Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Short Communication

RARRES3 (retinoic acid receptor responder (tazarotene induced) 3)

Tiffany Scharadin, Richard L Eckert

Department of Biochemistry and Molecular Biology, University of Maryland, School of Medicine, Baltimore, Maryland 21201, USA (TS, RLE)

Published in Atlas Database: January 2012

Online updated version : http://AtlasGeneticsOncology.org/Genes/RARRES3ID42051ch11q12.html
DOI: 10.4267/2042/47340

Identity

Other names: HRASLS4, MGC8906, PLA1/2-3, RIG1, TIG3

HGNC (Hugo): RARRES3

Location: 11q12.3

Note: Reported at 11q23 (DiSepio et al., 1998) but more recent results suggest TIG3 is at 11q12 (Auer et al., 2002).

DNA/RNA

Description

DNA size: 9658 bp with 4 exons.

Transcription

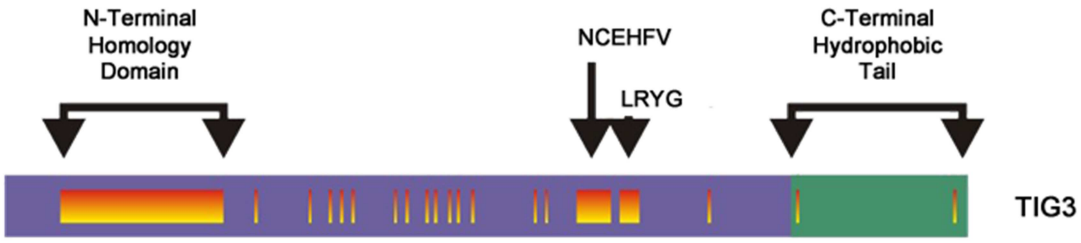
mRNA size: 779 bp, processed: 495 bp.

Protein

Note

The C-terminus of TIG3 is believed to be a membrane-anchoring domain which is involved in driving membrane localization and is also required for centrosome localization. Removal of this domain from TIG3 causes it to distribute diffusely throughout the cytoplasm and reduces its ability to decrease cell survival (Deucher et al., 2000; Sturniolo et al., 2003; Sturniolo et al., 2005; Jans et al., 2008; Tsai et al., 2009).

Schematic of the TIG3 gene. Thick red boxes indicate exons.



Schematic of the TIG3 protein. The purple indicates the hydrophilic N-terminus (amino acids 1-134) and green indicates the hydrophobic C-terminus (amino acids 134-164). The orange regions represent conserved elements with the H-rev107 family. Highly conserved regions are labeled.

Description

164 amino acids; 18 kDa protein; contains a hydrophilic N-terminus (1-134) and hydrophobic, membrane-anchoring domain (134-164).

Expression

Ubiquitously expressed; expression is reduced in hyperproliferative diseases including cancer.

Localisation

Cell membrane, centrosome (Scharadin et al., 2011).

Function

TIG3 is a type II tumor suppressor gene which regulates cell proliferation and survival (DiSepio et al., 1998).
Loss of TIG3 expression leads to hyperproliferative diseases including psoriasis and cancer.
Restoration of TIG3 expression to cancer cell lines decreases cell cycle progression and induces apoptosis causing an overall decrease in viable cells (DiSepio et al., 1998; Huang et al., 2002; Higuchi et al., 2003; Tsai et al., 2009; Scharadin et al., 2011).
Localization of TIG3 to the centrosome is believed to be responsible for this decrease in cell survival, which leads to an increase in p21 level, a G1/S phase block, an activation of the caspase cascade, and a reorganization of the microtubule network (Scharadin et al., 2011).
In contrast, expression of TIG3 in normal keratinocytes induces a process of terminal differentiation through the binding to and activation of type I transglutaminase and increase in cornified envelope formation to decrease cell survival (Sturniolo et al., 2003; Sturniolo et al., 2005; Jans et al., 2008). Localization of TIG3 to the cell membrane in keratinocytes is necessary for it to bind type I transglutaminase.

