Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section

Mini Review

SMARCA4 (SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4)

Pedro P Medina, Montse Sanchez-Cespedes

Department of Molecular, Cellular and Developmental Biology, Yale University, 266 Whitney Ave KBT 938, 06520. New Haven, CT, USA (PPM), Molecular pathology program, Spanish National Cancer Centre (CNIO), Melchor Fernandez Almagro, 3, 28029 Madrid, Spain (MSC)

Published in Atlas Database: April 2008

Online updated version: http://AtlasGeneticsOncology.org/Genes/SMARCA4ID42333ch19p13.html
DOI: 10.4267/2042/44430

Identity

Other names: BRG1; BRG-1; BAF190; FLJ39786; hSNF2b; NM_003072; SNF2-beta; SNF2B; SNF2L4; SNF2LB; SWI2
HGNC (Hugo): SMARCA4
Location: 19p13.2
Local order: telomere-DNM2-IL1RL1LG-MGC3262-SMARCA4-LDLR-AK075287-centromere.

DNA/RNA

Relative size of the 33 coding exons of SMARCA4. The entire exon 1 is UTR (untranslated region). Exon numeration corresponds to the prevalent transcript (matching the EST EU430759).

Description

The SMARCA4 is also known as BRG1 (hSWI/SNF brahma-related gene). It spans a total genomic size of 101347 bp and it is composed of 33 coding exons of varying lengths and 1 non-coding exon (exon 1).

Transcription

The human SMARCA4 transcript has approxi-mately 5500 bp and contains an open reading frame of 4845 bp, predicting a protein of 1614 amino acid residues. There are different transcripts arising from two alternative splicing sites within intron 28 and exon 30, which predict the translation of four different BRG1 protein isoforms. In addition, between exon 26 and 27 and exon 29 and 30 there are two additional exons that may constitute tissue specific transcripts.

Protein

Description

SMARCA4 has a molecular mass of 181349 Da. SMARCA4 is the catalytic subunit of the chromatin-remodelling complex SWI-SNF and influences transcriptional regulation by disrupting histone-DNA contacts in an ATP-dependent manner. In addition to an ATPase, the SWI/SNF complex is composed of a variety of accessory proteins, termed BAFs (BRG-1-associated factors).

Expression

Widely expressed.

Localisation

SMARCA4 localizes in the nucleus.

Function

The SMARCA4 harbours the ATPase activity required for the chromatin remodelling activity of the SWI/SNF complex. This complex uses the energy of ATP hydrolysis to modify the interactions among histones leading to modifica-tions of the chromatin structure and to the regulation of gene expression.

SMARCA4 conserved domains. Proline rich region, containing more than 25% of proline residues in the aminoacid sequence. HSA and BRK domains, containing motifs that may predict binding to DNA. ATPase/helicase domain, contains motifs present in the DEAD helicases superfamily, a diverse family of proteins involved in ATP-dependent RNA or DNA unwinding. Bromodomain, 110 aminoacid domain, found in many chromatin associated proteins. Bromodomains can interact specifically with acetylated lysine.

The SWI/SNF complex plays a role in differentiation, develop-ment and cell cycle control. SMARCA4 binds to or it is related to important tumor suppressor proteins, including BRCA2, LKB1, RB and FANCA. Moreover, the SWI/SNF complex has been shown to modulate the transcriptional activity of steroid receptors (e.g. glucocorticoids receptors, retinoic acid receptors, androgen and estrogen receptors), CMYC and RB. SMARCA4 acts as a tumor suppressor because:
i) it induces cell-growth arrest after ectopic expression in deficient tumor cells,
ii) SMARCA4-heterozygous mice have an increased predisposition to tumor development and,
iii) it is biallelically inactivated by homozygous deletions or combinations of deletions and mutations in several types of tumors, specially in lung cancer.

Homology

The mammalian SWI/SNF complex contains either SMARCA4 or SMARCA2 as its central ATPase subunit. Both ATPases share 80% homology in their aminoacid sequence. However, differences in expression patterns and in the phenotypes of Brm and Brg1 knockout mice suggest specific biological roles between both ATPases.
SMARCA2 and SMARCA4 are orthologous to the snf2/swi2 gene from S. cerevisiae and to the "brahma" (brm) gene from Drosophila. These encode proteins that are highly conserved along evolution, especially in the ATPase/helicase domain. Actually, SMARCA2 is 56% identical and 72% homologous to the Drosophila brm.

Implicated in

Various cancers

Note
SMARCA4 somatic mutations have been identified in some cancer cell lines including those from the lung, prostate, breast, pancreas and colon. While somatic mutations have been detected in a small subset of lung primary tumors, about one third of the lung cancer cell lines of the non-small cell lung cancer type harbour inactivating SMARCA4 somatic mutations. All mutations are homozygous and most of them predict truncated proteins. The type of mutations commonly observed include nonsense, indels and large deletions. Although less frequently, missense mutations have also been reported. Four of the aminoacid substitutions found in human lung and colorectal cancer, the p.W764R, p.G1160R, p.L1163P and p.S1176C represent changes in highly conserved residues within the ATPase/helicase domain. In vitro generated muta-tions of some highly conserved aminoacid within this motif lead to a seriously diminished catalytic activity of SMARCA4. SMARCA4 germ-line mu-tations have not been reported so far.

