

Gene Section

Review

NRIP1 (nuclear receptor interacting protein 1)

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Abstract

Review on NRIP1, with data on DNA, on the protein encoded, and where the gene is implicated.

Keywords

NRIP1; Transcription factor

Other names

FLJ77253, RIP140

HGNC (Hugo)

NRIP1

Location

21q11.2

Identity

DNA/RNA

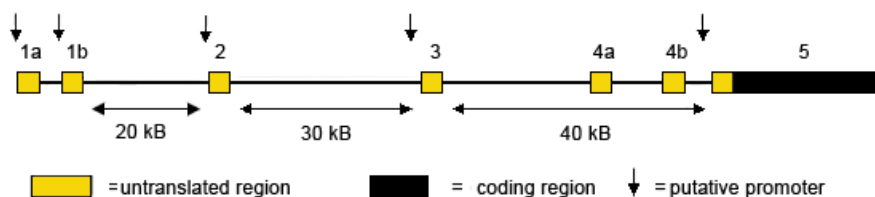


Figure 1: Schematic representation of NRIP1 gene that contains a total of seven exons and NRIP1 transcript.

Description

The gene encompasses approximately 100 Kb and may contain up to 7 exons. The entire protein-coding region is contained within the last exon.

Transcription

Transcription is complex. Alternative spliced transcripts containing distinct combinations of 5' non-coding exons occur. Alternative promoters have been described and are proposed to mediate tissue specific expression of NRIP1. NRIP1 is induced by a number of hormone nuclear receptors including the

receptors for estrogen, retinoic acid, androgen, progestins, vitamin D3, peroxisome proliferators-activated receptor-alpha (PPARalpha) and estrogen related receptor-alpha (ERRalpha). NRIP1 gene transcription is also induced by E2F transcription factors.

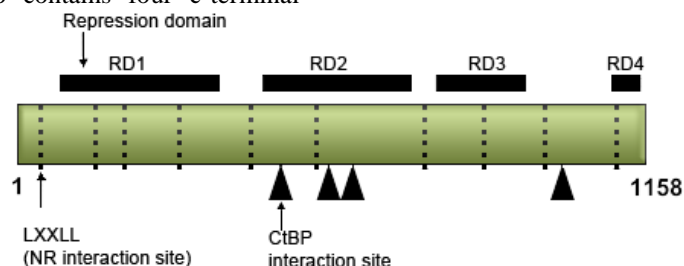
NRIP1 mRNA is widely expressed in various tissues and cell types.

Protein

NRIP1 (nuclear receptor interacting protein 1)

Description

NRIP1 consists of 1158 amino acids. NRIP1 contains ten LXXLL nuclear receptor interaction motifs and four transcriptional repression domains (RD 1-4). NRIP1 also contains four c-terminal



binding protein (CtBP) interaction motifs. NRIP1 activity is regulated by a variety of posttranslational modifications including acetylation, methylation, phosphorylation, sumoylation, and pyridoxal-phosphate (PLP) conjugation.

Expression

NRIP1 is expressed at low levels in most tissues and is induced in response to hormonal signals. NRIP1 is highly expressed in metabolic and reproductive organs and tissues including the liver, adipose tissue, skeletal muscle, ovary and endometrium.

Localisation

NRIP1 is mainly expressed in the nucleus and contains two putative nuclear localization signals (NLS).

Function

NRIP1 is a co-repressor of a large number of nuclear receptors. NRIP1 interacts preferentially with ligand-bound nuclear receptors and inhibits transactivation by recruitment of histone deacetylases and CtBP. Knockout mice studies revealed that NRIP1 has a physiologic role in energy homeostasis, muscle metabolism, adipocyte and hepatocyte function, mitochondrial activity, inflammation, reproduction and cognition. Data suggest that these roles are mediated by NRIP1 repression of nuclear receptor mediated gene expression including gene expression mediated by the estrogen receptor, liver X receptor, PPARs, steroidogenic factor 1 (SF1) and ERR.