Homology

TIG3 shares homology with the H-rev107 family of class II tumor suppressors and the NlpC/P60 superfamily (Hajnal et al., 1994; DiSepio et al., 1998; Husmann et al., 1998; Anantharaman and Aravind, 2003; Jahng et al., 2003).

Mutations

Note
No known mutations.

Implicated in

Various cancers

Note
TIG3 expression is reduced in several cancer including breast, skin, lymphoma, leukemia, kidney, ureter, colorectal, liver, biliary tract, ovary, and uterine.

Disease
Cancer is a disease characterized by uncontrolled cell proliferation.

Prognosis
Cancer prognosis is dependent upon several tumor-specific conditions, including location, size, and metastasis.

Oncogenesis
Loss of TIG3 mRNA and protein expression is observed in several cancers and may be necessary for oncogenesis (DiSepio et al., 1998; Casanova et al., 2001; Duvic et al., 2003; Shyu et al., 2003; Jiang et al., 2005; Lotz et al., 2005; Shyu et al., 2005). Tazarotene treatment of skin cancers leads to increased TIG3 expression and reduced proliferation (Duvic et al., 2000; Duvic et al., 2003). The loss of TIG3 is associated with increased cell proliferation and TIG3 loss may be necessary for cancer progression.

Hyperproliferative diseases

Note
Loss of TIG3 expression is associated with hyperproliferative diseases including psoriasis and cancer.
TIG3 mRNA and protein levels are reduced in psoriatic lesions.
Treatment with tazarotene leads to an increase in TIG3 levels and restoration of the normal epidermal condition (Duvic et al., 2000). Hypermethylation of the TIG3 promoter is a possible mechanism for reduced expression in psoriasis (Kwong et al., 2005).

Disease
Psoriasis is a common disorder of the skin which is characterized by inflammation and hyperproliferation of the epidermis.

Prognosis
Psoriasis is a non-fatal, chronic disorder that can be controlled with treatment.

Breakpoints

Note
No breakpoints known.

References

Hajnal A, Klemenz R, Schäfer R. Subtraction cloning of H-rev107, a gene specifically expressed in H-ras resistant fibroblasts. Oncogene. 1994 Feb;9(2):479-90

DiSepio D, Ghosn C, Eckert RL, Deucher A, Robinson N, Duvic M, Chandraratna RA, Nagpal S. Identification and characterization of a retinoid-induced class II tumor suppressor/growth regulatory gene. Proc Natl Acad Sci U S A. 1998 Dec 8;95(25):14811-5

Husmann K, Sers C, Fietze E, Mincheva A, Lichter P, Schäfer R. Transcriptional and translational downregulation of H-REV107, a class II tumour suppressor gene located on human chromosome 11q11-12. Oncogene. 1998 Sep 10;17(10):1305-12

Deucher A, Nagpal S, Chandraratna RA, Di Sepio D, Robinson NA, Dashti SR, Eckert RL. The carboxy-terminal hydrophobic domain of TIG3, a class II tumor suppressor protein, is required for appropriate cellular localization and optimal biological activity. Int J Oncol. 2000 Dec;17(6):1195-203

Duvic M, Helekar B, Schulz C, Cho M, DiSepio D, Hager C, DiMao D, Hazarika P, Jackson B, Breuer-McHam J, Young J, Clayman G, Lippman SM, Chandraratna RA, Robinson NA, Deucher A, Eckert RL, Nagpal S. Expression of a retinoid-inducible tumor suppressor, Tazarotene-inducible gene-3, is decreased in psoriasis and skin cancer. Clin Cancer Res. 2000 Aug;6(8):3249-59

Casanova B, de la Fuente MT, Garcia-Gila M, Sanz L, Silva A, Garcia-Marco JA, Garcia-Pardo A. The class II tumor-suppressor gene RARRES3 is expressed in B cell lymphocytic leukemias and down-regulated with disease progression. Leukemia. 2001 Oct;15(10):1521-6

Auer RL, Bertoni F, Jones C, Cotter FE. The class II tumour suppressor gene RARRES3 maps to 11q12, not 11q23. Leukemia. 2002 Jul;16(7):1396; author reply 1396-7

