

Gene Section

Mini Review

NRIP1 (nuclear receptor interacting protein 1)

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Identity

Other names: FLJ77253; RIP140

HGNC (Hugo): NRIP1

Location: 21q21.1

Local order: Cen-GAPDHP16-LOC100128341-NRIP1-CYCSP42-LOC100131399-Tel.

DNA/RNA

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 RIP140. RIP140 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).

RIP140 mRNA is widely expressed in various tissues and cell types.

Pseudogene

None known.

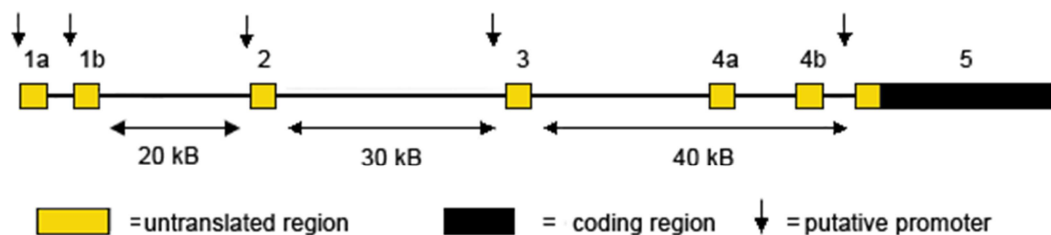
Description

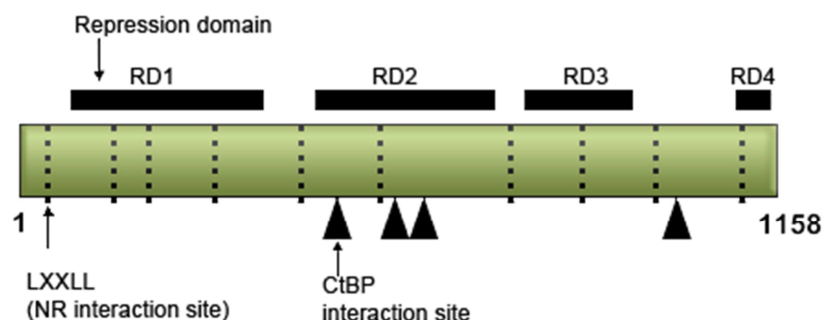
RIP140 consists of 1158 amino acids. RIP140 contains ten LXXLL nuclear receptor interaction motifs and four transcriptional repression domains (RD 1-4). RIP140 also contains four c-terminal binding protein (CtBP) interaction motifs. RIP140 activity is regulated by a variety of posttranslational modifications including acetylation, methylation, phosphorylation, sumoylation, and pyridoxal-phosphate (PLP) conjugation.

Protein

Expression

RIP140 is expressed at low levels in most tissues and is induced in response to hormonal signals. RIP140 is highly expressed in metabolic and reproductive organs and tissues including the liver, adipose tissue, skeletal muscle, ovary and endometrium.





Localisation

RIP140 is mainly expressed in the nucleus and contains two putative nuclear localization signals (NLS).

Function

RIP140 is a co-repressor of a large number of nuclear receptors. RIP140 interacts preferentially with ligand-bound nuclear receptors and inhibits transactivation by recruitment of histone deacetylases and CtBP. Knockout mice studies revealed that RIP140 has a physiologic role in energy homeostasis, muscle metabolism, adipocyte and hepatocyte function, mitochondrial activity and reproduction. Data suggest that these roles are mediated by RIP140 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.

RIP140 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 RIP140 in cancer cachexia has been suggested.

That RIP140 expression can be regulated by multiple nuclear receptors and their ligands and that RIP140 can inhibit the activity of multiple nuclear receptors implies a potential role in the biology of hormone-dependent cancers. This role in cancer is thus far only hypothetical.

Homology

RIP140 is highly conserved throughout vertebrates. There is only a single isoform in humans and mice.

Mutations

Note

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

Note

In a variety of cancer cell culture systems RIP140 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.

Cancer cachexia

Note

RIP140 was induced in livers of starved, septic, and tumor-bearing mice. Liver-specific knockdown of RIP140 led to increased hepatic TG release and alleviated hepatic steatosis in tumor-bearing, cachectic animals. RIP140 was found to control the expression of lipid-metabolizing genes in liver.

