

Gene Section

Review

POU4F1 (POU class 4 homeobox 1)

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Identity

Hugo: POU4F1

Other names: BRN3A; Brn-3a; FLJ13449; Oct-T1; RDC-1

Location: 13q31.1

Local order: Gene orientation: minus strand.

Note: Member of class IV POU domain transcription factor.

DNA/RNA

Description

The gene is about 4,468 bases encoded by two exons separated by a short intron.

Transcription

5', upstream promoter drives expression of longer Brn-3a transcript encoding for Brn-3a(l) protein which includes exons 1 and 2. Regulatory sequences within the intron control expression of short Brn-3a transcript entirely from exon 2, which encodes Brn-3a(s) protein.

Protein

Description

Protein product for Brn-3a(l) is 423 amino acids with estimated molecular weight of about 42.9 kDa whereas Brn-3a(s) protein is 339 amino acids; about 32 kDa.

Expression

Nervous System: Originally isolated from brain cDNA, Brn-3a is expressed in specific neurons of midbrain and hindbrain in CNS and in peripheral sensory neurons (trigeminal ganglia, dorsal root ganglia, spinal cord). It is first seen in neural crest cells that are destined to form sensory neurons and expression persists in mature

neurones. Brn-3a is also expressed in retinal ganglion cells and vestibular somatosensory cells, where it cooperates with Brn-3b and Brn-3c respectively to determine cell fate.

Non-neuronal cell: Brn-3a is also expressed in T-cells, heart, testis, ovary, breast epithelium.

Cancers: implicated in neuroblastoma, Ewing sarcoma, cervical cancers, prostate cancers.

Localisation

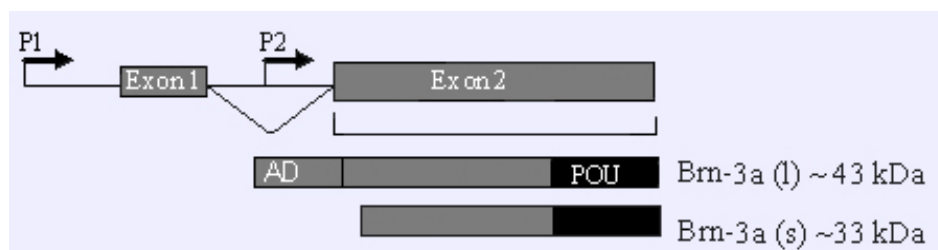
Nuclear.

Function

Brn-3a proteins act as transcription factors to regulate the expression of target genes, which can alter cell fate. In neuron, Brn-3a protects cells from apoptosis (by transactivating anti-apoptotic genes while repressing expression of pro-apoptotic proteins -see below). Brn-3a also enhances differentiation of neuronal cells in vitro and in-vivo by its ability to transactivate multiple neuronal target promoters. Brn-3a is required for the generation of proprioceptors in trigeminal ganglia.

The POU domain found at the C' terminal end of Brn-3a proteins is a bipartite DNA binding domain that can recognize and bind with high affinity and specificity to specific DNA sequences present in the promoters of target genes. DNA consensus sites recognized by Brn-3a include a core A/T rich octamer sequence e.g. ATAATTAAT with the POU-homeodomain (POU-HD) facilitating high affinity binding, whilst the POU-specific (POU-s) domain enhances specificity.

The POU domain of Brn-3a protein also has transactivation function and since Brn-3a(l) and Brn-3a(s) are identical in this region, both proteins can regulate specific subsets of target genes that require POU domain transactivation function e.g. neurofilament, SNAP 25, synaptophysin, Hsp-27.



Schematic diagram showing the two isoforms of Brn-3a protein that can be derived from the Brn-3a gene as a result of alternative promoter usage (P1 and P2). AD refers to N-terminal activation domain present only in Brn-3a(l). POU domain found at the C' terminal of the protein is common to both Brn-3a(l) and Brn-3a(s).

However, some Brn-3a target genes require the N' terminal transactivation domain that is found only in Brn-3a(l) protein and therefore these target genes can only be activated by Brn-3a(l) protein e.g. Bcl-2, Bcl-XL, alpha-internexin. Other target genes regulated by Brn-3a include TrkA, neuroD1 and neuroD4, Nav1.7 sodium channel, Doppel glycoprotein, iNOS, p53, NGFI-A, Hsp-27, tyrosine hydroxylase. Brn-3a also auto-regulate its own expression.

