear.

Function

RIZ Gene products are endowed with DNA-binding as well as transcription factor-binding activities, as evidenced by the independent isolation of RIZ as a retinoblastoma-binding protein (RIZ), a DNA-binding protein (MTB-Zf), or as a GATA3 transcription factor binding protein (G3B).
MTB-Zf (essentially identical to RIZ2) binds to the MTE DNA element GTCATATGAC of human heme-oxygenase-1 gene and can weakly activate transcription.
G3B (RIZ) interacts with the transcription factor GATA-3, regulating the expression of several genes critical for T-cell function and development.
RIZ proteins bind the estrogen receptor in a hormone-dependent manner, acting as a co-activator.
Estradiol binding to estrogen receptor complex converts RIZ activity from transcriptional repressor into co-activator.
Specific siRNA silencing of RIZ1 form increases the MCF-7 breast cancer cells growth rate. RIZ proteins act as transcriptional repressors binding to GC-rich or Sp-1-binding elements.



Mutations

Germinal

RIZ1 K.O. mice showed a high incidence of diffuse large B-cell lymphomas and a broad spectrum of unusual tumors.

Somatic

Deletion of the 1p36 region is frequent in several human cancers including neuroblastoma, breast cancer, intestinal tumors, and malignant melanoma.

Frameshift mutations in the two poly adenine tracts, A(8) and A(9), generating truncated RIZ1/2 proteins lacking the COOH-terminal PR-binding motif, were found in MSI-high (MSI-H) primary cancers occurring in the pancreas, stomach, endometrium and colorectum.

The single base substitution that changed A563 in the coding sequence (immediately C-terminal to the PR domain) to a G was found specially in diffuse large B-cell lymphomas (DLBL).

Missense mutation of RIZ1 changing nucleotide G317 to A was discovered in Saos2 human osteosarcoma cells.

RIZ harbors a naturally occurring CCT insertion/deletion polymorphism in exon 8 producing a proline insertion/deletion, modulating the impact of estradiol on bone mineral density (BMD).

Implicated in

Breast cancer

Disease

The RIZ gene might have a role in human breast cancer. In fact, RIZ1 expression is decreased or lost in human breast cancer, whereas RIZ2 expression is normal.

Gastric cancer

Disease

RIZ1 might be a specific target of inactivation in human gastric cancer. Methylation of the RIZ1 promoter was detected in 37% of 30 cases and inactivation of the second allele occurred through frameshift mutation, loss of heterozygosity (LOH) or promoter methylation. Furthermore frameshift mutations in the two coding polyadenosine tracks of RIZ were found in 19 (48%) of 40 gastric carcinomas.

Endometrial carcinoma

Disease

RIZ inactivation is highly selected during the clonal evolution of these tumors. Six (33%) of 18 endometrial carcinomas present frameshift mutation in the two coding polyadenosine tracts of RIZ.

Colorectal carcinoma

Disease

RIZ might have a role in human colorectal tumorigenesis. The region 1p36 is frequently deleted in colorectal cancer; Furthermore, 37.5% of microsatellite-unstable colorectal tumors presents frameshift mutation, consisting of 1- or 2-bp deletions of a coding $(A)_8$ or $(A)_9$ tract, of the RIZ gene.

Leukaemia

Disease

Suppression of RIZ1 expression or enhancement of RIZ2 expression may have an important role in leukaemogenesis. The expression of RIZ1 was significantly decreased in leukaemia cell lines (14 out of 17, 82%) and in patients with acute myeloblastic leukaemia (8 out of 14, 57%). In contrast, RIZ2 expression was increased in patients with acute lymphoblastic leukaemia (8 out of 11, 73%) compared with normal bone marrow cells.

Ovarian carcinoma

Disease

Reduced expression of RIZ1 may play an important role in the pathogenesis and/or development of epithelial ovarian carcinoma, and is considered to be caused in part by aberrant DNA methylation. Decreased expression of RIZ1 was significantly correlated with histological subtypes ($P < 0.0001$), high tumor grade ($P = 0.0153$), advanced clinical stage ($P = 0.0345$), and high Ki67 index ($P = 0.0117$).

Neuroblastoma

Disease

Advanced stages of neuroblastoma is genetically characterized by deletions or LOH for the short arm of chromosome 1 suggesting that in the deleted region there is a locus for putative suppressor gene.

Hepatoma

Disease

Hepatomas present deletion of the chromosome 1 short arm suggesting that in this region is localized a gene whose functional loss may be involved in hepatocellular carcinogenesis.

Prostate cancer

Disease

RIZ1 may be associated with prostate carcino-genesis. Transcriptional inactivation of RIZ1 gene by aberrant DNA methylation of promoter CpG island is detected in 20 (42.6%) of the 47 prostate cancer tissues.

Thyroid carcinoma

Disease

RIZ1 have probably an important role in thyroid tumorigenesis. RIZ1 is lost in thyroid tumor cell line and is also significantly reduced in thyroid carcinomas when compared with normal thyroid tissues and benign tumors. The loss of RIZ1 is mediated by aberrant cytosine methylation of the RIZ1 promoter.

