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Gene Section
Review

TRO (trophinin)

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Abstract

Review on TRO, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: MAGE-d3, MAGED3

HGNC (Hugo): TRO

Location: Xp11.21

DNA/RNA

Description

TRO locates on X chromosome Xp11.21-22 (Pack et al., 1997). It contains 14 exons spanning 10,8 kb of genomic DNA (Aoyama et al., 2005).

Transcription

Although TRO produces a transcript with an open reading frame encoding a 138-kDa protein, previous studies did not detect this protein in vivo and in vitro (Nadano et al., 2002).
Instead, TRO produces two distinct proteins, magphinin (MAGE D3) and trophinin (Aoyama et al., 2008; Aoyama et al., 2005; Saburi et al., 2001). Translation for magphinin starts at AUG codon in exon 2, whereas translation for TRO starts at AUG codon in exon
12. Entire trophinin protein is encoded by exon 12. There are no sequence overlaps between magphinin and trophinin proteins (figure 2).

Pseudogene

None.

Protein

Description

Human trophinin is a 69 kDa protein composed of 749 amino acid residues.
Trophinin protein contains many decapeptide repeats (figure 3). Although trophinin is not a typical membrane protein and does not contain clear membrane spanning domain, experimental data indicated that trophinin is transmembrane protein. N-terminal region of trophinin is in the cytoplasm, and other region composed of decapeptide repeats is extracellular.
Trophinin was identified by functional cloning as the molecule potentially mediating the initial adhesion of the human embryo to the uterine epithelia between trophoblastic and endometrial cells (Fukuda et al., 1995; Nakayama et al., 2003; Sugihara et al., 2007; Suzuki et al., 1998; Tamura et al., 2011).

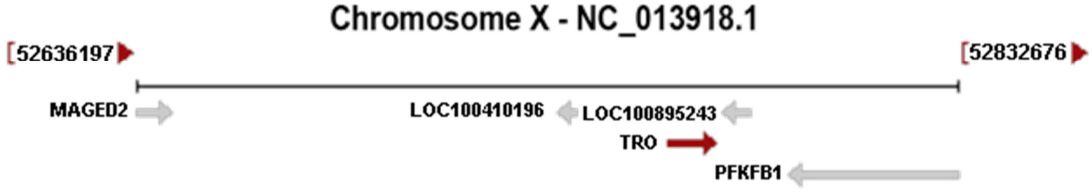

Figure 1. Genomic organization of TRO.