Prognosis
The lost of either SMARCA4 or SMARCA2, detected by immunostaining, predicts decreased survival in some cancer patients.

To be noted

Note
SMARCA4 is somatically mutated in a significant proportion of tumors, in particular lung cancer. Thus, SMARCA4 is a bona fide tumor suppressor gene and is clearly implicated in cancer develop-ment.
SMARCB1, encoding another subunit of the SWI/SNF complex, is subject to bi-allelic muta-tions (germinal and somatic) in rhabdoid tumours, a very aggressive form of paediatric cancers.

References

Khavari PA, Peterson CL, Tamkun JW, Mendel DB, Crabtree GR. BRG1 contains a conserved domain of the SWI2/SNF2 family necessary for normal mitotic growth and transcription. Nature. 1993 Nov 11;366(6451):170-4

Versteege I, Sévenet N, Lange J, Rousseau-Merck MF, Ambros P, Handgretinger R, Aurias A, Delattre O. Truncating mutations of hSNF5/INI1 in aggressive paediatric cancer. Nature. 1998 Jul 9;394(6689):203-6

DeCristofaro MF, Betz BL, Wang W, Weissman BE. Alteration of hSNF5/INI1/BAF47 detected in rhabdoid cell lines and primary rhabdomyosarcomas but not Wilms' tumors. Oncogene. 1999 Dec 9;18(52):7559-65

Muchardt C, Yaniv M. ATP-dependent chromatin remodelling: SWI/SNF and Co. are on the job. J Mol Biol. 1999 Oct 22;293(2):187-98

Bultman S, Gebuhr T, Yee D, La Mantia C, Nicholson J, Gilliam A, Randazzo F, Metzger D, Chambon P, Crabtree G, Magnuson T. A Brg1 null mutation in the mouse reveals functional differences among mammalian SWI/SNF complexes. Mol Cell. 2000 Dec;6(6):1287-95

Strobeck MW, Knudsen KE, Fribourg AF, DeCristofaro MF, Weissman BE, Imbalzano AN, Knudsen ES. BRG-1 is required

for RB-mediated cell cycle arrest. Proc Natl Acad Sci U S A. 2000 Jul 5;97(14):7748-53

Wong AK, Shanahan F, Chen Y, Lian L, Ha P, Hendricks K, Ghaffari S, Iliev D, Penn B, Woodland AM, Smith R, Salada G, Carillo A, Laity K, Gupte J, Swedlund B, Tavtigian SV, Teng DH, Lees E. BRG1, a component of the SWI-SNF complex, is mutated in multiple human tumor cell lines. Cancer Res. 2000 Nov 1;60(21):6171-7

Decristofaro MF, Betz BL, Rorie CJ, Reisman DN, Wang W, Weissman BE. Characterization of SWI/SNF protein expression in human breast cancer cell lines and other malignancies. J Cell Physiol. 2001 Jan;186(1):136-45

Muchardt C, Yaniv M. When the SWI/SNF complex remodels...the cell cycle. Oncogene. 2001 May 28;20(24):3067-75

Fukuoka J, Fujii T, Shih JH, Dracheva T, Meerzaman D, Player A, Hong K, Settnek S, Gupta A, Buetow K, Hewitt S, Travis WD, Jen J. Chromatin remodeling factors and BRM/BRG1 expression as prognostic indicators in non-small cell lung cancer. Clin Cancer Res. 2004 Jul 1;10(13):4314-24

Medina PP, Carretero J, Fraga MF, Esteller M, Sidransky D, Sanchez-Cespedes M. Genetic and epigenetic screening for gene alterations of the chromatin-remodeling factor, SMARCA4/BRG1, in lung tumors. Genes Chromosomes Cancer. 2004 Oct;41(2):170-7

Roberts CW, Orkin SH. The SWI/SNF complex--chromatin and cancer. Nat Rev Cancer. 2004 Feb;4(2):133-42

Bultman SJ, Gebuhr TC, Magnuson T. A Brg1 mutation that uncouples ATPase activity from chromatin remodeling reveals an essential role for SWI/SNF-related complexes in beta-globin expression and erythroid development. Genes Dev. 2005 Dec 1;19(23):2849-61

Medina PP, Carretero J, Ballestar E, Angulo B, Lopez-Rios F, Esteller M, Sanchez-Cespedes M. Transcriptional targets of the chromatin-remodelling factor SMARCA4/BRG1 in lung cancer cells. Hum Mol Genet. 2005 Apr 1;14(7):973-82

Smith CL, Peterson CL. A conserved Swi2/Snf2 ATPase motif couples ATP hydrolysis to chromatin remodeling. Mol Cell Biol. 2005 Jul;25(14):5880-92

Medina PP, Romero OA, Kohno T, Montuenga LM, Pio R, Yokota J, Sanchez-Cespedes M. Frequent BRG1/SMARCA4-inactivating mutations in human lung cancer cell lines. Hum Mutat. 2008 May;29(5):617-22

This article should be referenced as such:

Medina PP, Sanchez-Cespedes M. SMARCA4 (SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4). Atlas Genet Cytogenet Oncol Haematol. 2009; 13(3):215-217.