NRIP1 has been shown to regulate retinoic acid mediated differentiation and growth suppression of human embryonal carcinoma cells and the proliferation of breast cancer cells in vitro. A potential role for NRIP1 in cancer cachexia has been suggested. Interestingly, NRIP1 also regulates the activity of other transcription factors including E2Fs and NFκB.

The fact that NRIP1 expression can be regulated by multiple transcription factors and especially nuclear receptors and their ligands and that NRIP1 can inhibit the activity of multiple nuclear receptors implies a potential role in the biology of hormone-dependent cancers. This role in cancer biology which

has recently been described in colon, stomach, breast and cervix.

Homology

NRIP1 is highly conserved throughout vertebrates. There is only a single isoform in humans and mice.

Mutations

Germinal

Several synonymous and non-synonymous SNPs have been identified. To date no somatic tumor mutations have been noted.

- Arg448Gly has been associated with endometriosis.
- Gly75Gly has been associated with male infertility.

Implicated in

Hormone dependent cancers

In a variety of cancer cell culture systems mouse models and tissue arrays, NRIP1 has been shown to regulate the activity of a number of nuclear receptors involved in hormone-dependent cancers including estrogen, retinoid, progesterone and androgen receptors. Moreover, NRIP1 mRNA is finely regulated during cell cycle progression, modulating cell growth and apoptosis. Finally, NRIP1 overexpression is associated with a significantly shorter overall survival of cervical cancer patients and discriminates luminal breast cancers.

Cancer cachexia

NRIP1 was induced in livers of starved, septic, and tumor-bearing mice. Liver-specific knockdown of NRIP1 led to increased hepatic TG release and alleviated hepatic steatosis in tumor-bearing, cachectic animals. NRIP1 was found to control the expression of lipid-metabolizing genes in liver.

Obesity and metabolic disorders

NRIP1 knockout mice are lean and are resistant to high-fat diet induced obesity. NRIP1 regulates genes involved in energy homeostasis in metabolic organs. Moreover, low level of NRIP1 restores the rates of fatty-acids uptake in the basal state, in part via a

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reduction in upstream insulin signaling. In addition, increased NRIP1 level may be closely associated with inflammation and disorder of lipid and glucose metabolism in diabetic patients. In addition, detectable serum NRIP1 protein level changes is associated with weight loss in humans.

Infertility

NRIP1 knockout mice are infertile due to a defect in ovulation. Also the above-mentioned SNPs have been proposed to be associated with endometriosis and male fertility.

Gastro-intestinal homeostasis and tumorigenesis

Using molecular and cellular approaches, transgenic mouse models and human colorectal biopsies, NRIP1 has been shown to inhibit cell proliferation and apoptosis in the murine intestinal epithelium. In addition, NRIP1 exerts a negative control on Wnt/beta-catenin signaling by positively regulating the expression of the tumor suppressor gene APC. High NRIP1 expression is associated with a significantly longer overall survival of colorectal cancer patients. Interestingly, whereas NRIP1 expression tends to decrease in colorectal cancers as compared to adjacent normal tissues, an increase of its expression was noticed in gastric cancer as compared to normal stomach.

Cognition and neural cells

The NRIP1 gene depletion in mice results in learning and memory deficits as well as stress response, bringing to light a major role for this transcriptional coregulator in the neurophysiological developmental mechanisms underlying cognitive functions. In addition, NRIP1 plays a relevant role in Down syndrome mitochondrial dysfunction. Moreover, NRIP1 expression increases during neural differentiation of human embryonic stem cells and is negatively correlated with stem cell markers Oct4 and Sox2 during early stages of neural differentiation.

Aging and longevity

The deletion of NRIP1 in female mice can significantly extend longevity compared to wild-type females.

Immunity and inflammation

Overexpression of NRIP1 in macrophages results in M1-like polarization and expansion during the inflammatory response. Conversely, decreased expression of NRIP1 in macrophages reduces the number of M1-like macrophages and increases the number of alternatively polarized cells, which collectively promote endotoxin tolerance and relieve inflammation.

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