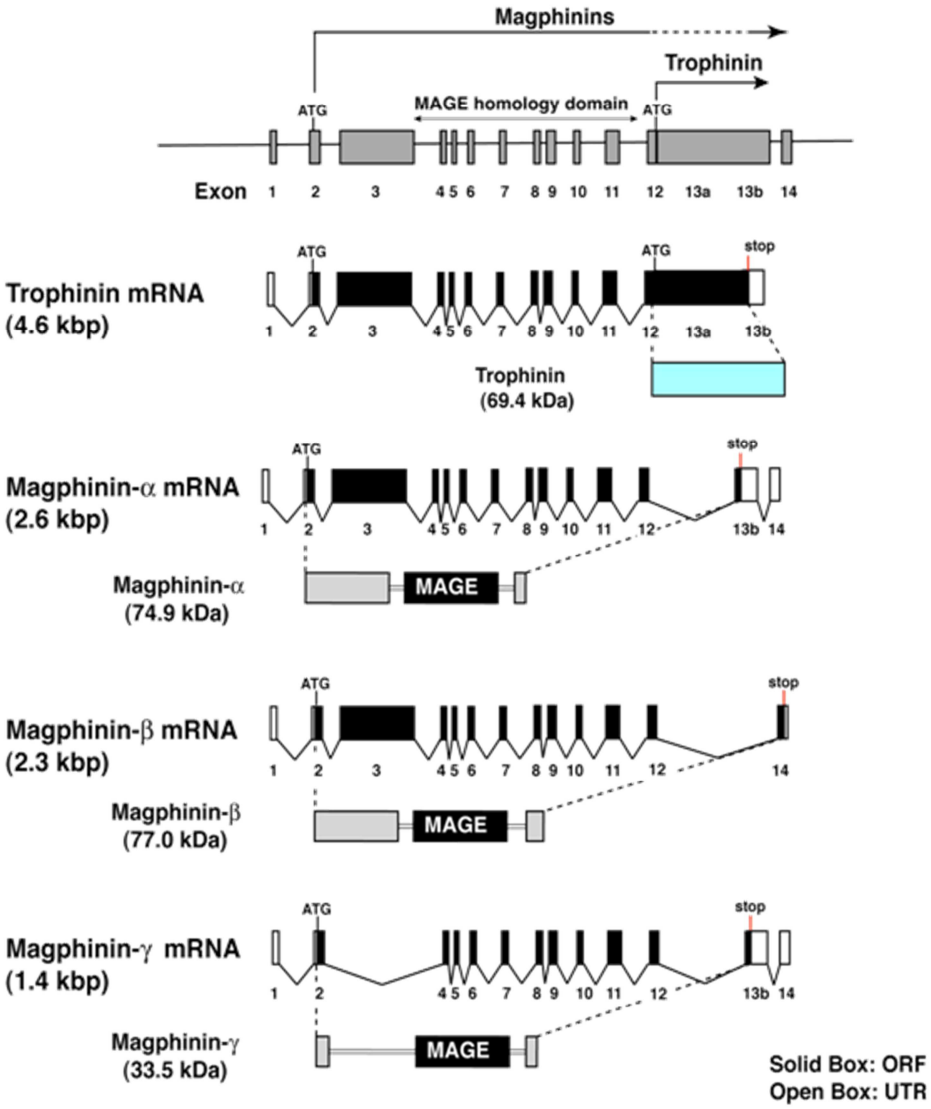

Figure 2. TRO gene structure, trophinin/magphinin transcripts and proteins. Diagram shows exon, introns of the human TRO. Predicted alternatively spliced mRNAs and polypeptides of human magphini and trophinin are based on the EST database and previous study of mouse Tro (Aoyama et al., 2008; Saburi et al., 2001). Exons are shown by shaded boxes, open reading frames (ORFs) are shown by solid boxes, and untranslated regions (UTRs) are represented by open boxes. Human magphinin proteins do not share peptide sequence with trophinin protein (blue). The predicted molecular sizes of human trophinin, magphinin-α, -β, and -γ are 69,4, 74,9, 77,0 and 33,5 kDa, respectively.

Trophinin associates with two cytoplasmic proteins bystin and tastin, of which complex functions as cell adhesion machinery through trophinin-trophinin binding between trophinin-expressing cells. Trophinin, bystin and tastin also function as molecular switch in signal transduction. Thus in trophoblastic cells trophinin-medited cell adhesion promotes cell growth and invasion (Sugihara et al., 2007), whereas in endometrial epithelial cells trophinin-mediated cell adhesion triggers apoptosis to accept invading embryo (Tamura et al., 2011).

Expression

TRO expressed strongly in trophectoderm cells and endometrial epithelial cells during embryo implantation (Fukuda et al., 1995; Nakayama et al., 2003; Suzuki et al., 1999). In early pregnancy human placenta (6 weeks), TRO transcripts and protein were found in syncytiotrophoblast in the chorionic villi, and in endometrial decidual cells at the utero placental interface. Trophinin disappears from placenta in later stage of pregnancy (more than 10 weeks), trophinin disappears from human placenta (Suzuki et al., 1999).

In the pregnant mouse uterus, trophinin transcripts are expressed during the time coinciding with those of blastocyst implantation (Suzuki et al., 2000).

In addition, TRO is strongly expressed in post mitotic neurons. In adult rat brain, trophinin is expressed in the subventricular zone, one of the region where active neurogenesis occurs (Ma et al., 2006).