Obesity and metabolic disorders

Note

RIP140 knockout mice are lean and are resistant to high-fat diet induced obesity. RIP140 regulates genes involved in energy homeostasis in metabolic organs.

Infertility

Note

Female RIP140 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.

References

- Cavaillès V, Dauvois S, L'Horset F, Lopez G, Hoare S, Kushner PJ, Parker MG. Nuclear factor RIP140 modulates transcriptional activation by the estrogen receptor. *EMBO J*. 1995 Aug 1;14(15):3741-51
- Wei LN, Hu X, Chandra D, Seto E, Farooqui M. Receptor-interacting protein 140 directly recruits histone deacetylases for gene silencing. *J Biol Chem*. 2000 Dec 29;275(52):40782-7
- White R, Leonardsson G, Rosewell I, Ann Jacobs M, Milligan S, Parker M. The nuclear receptor co-repressor nrp1 (RIP140) is essential for female fertility. *Nat Med*. 2000 Dec;6(12):1368-74
- Kerley JS, Olsen SL, Freemantle SJ, Spinella MJ. Transcriptional activation of the nuclear receptor corepressor RIP140 by retinoic acid: a potential negative-feedback regulatory mechanism. *Biochem Biophys Res Commun*. 2001 Jul 27;285(4):969-75
- Vo N, Fjeld C, Goodman RH. Acetylation of nuclear hormone receptor-interacting protein RIP140 regulates binding of the transcriptional corepressor CtBP. *Mol Cell Biol*. 2001 Sep;21(18):6181-8