In addition to its direct effects on specific target genes, Brn-3a can also alter gene expression by its interaction with other cellular factors. For example, Brn-3a interacts physically with p53 protein, and modifies its effects on specific target genes that regulate cell fate. Thus Brn-3a cooperates with p53 to increase the expression of the cell cycle regulator, p21cip1/waf1 whilst antagonising p53 mediated expression of pro-apoptotic target genes, Bax and Noxa.

Brn-3a other interacting partner includes Rin1 (on target gene, Egr1), HIPK1 (alters TrkA expression), EWS - Fli1 fusion protein (represses Brn-3a mediated effects on survival / differentiation genes).

In addition to cellular target genes, Brn-3a also controls expression of viral genes such as those encoding the human papilloma virus (HPV) immediate early E6/E7 gene (required for HPV transformation of cervical cells) by binding to and transactivating the viral promoter. It is thought that the ability of Brn-3a to transactivate this promoter contributes to its effects in transformation of cervical cancer cells.

Homology

High homology with other POU4 family members in the POU domain (C' terminal end of the protein), and in the POU4 box (region of homology within the N' terminal transactivation domain, present only in Brn-3a(l)). Family members include mammalian POU4f2 (Brn-3b), POU4f3 (Brn-3c), drosophila I-POU and nematode, unc-86.

Implicated in

Normal development of sensory neurons in CNS and PNS

Note: Loss of Brn-3a by homologous recombination in mice resulted in significant loss of sensory neurons

(e.g. in the midbrain, trigeminal ganglia, dorsal root ganglia) during development. Mutants die within the first day of birth. Studies using cultured neural crest cells demonstrate that Brn-3a expressing cells are destined for sensory lineage. Brn-3a is required for the survival of these cells and achieves this partly by inhibiting expression of p53 mediated, pro-apoptotic target genes. Neural crest cells cultured from Brn-3a knockout mice, undergo significant apoptosis as a result of increased expression of p53 pro-apoptotic target genes, bax and Noxa.

Neuroblastomas

Oncogenesis

Brn-3a mRNA is significantly reduced in neuroblastoma tumour biopsies. Studies undertaken using neuroblastoma cell lines showed that Brn-3a is expressed at low levels when the cells are actively proliferating. However, when cells are induced to cease dividing and undergo differentiation, Brn-3a is significantly increased in cells. Forced over-expression of Brn-3a protects cells from apoptosis but also induces differentiation and neurite outgrowth. Therefore, the significant decrease of Brn-3 in neuroblastoma tumours may contribute to the oncogenic changes in the cells.

Neuroendocrine tumours

Oncogenesis

Brn-3a was shown to be elevated in highly aggressive neuroendocrine tumours SCCL tumours and ACTH producing pituitary tumours.

Ewing sarcoma

Oncogenesis

Brn-3a was detected in some Ewing sarcomas, which are tumours derived from primitive neural ectodermal lineage. These tumours are characterised by rearrangement of genes encoding the Ewing sarcoma (EWS) protein, and members of the Ets family of transcription factors. The most common fusion protein, EWS/Fli1, produces cellular transformation. Brn-3a interacts with the EWS/Fli1 fusion protein, and this interaction prevents Brn-3a mediated transactivation of genes required for cell cycle arrest e.g. p21cip1/waf1 and neurite outgrowth e.g. SNAP-25.

Cervical cancer

Oncogenesis

Brn-3a is expressed at high levels in high-grade cervical intra-epithelial neoplasia (CIN 3) compared to normal cervical biopsies. In this context, Brn-3a may contribute to tissue formation by binding to regulatory regions of Human Papilloma Viruses, HPV-16 and HPV18 and regulate expression of their oncogenic E6 and E7 genes.

Prostate cancer

Oncogenesis

Brn-3a was also detected in prostate cancers with up to 50% of tumours showing significant increase in expression of Brn-3a short isoforms.

Systemic lupus erythematosus

Note: Brn-3a is elevated in approximately 43% of patients with SLE and this correlates with enhanced levels of auto-antibodies to the protein. Increased Brn-3a also correlates with enhanced expression of HSP 90 protein in serum of SLE patients.

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