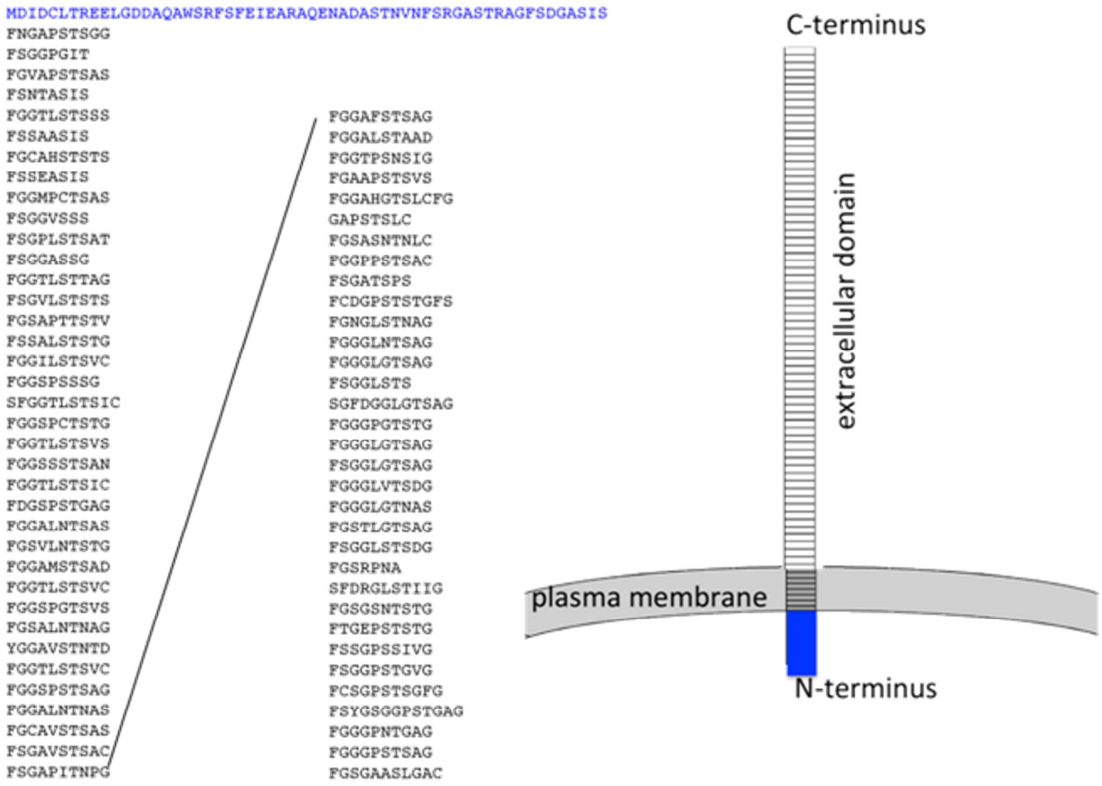

Figure 3. Structure of human trophinin protein. Left: peptide sequence of human trophinin. Cytoplasmic domain (blue) including N-terminus is followed by decapeptide repeats (black), which conform transmembrane domain and extracellular domain including C-terminus. Decapeptide repeats are thought to provide basis for cell adhesion machinery by hemophilic trophinin-trophinin binding. Right: proposed topology of trophinin protein, with decapeptide repeats as outer cellular and N-terminal region in the cytoplasm.

Trophinin is expressed in brain and mature sperm in testis. Low levels TRO expression is detected in a variety of tissues, including liver, kidney, stomach, muscle and skin.

Trophinin is expressed in testicular cancer (Hatakeyama et al., 2004), colon cancer (Harada et al., 2007), lung cancer (Chen et al., 2007).

Localisation

Trophinin protein was found in the pinopodes, unique structure found in endometrial epithelial cells at embryo implantation site, which was mimicked by primary culture of human endometrial epithelial cells in medium containing human chorionic gonadotropin (hCG) (Sugihara et al., 2008). In cultured cells, trophinin was found in the nuclear membranes and cytoplasm (Aoyama et al., 2005).

In both human and mouse, trophinin protein was found in the tail of matured sperm cells.

Function

Trophinin function in human embryo implantation: Trophinin expressed on an apical cell membranes of trophectoderm cells of blastocyst and endometrial epithelial cells mediates cell adhesion between these two cell types through hemophilic trophinin-trophinin binding (Fukuda et al., 1995). The signal of trophinin-mediated cell adhesion is transmitted to the cytoplasm, leading into trophectoderm cell activation for proliferation and invasion (Fukuda and Sugihara, 2007; Fukuda and Sugihara, 2008; Fukuda and Sugihara, 2012; Sugihara et al., 2007). Thus trophinin functions as a molecular switch in signal transduction. The mechanism underlying this trophinin-ligation triggered cell activation involves receptor tyrosine kinase ErbB4 and bystin as shown in figure 4. In endometrial epithelial cells, trophinin-mediated cell adhesion triggered signal transduction through PKC-γ, leading into apoptosis to accept invading embryo (Tamura et al., 2011). In ectopic tubal pregnancies, high levels of trophinin was found in both trophoblasts and tubal epithelia. Trophinin expression in maternal cells was particularly high in the area adjacent to the trophoblasts, whereas trophinin was barely detectable in intact fallopian tubes from women with in utero pregnancies or without pregnancies. The human chorionic gonadotrophin (hCG), trophinin expression was enhanced in epithelial cells. As both beta-subunit of hCG and trophinin genes have diverged in mammals, the study suggests a unique role of hCG and trophinin in human embryo implantation (Nakayama et al., 2003).

