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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

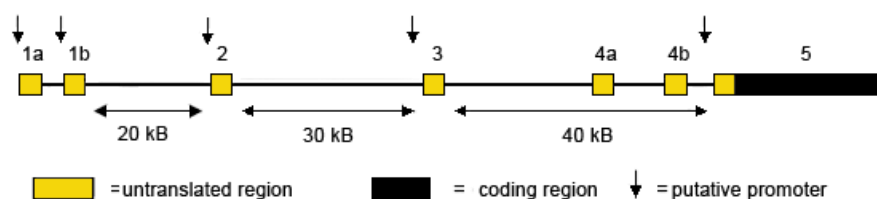


Figure 1: Schematic representation of NRIP1 gene that contains a total of two exons and NRIP1 transcript.

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.

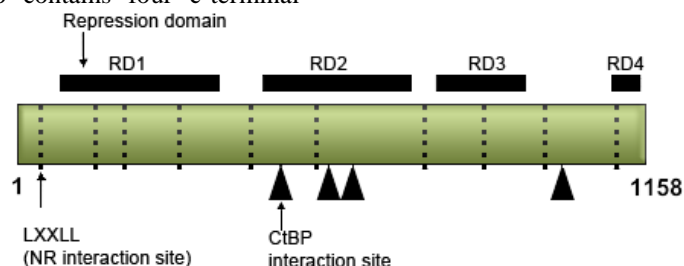
NRIP1 mRNA is widely expressed in various tissues and cell types.

Protein

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

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.

References

- Augereau P, Badia E, Fuentes M, Rabenoelina F, Corniou M, Derocq D, Balaguer P, Cavailles V. Transcriptional regulation of the human NRIP1/RIP140 gene by estrogen is modulated by dioxin signalling. *Mol Pharmacol*. 2006 Apr;69(4):1338-46
- Aziz MH, Chen X, Zhang Q, DeFrain C, Osland J, Luo Y, Shi X, Yuan R. Suppressing NRIP1 inhibits growth of breast cancer cells in vitro and in vivo. *Oncotarget*. 2015 Nov 24;6(37):39714-24
- Berriel Diaz M, Krones-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
- Blondrath K, Steel JH, Katsouri L, Ries M, Parker MG, Christian M, Sastre M. The nuclear cofactor receptor interacting protein-140 (RIP140) regulates the expression of genes involved in Aβ generation *Neurobiol Aging*. 2016 Nov;47:180-191
- 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
- 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
- Cavallès 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
- Constantinescu S, Turcotte LP. Amelioration of palmitate-induced metabolic dysfunction in L6 muscle cells expressing low levels of receptor-interacting protein 140 *Can J Physiol Pharmacol*. 2015 Nov;93(11):913-22
- De Marinis Y, Sun J, Bompada P, Domènech Omella J, Luan C, Halu A, Renström E, Sharma A, Ridderstråle M. Regulation of Nuclear Receptor Interacting Protein 1 (NRIP1) Gene Expression in Response to Weight Loss and Exercise in Humans Obesity (Silver Spring). 2017 Aug;25(8):1400-1409
- Docquier A, Garcia A, Savatier J, Boulahtouf A, Bonnet S, Bellet V, Busson M, Margeat E, Jalaguier S, Royer C, Balaguer P, Cavallès V. Negative regulation of estrogen signaling by ERβ and RIP140 in ovarian cancer cells *Mol Endocrinol*. 2013 Sep;27(9):1429-41
- Duclot F, Lapierre M, Fritsch S, White R, Parker MG, Maurice T, Cavallès V. Cognitive impairments in adult mice with constitutive inactivation of RIP140 gene expression *Genes Brain Behav*. 2012 Feb;11(1):69-78
- Fritah A, Steel JH, Parker N, Nikolopoulou E, Christian M, Carling D, Parker MG. Absence of RIP140 reveals a pathway regulating glut4-dependent glucose uptake in oxidative skeletal muscle through UCP1-mediated activation of AMPK *PLoS One*. 2012;7(2):e32520
- 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 progestin responsiveness of breast cancer cells *Mol Endocrinol*. 2005 Nov;19(11):2713-35

NRIP1 (nuclear receptor interacting protein 1)