Lung cancer

Disease

RIZ polymorphisms may be an important predictive markers for lung cancer susceptibility. In fact, the +92337G > A and +95701C > A polymorphisms are associated with reduced risk of lung adenocarci-nomas.

Ostheoporosis

Disease

The RIZ P704 insertion (+)/deletion (-) polymorphism modulates the impact of estradiol on bone mineral density (BMD). The RIZ P704 +/+ genotype is a risk factor for low BMD in elderly subjects with low estradiol levels, whereas the RIZ P704 +/+ genotype was associated with high BMD in premenopausal women.

References

Dracopoli NC, Harnett P, Bale SJ, Stanger BZ, Tucker MA, Housman DE, Kefford RF. Loss of alleles from the distal short arm of chromosome 1 occurs late in melanoma tumor progression. Proc Natl Acad Sci U S A. 1989 Jun;86(12):4614-8

Genuardi M, Tsihira H, Anderson DE, Saunders GF. Distal deletion of chromosome Ip in ductal carcinoma of the breast. Am J Hum Genet. 1989 Jul;45(1):73-82

Simon D, Knowles BB, Weith A. Abnormalities of chromosome 1 and loss of heterozygosity on 1p in primary hepatomas. Oncogene. 1991 May;6(5):765-70

Fong CT, White PS, Peterson K, Sapienza C, Cavenee WK, Kern SE, Vogelstein B, Cantor AB, Look AT, Brodeur GM. Loss of heterozygosity for chromosomes 1 or 14 defines subsets of advanced neuroblastomas. Cancer Res. 1992 Apr 1;52(7):1780-5

Bardi G, Pandis N, Fenger C, Kronborg O, Bomme L, Heim S. Deletion of 1p36 as a primary chromosomal aberration in intestinal tumorigenesis. Cancer Res. 1993 Apr 15;53(8):1895-8

Buyse IM, Shao G, Huang S. The retinoblastoma protein binds to RIZ, a zinc-finger protein that shares an epitope with the adenovirus E1A protein. Proc Natl Acad Sci U S A. 1995 May 9;92(10):4467-71

Nagai H, Negrini M, Carter SL, Gillum DR, Rosenberg AL, Schwartz GF, Croce CM. Detection and cloning of a common region of loss of heterozygosity at chromosome 1p in breast cancer. Cancer Res. 1995 Apr 15;55(8):1752-7

Shapiro VS, Lee P, Winoto A. Identification and cloning of the G3B cDNA encoding a 3' segment of a protein binding to GATA-3. Gene. 1995 Oct 3;163(2):329-30

Muraosa Y, Takahashi K, Yoshizawa M, Shibahara S. cDNA cloning of a novel protein containing two zinc-finger domains that may function as a transcription factor for the human heme-oxygenase-1 gene. Eur J Biochem. 1996 Feb 1;235(3):471-9

Buyse IM, Huang S. In vitro analysis of the E1A-homologous sequences of RIZ. J Virol. 1997 Aug;71(8):6200-3

Liu L, Shao G, Steele-Perkins G, Huang S. The retinoblastoma interacting zinc finger gene RIZ produces a PR domain-lacking product through an internal promoter. J Biol Chem. 1997 Jan 31;272(5):2984-91

Xie M, Shao G, Buyse IM, Huang S. Transcriptional repression mediated by the PR domain zinc finger gene RIZ. J Biol Chem. 1997 Oct 17;272(42):26360-6

He L, Yu JX, Liu L, Buyse IM, Wang MS, Yang QC, Nakagawara A, Brodeur GM, Shi YE, Huang S. RIZ1, but not the alternative RIZ2 product of the same gene, is underexpressed in breast cancer, and forced RIZ1 expression causes G2-M cell cycle arrest and/or apoptosis. Cancer Res. 1998 Oct 1;58(19):4238-44

Huang S. The retinoblastoma protein-interacting zinc finger gene RIZ in 1p36-linked cancers. Front Biosci. 1999 Jun 15;4:D528-32

Jiang G, Liu L, Buyse IM, Simon D, Huang S. Decreased RIZ1 expression but not RIZ2 in hepatoma and suppression of hepatoma tumorigenicity by RIZ1. Int J Cancer. 1999 Nov 12;83(4):541-6

Medici N, Abbondanza C, Nigro V, Rossi V, Piluso G, Belsito A, Gallo L, Roscigno A, Bontempo P, Puca AA, Molinari AM, Moncharmont B, Puca GA. Identification of a DNA binding protein cooperating with estrogen receptor as RIZ (retinoblastoma interacting zinc finger protein). Biochem Biophys Res Commun. 1999 Nov 2;264(3):983-9

Abbondanza C, Medici N, Nigro V, Rossi V, Gallo L, Piluso G, Belsito A, Roscigno A, Bontempo P, Puca AA, Molinari AM, Moncharmont B, Puca GA. The retinoblastoma-interacting zinc-finger protein RIZ is a downstream effector of estrogen action. Proc Natl Acad Sci U S A. 2000 Mar 28;97(7):3130-5