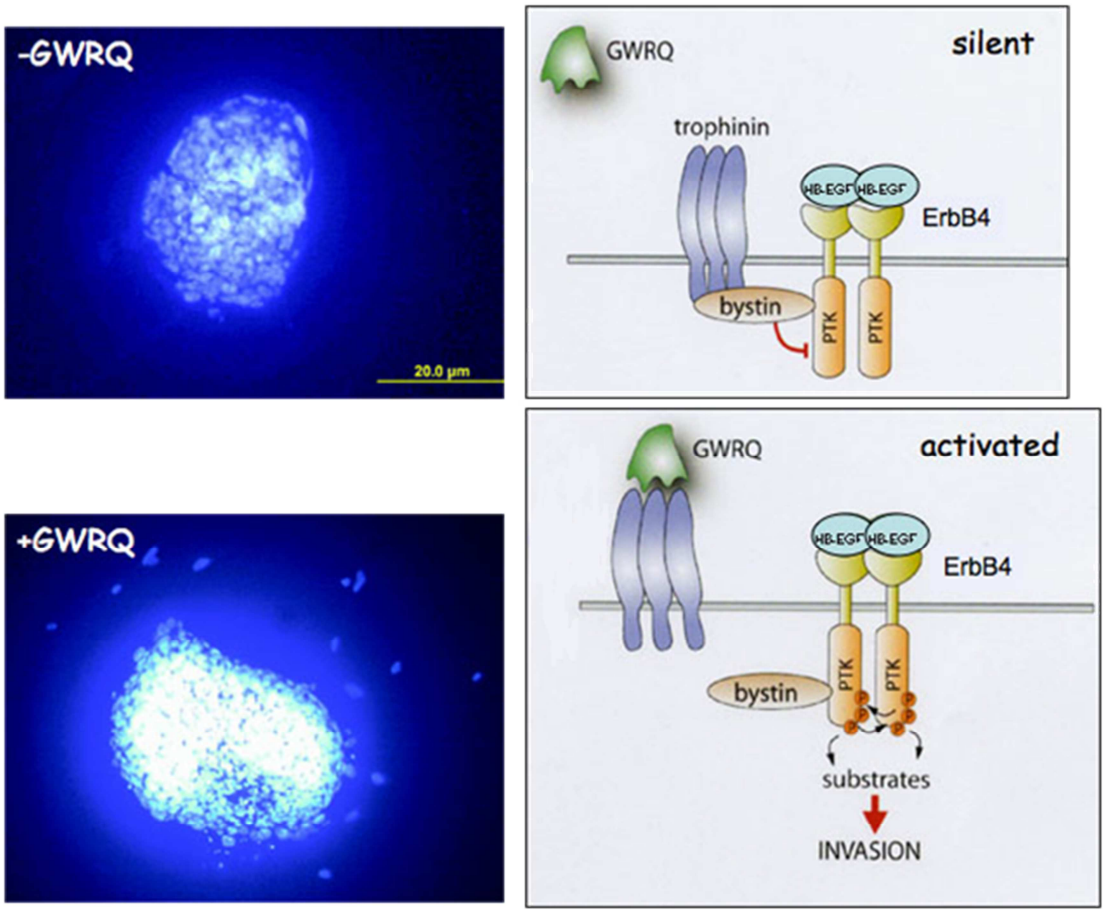

Figure 4. Molecular switch by trophinin in trophectoderm cells of human embryo implantation. Monkey blastocyst cultured in vitro was activated by GWRQ peptide, that mimics trophinin-mediated cell adhesion through the mechanism of ErbB4 receptor tyrosine kinase (Sugihara et al., 2007).

Tro gene knock-out mouse did not show infertility (Nadano et al., 2002).

This evidence in mouse, and induction of TRO expression by hCG (Nakayama et al., 2003; Sugihara et al., 2008), and significant genetic diversion CGβ between non-human primate and human (Maston and Ruvolo, 2002) suggest that function of trophinin in embryo implantation is unique to humans.