- Lin R, Nagai Y, Sladek R, Bastien Y, Ho J, Petrecca K, Sotiropoulou G, Diamandis EP, Hudson TJ, White JH. Expression profiling in squamous carcinoma cells reveals pleiotropic effects of vitamin D3 analog EB1089 signaling on cell proliferation, differentiation, and immune system regulation. *Mol Endocrinol*. 2002 Jun;16(6):1243-56
- Lin R, Nagai Y, Sladek R, Bastien Y, Ho J, Petrecca K, Sotiropoulou G, Diamandis EP, Hudson TJ, White JH. Expression profiling in squamous carcinoma cells reveals pleiotropic effects of vitamin D3 analog EB1089 signaling on cell proliferation, differentiation, and immune system regulation. *Mol Endocrinol*. 2002 Jun;16(6):1243-56
- White KA, Yore MM, Warburton SL, Vaseva AV, Rieder E, Freemantle SJ, Spinella MJ. Negative feedback at the level of nuclear receptor coregulation. Self-limitation of retinoid signaling by RIP140. *J Biol Chem*. 2003 Nov 7;278(45):43889-92
- Leonardsson G, Steel JH, Christian M, Pocock V, Milligan S, Bell J, So PW, Medina-Gomez G, Vidal-Puig A, White R, Parker MG. Nuclear receptor corepressor RIP140 regulates fat accumulation. *Proc Natl Acad Sci U S A*. 2004 Jun 1;101(22):8437-42
- Caballero V, Ruiz R, Sainz JA, Cruz M, López-Nevot MA, Galán JJ, Real LM, de Castro F, López-Villaverde V, Ruiz A. Preliminary molecular genetic analysis of the Receptor Interacting Protein 140 (RIP140) in women affected by endometriosis. *J Exp Clin Assist Reprod*. 2005 Aug 30;2:11
- Galan JJ, Buch B, Cruz N, Segura A, Moron FJ, Bassas L, Martinez-Pineiro L, Real LM, Ruiz A. Multilocus analyses of estrogen-related genes reveal involvement of the ESR1 gene in male infertility and the polygenic nature of the pathology. *Fertil Steril*. 2005 Oct;84(4):910-8
- Graham JD, Yager ML, Hill HD, Byth K, O'Neill GM, Clarke CL. Altered progesterone receptor isoform expression remodels progesterone responsiveness of breast cancer cells. *Mol Endocrinol*. 2005 Nov;19(11):2713-35
- White KA, Yore MM, Deng D, Spinella MJ. Limiting effects of RIP140 in estrogen signaling: potential mediation of anti-estrogenic effects of retinoic acid. *J Biol Chem*. 2005 Mar 4;280(9):7829-35
- Augereau P, Badia E, Balaguer P, Carascossa S, Castet A, Jalaguier S, Cavaillès V. Negative regulation of hormone signaling by RIP140. *J Steroid Biochem Mol Biol*. 2006 Dec;102(1-5):51-9
- Augereau P, Badia E, Fuentes M, Rabenoelina F, Corniou M, Derocq D, Balaguer P, Cavaillès V. Transcriptional regulation of the human NRIP1/RIP140 gene by estrogen is modulated by dioxin signalling. *Mol Pharmacol*. 2006 Apr;69(4):1338-46
- Carroll JS, Meyer CA, Song J, Li W, Geistlinger TR, Eeckhoute J, Brodsky AS, Keeton EK, Fertuck KC, Hall GF, Wang Q, Bekiranov S, Sementchenko V, Fox EA, Silver PA, Gingeras TR, Liu XS, Brown M. Genome-wide analysis of estrogen receptor binding sites. *Nat Genet*. 2006 Nov;38(11):1289-97
- Nichol D, Christian M, Steel JH, White R, Parker MG. RIP140 expression is stimulated by estrogen-related receptor alpha during adipogenesis. *J Biol Chem*. 2006 Oct 27;281(43):32140-7
- Powelka AM, Seth A, Virbasius JV, Kiskinis E, Nicoloso SM, Guilherme A, Tang X, Straubhaar J, Cherniack AD, Parker MG, Czech MP. Suppression of oxidative metabolism and mitochondrial biogenesis by the transcriptional corepressor RIP140 in mouse adipocytes. *J Clin Invest*. 2006 Jan;116(1):125-36
- Heim KC, White KA, Deng D, Tomlinson CR, Moore JH, Freemantle SJ, Spinella MJ. Selective repression of retinoic acid target genes by RIP140 during induced tumor cell differentiation of pluripotent human embryonal carcinoma cells. *Mol Cancer*. 2007 Sep 19;6:57
- Herzog B, Hallberg M, Seth A, Woods A, White R, Parker MG. The nuclear receptor cofactor, receptor-interacting protein 140, is required for the regulation of hepatic lipid and glucose metabolism by liver X receptor. *Mol Endocrinol*. 2007 Nov;21(11):2687-97
- Seth A, Steel JH, Nichol D, Pocock V, Kumaran MK, Fritah A, Moberley M, Ryder TA, Rowleron A, Scott J, Poutanen M, White R, Parker M. The transcriptional corepressor RIP140 regulates oxidative metabolism in skeletal muscle. *Cell Metab*. 2007 Sep;6(3):236-45
- Berriel Diaz M, Kronen-Herzig A, Metzger D, Ziegler A, Vegiopoulos A, Klingenspor M, Müller-Decker K, Herzig S. Nuclear receptor cofactor receptor interacting protein 140 controls hepatic triglyceride metabolism during wasting in mice. *Hepatology*. 2008 Sep;48(3):782-91
- Mostaqul Huq MD, Gupta P, Wei LN. Post-translational modifications of nuclear co-repressor RIP140: a therapeutic target for metabolic diseases. *Curr Med Chem*. 2008;15(4):386-92
- Rytinki MM, Palvimo JJ. SUMOylation modulates the transcription repressor function of RIP140. *J Biol Chem*. 2008 Apr 25;283(17):11586-95
- White R, Morganstein D, Christian M, Seth A, Herzog B, Parker MG. Role of RIP140 in metabolic tissues: connections to disease. *FEBS Lett*. 2008 Jan 9;582(1):39-45
- Heim KC, Gamsby JJ, Hever MP, Freemantle SJ, Loros JJ, Dunlap JC, Spinella MJ. Retinoic acid mediates long-paced oscillations in retinoid receptor activity: evidence for a potential role for RIP140. *PLoS One*. 2009 Oct 28;4(10):e7639
- Huq MD, Ha SG, Barcelona H, Wei LN. Lysine methylation of nuclear co-repressor receptor interacting protein 140. *J Proteome Res*. 2009 Mar;8(3):1156-67

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