Chadwick RB, Jiang GL, Bennington GA, Yuan B, Johnson CK, Stevens MW, Niemann TH, Peltomaki P, Huang S, de la Chapelle A. Candidate tumor suppressor RIZ is frequently involved in colorectal carcinogenesis. Proc Natl Acad Sci U S A. 2000 Mar 14;97(6):2662-7

Fang W, Piao Z, Simon D, Sheu JC, Huang S. Mapping of a minimal deleted region in human hepatocellular carcinoma to 1p36.13-p36.23 and mutational analysis of the RIZ (PRDM2) gene localized to the region. Genes Chromosomes Cancer. 2000 Jul;28(3):269-75

Piao Z, Fang W, Malkhosyan S, Kim H, Horii A, Perucho M, Huang S. Frequent frameshift mutations of RIZ in sporadic gastrointestinal and endometrial carcinomas with microsatellite instability. Cancer Res. 2000 Sep 1;60(17):4701-4

Du Y, Carling T, Fang W, Piao Z, Sheu JC, Huang S. Hypermethylation in human cancers of the RIZ1 tumor suppressor gene, a member of a histone/protein methyltransferase superfamily. Cancer Res. 2001 Nov 15;61(22):8094-9

Sakurada K, Furukawa T, Kato Y, Kayama T, Huang S, Horii A. RIZ, the retinoblastoma protein interacting zinc finger gene, is mutated in genetically unstable cancers of the pancreas, stomach, and colorectum. Genes Chromosomes Cancer. 2001 Feb;30(2):207-11

Steele-Perkins G, Fang W, Yang XH, Van Gele M, Carling T, Gu J, Buyse IM, Fletcher JA, Liu J, Bronson R, Chadwick RB, de la Chapelle A, Zhang X, Speleman F, Huang S. Tumor formation and inactivation of RIZ1, an Rb-binding member of a nuclear protein-methyltransferase superfamily. Genes Dev. 2001 Sep 1;15(17):2250-62

Canote R, Du Y, Carling T, Tian F, Peng Z, Huang S. The tumor suppressor gene RIZ in cancer gene therapy (review). Oncol Rep. 2002 Jan-Feb;9(1):57-60

Sasaki O, Meguro K, Tohmiya Y, Funato T, Shibahara S, Sasaki T. Altered expression of retinoblastoma protein-interacting zinc finger gene, RIZ, in human leukaemia. Br J Haematol. 2002 Dec;119(4):940-8

Tokumaru Y, Nomoto S, Jerónimo C, Henrique R, Harden S, Trink B, Sidransky D. Biallelic inactivation of the RIZ1 gene in human gastric cancer. Oncogene. 2003 Oct 9;22(44):6954-8

Carling T, Kim KC, Yang XH, Gu J, Zhang XK, Huang S. A histone methyltransferase is required for maximal response to female sex hormones. Mol Cell Biol. 2004 Aug;24(16):7032-42

Gazzerro P, Abbondanza C, D'Arcangelo A, Rossi M, Medici N, Moncharmont B, Puca GA. Modulation of RIZ gene expression is associated to estradiol control of MCF-7 breast cancer cell proliferation. Exp Cell Res. 2006 Feb 1;312(3):340-9

Lal G, Padmanabha L, Smith BJ, Nicholson RM, Howe JR, O'Dorisio MS, Domann FE Jr. RIZ1 is epigenetically inactivated by promoter hypermethylation in thyroid carcinoma. Cancer. 2006 Dec 15;107(12):2752-9

Akahira J, Suzuki F, Suzuki T, Miura I, Kamogawa N, Miki Y, Ito K, Yaegashi N, Sasano H. Decreased expression of RIZ1 and its clinicopathological significance in epithelial ovarian carcinoma: correlation with epigenetic inactivation by aberrant DNA methylation. Pathol Int. 2007 Nov;57(11):725-33

Grundberg E, Akesson K, Kindmark A, Gerdhem P, Holmberg A, Mellström D, Ljunggren O, Orwoll E, Mallmin H, Ohlsson C, Brändström H. The impact of estradiol on bone mineral density is modulated by the specific estrogen receptor-alpha cofactor retinoblastoma-interacting zinc finger protein-1 insertion/deletion polymorphism. J Clin Endocrinol Metab. 2007 Jun;92(6):2300-6

Hasegawa Y, Matsubara A, Teishima J, Seki M, Mita K, Usui T, Oue N, Yasui W. DNA methylation of the RIZ1 gene is associated with nuclear accumulation of p53 in prostate cancer. Cancer Sci. 2007 Jan;98(1):32-6

Yoon KA, Park S, Hwangbo B, Shin HD, Cheong HS, Shin HR, Lee JS. Genetic polymorphisms in the Rb-binding zinc finger gene RIZ and the risk of lung cancer. Carcinogenesis. 2007 Sep;28(9):1971-7

This article should be referenced as such:

Di Zazzo E, Montcharmont B. PRDM2 (PR domain containing 2, with ZNF domain). Atlas Genet Cytogenet Oncol Haematol. 2009; 13(1):24-27.