Trophinin function in sperm motility: Trophinin suppresses sperm tail motility in human and mouse, which can be activated by trophinin-binding peptide (Hatakeyama et al., 2008; Park et al., 2012).

Trophinin function in neuronal cells: In adult rat brain, trophinin is expressed in the subventricular zone together with bystin, implicated to active neurogenesis in this region (Ma et al., 2006).

Homology

None.

Mutations

Note

No mutation of TRO in human is known.

Implicated in

Various cancers

Note

Trophinin is overexpressed in some human cancers including colon cancer (Harada et al., 2007) and testicular cancer (Hatakeyama et al., 2004), which coincides with hCG. In these cancers, trophinin expression correlates to invasiveness. Correlation of trophinin to cancer invasiveness were reported in lung cancer (Chen et al., 2007) and bladder carcinoma cells (Chang et al., 2009). On the other hand, trophinin is negatively correlated to the malignancy in ovarian cancer (Baba et al., 2007; Fukuda et al., 2008).

References

Fukuda MN, Sato T, Nakayama J, Klier G, Mikami M, Aoki D, Nozawa S. Trophinin and tastin, a novel cell adhesion molecule complex with potential involvement in embryo implantation. Genes Dev. 1995 May 15;9(10):1199-210

Pack SD, Tanigami A, Ledbetter DH, Sato T, Fukuda MN. Assignment of trophoblast/endometrial epithelium cell adhesion molecule trophinin gene TRO to human

chromosome bands Xp11.22-->p11.21 by in situ hybridization. Cytogenet Cell Genet. 1997;79(1-2):123-4

Suzuki N, Zara J, Sato T, Ong E, Bakhiet N, Oshima RG, Watson KL, Fukuda MN. A cytoplasmic protein, bystin, interacts with trophinin, tastin, and cytokeratin and may be involved in trophinin-mediated cell adhesion between trophoblast and endometrial epithelial cells. Proc Natl Acad Sci U S A. 1998 Apr 28;95(9):5027-32

Suzuki N, Nakayama J, Shih IM, Aoki D, Nozawa S, Fukuda MN. Expression of trophinin, tastin, and bystin by trophoblast and endometrial cells in human placenta. Biol Reprod. 1999 Mar;60(3):621-7

Suzuki N, Nadano D, Paria BC, Kupriyanov S, Sugihara K, Fukuda MN. Trophinin expression in the mouse uterus coincides with implantation and is hormonally regulated but not induced by implanting blastocysts. Endocrinology. 2000 Nov;141(11):4247-54

Saburi S, Nadano D, Akama TO, Hirama K, Yamanouchi K, Naito K, Tojo H, Tachi C, Fukuda MN. The trophinin gene encodes a novel group of MAGE proteins, magphinins, and regulates cell proliferation during gametogenesis in the mouse. J Biol Chem. 2001 Dec 28;276(52):49378-89

Maston GA, Ruvolo M. Chorionic gonadotropin has a recent origin within primates and an evolutionary history of selection. Mol Biol Evol. 2002 Mar;19(3):320-35

Nadano D, Sugihara K, Paria BC, Saburi S, Copeland NG, Gilbert DJ, Jenkins NA, Nakayama J, Fukuda MN. Significant differences between mouse and human trophinins are revealed by their expression patterns and targeted disruption of mouse trophinin gene. Biol Reprod. 2002 Feb;66(2):313-21

Nakayama J, Aoki D, Suga T, Akama TO, Ishizone S, Yamaguchi H, Imakawa K, Nadano D, Fazleabas AT, Katsuyama T, Nozawa S, Fukuda MN. Implantation-dependent expression of trophinin by maternal fallopian tube epithelia during tubal pregnancies: possible role of human chorionic gonadotrophin on ectopic pregnancy. Am J Pathol. 2003 Dec;163(6):2211-9

Hatakeyama S, Ohyama C, Minagawa S, Inoue T, Kakinuma H, Kyan A, Arai Y, Suga T, Nakayama J, Kato T, Habuchi T, Fukuda MN. Functional correlation of trophinin expression with the malignancy of testicular germ cell tumor. Cancer Res. 2004 Jun 15;64(12):4257-62