- 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
- 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
- Ho PC, Chang KC, Chuang YS, Wei LN. Cholesterol regulation of receptor-interacting protein 140 via microRNA-33 in inflammatory cytokine production *FASEB J* 2011 May;25(5):1758-66
- Ho PC, Wei LN. Biological activities of receptor-interacting protein 140 in adipocytes and metabolic diseases *Curr Diabetes Rev* 2012 Nov;8(6):452-7
- Hu YC, Yi ZJ, Zhou Y, Li PZ, Liu ZJ, Duan SG, Gong JP. Overexpression of RIP140 suppresses the malignant potential of hepatocellular carcinoma by inhibiting NFB-mediated alternative polarization of macrophages *Oncol Rep* 2017 May;37(5):2971-2979
- 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
- Izzo A, Manco R, Bonfiglio F, Cal G, De Cristofaro T, Patergnani S, Cicatiello R, Scrima R, Zannini M, Pinton P, Conti A, Nitsch L. NRIP1/RIP140 siRNA-mediated attenuation counteracts mitochondrial dysfunction in Down syndrome *Hum Mol Genet* 2014 Aug 15;23(16):4406-19
- Jalaguier S, Teyssier C, Nait Achour T, Lucas A, Bonnet S, Rodriguez C, Elarouci N, Lapiere M, Cavailles V. Complex regulation of LCoR signaling in breast cancer cells *Oncogene* 2017 Aug 17;36(33):4790-4801
- Karasawa T, Takahashi M. RIP140 as a novel therapeutic target in the treatment of atherosclerosis *J Mol Cell Cardiol* 2015 Apr;81:136-8
- 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
- Lapiere M, Docquier A, Castet-Nicolas A, Gitenay D, Jalaguier S, Teyssier C, Cavailles V. The emerging role of the transcriptional coregulator RIP140 in solid tumors *Biochim Biophys Acta* 2015 Aug;1856(1):144-50
- Lei JJ, Peng RJ, Kuang BH, Yuan ZY, Qin T, Liu WS, Guo YM, Han HQ, Lian YF, Deng CC, Zhang HJ, Chen LZ, Feng QS, Xu M, Feng L, Bei JX, Zeng YX. NOP14 suppresses breast cancer progression by inhibiting NRIP1/Wnt/ β -catenin pathway *Oncotarget* 2015 Sep 22;6(28):25701-14
- 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
- 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 YW, Montassier E, Knights D, Wei LN. Gut microbiota from metabolic disease-resistant, macrophage-specific RIP140 knockdown mice improves metabolic phenotype and gastrointestinal integrity *Sci Rep* 2016 Dec 8;6:38599
- Liu PS, Lin YW, Lee B, McCrady-Spitzer SK, Levine JA, Wei LN. Reducing RIP140 expression in macrophage alters ATM infiltration, facilitates white adipose tissue browning, and prevents high-fat diet-induced insulin resistance *Diabetes* 2014 Dec;63(12):4021-31
- Luan C, Chen X, Hu Y, Hao Z, Osland JM, Chen X, Gerber SD, Chen M, Gu H, Yuan R. Overexpression and potential roles of NRIP1 in psoriasis *Oncotarget* 2016 Nov 8;7(45):74236-74246
- 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
- Nautiyal J, Christian M, Parker MG. Distinct functions for RIP140 in development, inflammation, and metabolism *Trends Endocrinol Metab* 2013 Sep;24(9):451-9
- 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
- Rytinki MM, Palvimo JJ. SUMOylation modulates the transcription repressor function of RIP140 *J Biol Chem* 2008 Apr 25;283(17):11586-95
- Seth A, Steel JH, Nichol D, Pocock V, Kumaran MK, Fritah A, Mobberley M, Ryder TA, Rowleson 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
- Triki M, Ben Ayed-Guerfali D, Saguem I, Charfi S, Ayedi L, Sellami-Boudawara T, Cavailles V, Mokdad-Gargouri R. RIP140 and LCoR expression in gastrointestinal cancers *Oncotarget* 2017 Nov 25;8(67):111161-111175
- Triki M, Lapiere M, Cavailles V, Mokdad-Gargouri R. Expression and role of nuclear receptor coregulators in colorectal cancer *World J Gastroenterol* 2017 Jul 7;23(25):4480-4490
- Vattai A, Cavailles V, Sixou S, Beyer S, Kuhn C, Peryanova M, Heidegger H, Hermelink K, Mayr D, Mahner S, Dannecker C, Jeschke U, Kost B. Investigation of RIP140 and LCoR as independent markers for poor prognosis in cervical cancer *Oncotarget* 2017 Oct 31;8(62):105356-105371
- 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
- Wang J, Chen X, Osland J, Gerber DS, Luan C, Delfino K, Goodwin L, Yuan R. Deletion of Nrip1 extends female mice longevity, increases autophagy, and delays cell senescence *J Gerontol A Biol Sci Med Sci* 2018 Jan 13
- 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

NRIP1 (nuclear receptor interacting protein 1)

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

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

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

Xia K, Zhang P, Hu J, Hou H, Xiong M, Xiong J, Yan N. Synergistic effect of receptor-interacting protein 140 and simvastatin on the inhibition of proliferation and survival of hepatocellular carcinoma cells Oncol Lett 2018 Apr;15(4):4344-4350

Xue J, Zhao H, Shang G, Zou R, Dai Z, Zhou D, Huang Q, Xu Y. RIP140 is associated with subclinical inflammation in type 2 diabetic patients Exp Clin Endocrinol Diabetes 2013 Jan;121(1):37-42

Yi ZJ, Gong JP, Zhang W. Transcriptional co-regulator RIP140: An important mediator of the inflammatory response and its associated diseases (Review) Mol Med Rep 2017 Aug;16(2):994-1000

Zhao ZR, Yu WD, Shi C, Liang R, Chen X, Feng X, Zhang X, Mu Q, Shen H, Guo JZ. Correlation between receptor-interacting protein 140 expression and directed differentiation of human embryonic stem cells into neural stem cells Neural Regen Res 2017 Jan;12(1):118-124

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