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

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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-IL1RL1LIG-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 numbering 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 approximately 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

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 modifications of the chromatin structure and to the regulation of gene expression.
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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. Bromodoms 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 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 mutations 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.

SMARCBI, 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


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