Aoyama J, Nakayama Y, Sugiyama D, Saburi S, Nadano D, Fukuda MN, Yamaguchi N. Apical cell adhesion molecule, trophinin, localizes to the nuclear envelope. FEBS Lett. 2005 Nov 21;579(28):6326-32

Ma L, Yin M, Wu X, Wu C, Yang S, Sheng J, Ni H, Fukuda MN, Zhou J. Expression of trophinin and bystin identifies distinct cell types in the germinal zones of adult rat brain. Eur J Neurosci. 2006 May;23(9):2265-76

Baba T, Mori S, Matsumura N, Kariya M, Murphy SK, Kondoh E, Kusakari T, Kuroda H, Mandai M, Higuchi T, Takakura K, Fukuda MN, Fujii S. Trophinin is a potent prognostic marker of ovarian cancer involved in platinum sensitivity. Biochem Biophys Res Commun. 2007 Aug 24;360(2):363-9

Chen KY, Lee YC, Lai JM, Chang YL, Lee YC, Yu CJ, Huang CY, Yang PC. Identification of trophinin as an enhancer for cell invasion and a prognostic factor for early stage lung cancer. Eur J Cancer. 2007 Mar;43(4):782-90

Fukuda MN, Sugihara K. Signal transduction in human embryo implantation. Cell Cycle. 2007 May 15;6(10):1153-6

Harada O, Suga T, Suzuki T, Nakamoto K, Kobayashi M, Nomiyama T, Nadano D, Ohyama C, Fukuda MN, Nakayama J. The role of trophinin, an adhesion molecule unique to human trophoblasts, in progression of colorectal cancer. Int J Cancer. 2007 Sep 1;121(5):1072-8

Sugihara K, Sugiyama D, Byrne J, Wolf DP, Lowitz KP, Kobayashi Y, Kabir-Salmani M, Nadano D, Aoki D, Nozawa S, Nakayama J, Mustelin T, Ruoslahti E, Yamaguchi N, Fukuda MN. Trophoblast cell activation by trophinin ligation is implicated in human embryo implantation. Proc Natl Acad Sci U S A. 2007 Mar 6;104(10):3799-804

Aoyama J, Akazawa Y, Kasahara K, Higashiyama Y, Kikuchi I, Fukumoto Y, Saburi S, Nakayama Y, Fukuda MN, Yamaguchi N. Nuclear localization of magphinins, alternative splicing products of the human trophinin gene. J Cell Biochem. 2008 Feb 15;103(3):765-77

Fukuda MN, Sugihara K. An integrated view of L-selectin and trophinin function in human embryo implantation. J Obstet Gynaecol Res. 2008 Apr;34(2):129-36

Fukuda MN, Sugihara K, Nakayama J. Trophinin: what embryo implantation teaches us about human cancer. Cancer Biol Ther. 2008 Aug;7(8):1165

Hatakeyama S, Sugihara K, Lee SH, Nadano D, Nakayama J, Ohyama C, Fukuda MN. Enhancement of human sperm motility by trophinin binding peptide. J Urol. 2008 Aug;180(2):767-71

Sugihara K, Kabir-Salmani M, Byrne J, Wolf DP, Lessey B, Iwashita M, Aoki D, Nakayama J, Fukuda MN. Induction of trophinin in human endometrial surface epithelia by CGbeta and IL-1beta. FEBS Lett. 2008 Jan 23;582(2):197-202

Chang XZ, Yu J, Zhang XH, Yin J, Wang T, Cao XC. Enhanced expression of trophinin promotes invasive and metastatic potential of human gallbladder cancer cells. J Cancer Res Clin Oncol. 2009 Apr;135(4):581-90

Tamura N, Sugihara K, Akama TO, Fukuda MN. Trophinin-mediated cell adhesion induces apoptosis of human endometrial epithelial cells through PKC-δ. Cell Cycle. 2011 Jan 1;10(1):135-43

Fukuda MN, Sugihara K. Trophinin in cell adhesion and signal transduction. Front Biosci (Elite Ed). 2012 Jan 1;4:342-50

Park SK, Yoon J, Wang L, Shibata TK, Motamedchaboki K, Shim KJ, Chang MS, Lee SH, Tamura N, Hatakeyama S, Nadano D, Sugihara K, Fukuda MN. Enhancement of mouse sperm motility by trophinin-binding peptide. Reprod Biol Endocrinol. 2012 Nov 29;10:101

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