Huang SL, Shyu RY, Yeh MY, Jiang SY. The retinoid-inducible gene I: effect on apoptosis and mitogen-activated kinase signal pathways. Anticancer Res. 2002 Mar-Apr;22(2A):799-804

Anantharaman V, Aravind L. Evolutionary history, structural features and biochemical diversity of the NlpC/P60 superfamily of enzymes. Genome Biol. 2003;4(2):R11

Duvic M, Ni X, Talpur R, Herne K, Schulz C, Sui D, Ward S, Joseph A, Hazarika P. Tazarotene-induced gene 3 is suppressed in basal cell carcinomas and reversed in vivo by tazarotene application. J Invest Dermatol. 2003 Oct;121(4):902-9

Higuchi E, Chandraratna RA, Hong WK, Lotan R. Induction of TIG3, a putative class II tumor suppressor gene, by retinoic acid in head and neck and lung carcinoma cells and its association with suppression of the transformed phenotype. Oncogene. 2003 Jul 24;22(30):4627-35

Jahng WJ, Xue L, Rando RR. Lecithin retinol acyltransferase is a founder member of a novel family of enzymes. Biochemistry. 2003 Nov 11;42(44):12805-12

Shyu RY, Jiang SY, Chou JM, Shih YL, Lee MS, Yu JC, Chao PC, Hsu YJ, Jao SW. RARRES3 expression positively correlated to tumour differentiation in tissues of colorectal adenocarcinoma. Br J Cancer. 2003 Jul 7;89(1):146-51

Sturniolo MT, Dashti SR, Deucher A, Rorke EA, Broome AM, Chandraratna RA, Keepers T, Eckert RL. A novel tumor suppressor protein promotes keratinocyte terminal differentiation via activation of type I transglutaminase. J Biol Chem. 2003 Nov 28;278(48):48066-73

Jiang SY, Chou JM, Leu FJ, Hsu YY, Shih YL, Yu JC, Lee MS, Shyu RY. Decreased expression of type II tumor suppressor gene RARRES3 in tissues of hepatocellular carcinoma and cholangiocarcinoma. World J Gastroenterol. 2005 Feb 21;11(7):948-53

Kwong J, Lo KW, Chow LS, Chan FL, To KF, Huang DP. Silencing of the retinoid response gene TIG1 by promoter hypermethylation in nasopharyngeal carcinoma. Int J Cancer. 2005 Jan 20;113(3):386-92

Lotz K, Kellner T, Heitmann M, Nazarenko I, Noske A, Malek A, Gontarewicz A, Schäfer R, Sers C. Suppression of the TIG3 tumor suppressor gene in human ovarian carcinomas is mediated via mitogen-activated kinase-dependent and -independent mechanisms. Int J Cancer. 2005 Oct 10;116(6):894-902

Shyu RY, Chang SC, Yu JC, Hsu SJ, Chou JM, Lee MS, Jiang SY. Expression and regulation of retinoid-inducible gene 1 (RIG1) in breast cancer. Anticancer Res. 2005 May-Jun;25(3c):2453-60

Sturniolo MT, Chandraratna RA, Eckert RL. A novel transglutaminase activator forms a complex with type 1 transglutaminase. Oncogene. 2005 Apr 21;24(18):2963-72

Jans R, Sturniolo MT, Eckert RL. Localization of the TIG3 transglutaminase interaction domain and demonstration that the amino-terminal region is required for TIG3 function as a keratinocyte differentiation regulator. J Invest Dermatol. 2008 Mar;128(3):517-29

Tsai FM, Shyu RY, Lin SC, Wu CC, Jiang SY. Induction of apoptosis by the retinoid inducible growth regulator RIG1 depends on the NC motif in HtTA cervical cancer cells. BMC Cell Biol. 2009 Feb 26;10:15

Scharadin TM, Jiang H, Jans R, Rorke EA, Eckert RL. TIG3 tumor suppressor-dependent organelle redistribution and apoptosis in skin cancer cells. PLoS One. 2011;6(8):e23230

This article should be referenced as such:

Scharadin T, Eckert RL. RARRES3 (retinoic acid receptor responder (tazarotene induced) 3). Atlas Genet Cytogenet Oncol Haematol. 2012; 16(6):417-419.