

Gene Section

Review

SDCBP (syndecan binding protein (syntenin))

Rosaria Gangemi, Ulrich Pfeffer, Silvano Ferrini

Lab of Immunotherapy and Functional Genomics Istituto Nazionale per la Ricerca sul Cancro, 16132 Genova, Italy (RG, UP, SF)

Published in Atlas Database: October 2012

Online updated version : <http://AtlasGeneticsOncology.org/Genes/SDCBPID44377ch8q12.html>
DOI: 10.4267/2042/48864

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.
© 2013 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Identity

Other names: MDA-9, ST1, SYCL, TACIP18

HGNC (Hugo): SDCBP

Location: 8q12.1

Local order: The human SDCBP gene maps on 8q12 between the NSMAF (neutral sphingomyelinase activation associated factor) and the CYP7A1 (cytochrome P450, family 7, subfamily A, polypeptide 1) loci, which are both in the opposite orientation.

Note

No translocations reported.

DNA/RNA

Description

The SDCBP gene is comprised of 9 exons, spanning 2,96 kb on chromosome 8q12.

The SDCBP promoter region has not been functionally explored, although two studies (Lin et al., 1998; Stier et al., 2000) describe SDCBP as an interferon-gamma and TNF-alpha inducible gene. Among predicted transcription factor binding sites upstream the transcription start site of SDCBP there are: Nf-KappaB, Nf-KappaB1 and p53.

Transcription

Five alternatively spliced transcript variants of SDCBP, each comprising 9 exons, have been described.

Protein

Description

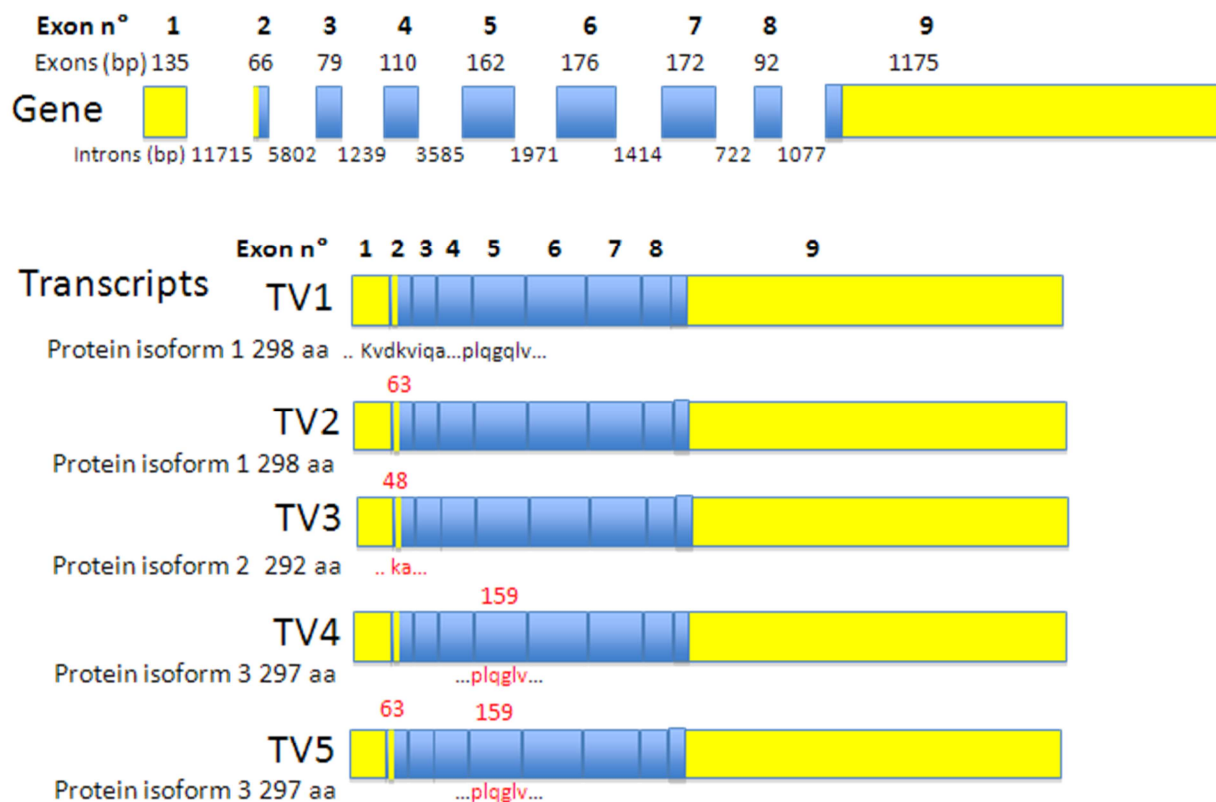
SDCBP gene codes for a syntenin protein of 298 amino acid residues with a predicted molecular mass of 33 kDa (Lin et al., 1998; Grootjans et al., 1997). Three isoforms are produced by alternative splicing: isoform 1 (NP_001007068.1) which represents the full-length protein of 298 aa; isoform 2 (NP_001007069) of 292 aa missing residues 12-17; isoform 3 (NP_001007070) of 297 aa missing residue 81.

Syntenin is a scaffolding protein, endowed with several biological activities and involved in cancer metastases development (reviewed in Das et al., 2012a). The molecule has four domains: an N-terminal domain (aa 1-113) with no homology to known structural motifs, two PDZ domains (PDZ-1 aa 114-193 and PDZ-2 aa 198-273) and a COOH-terminal domain. The crystal structure of the two PDZ domains showed independent interaction of each domain with protein targets (Cierpicki et al., 2005; Kang et al., 2004).

Postranslational modifications: syntenin can be phosphorylated on tyrosine (Sulka et al., 2009) and serine residues (Rajesh et al., 2011).

Expression

SDCBP is expressed in fetal kidney, liver, lung and brain. In adult high expression is present in heart and placenta (Lin et al., 1998; Zimmermann et al., 2001).



SDCBP gene organization, mRNA and encoded proteins. The SDCBP gene is comprised of 9 exons and results in 5 alternatively spliced transcript variants (TV), which encode for three different protein isoforms (additional transcripts variants were also reported). Coding exons are in blue and UTRs in yellow. Transcript variants 1 and 2 differ only in their 5' UTR regions and encode for the same full-length protein, named isoform 1. Transcript variant 3 derives from the usage of an alternative in frame splice-site in the 5' coding region (exon 1) and encodes for the protein isoform 2, lacking 6 residues. Transcript variant 4 uses an alternative splice site in exon 5 resulting in a protein isoform lacking one residue (isoform 3). Transcript variant 5 differs from variant 4 in the 5' UTR and encodes for the same protein isoform 3. Protein isoform 2 and 3 partial aa sequences that differ from isoform 1 are in red characters.

It is also expressed in several human tumor cell lines. Several types of tumors express high levels of SDCBP such as gastric, colon and breast carcinomas (Koo et al., 2002), cutaneous (Helmke et al., 2004) and uveal melanoma (Gangemi et al., 2012).

Localisation

SDCBP protein is localized to adherens junctions, focal adhesion plaques, inner side of the cell membrane, cytoplasm, endoplasmic reticulum, cytoskeleton (Zimmermann et al., 2001), nucleus (Gangemi et al., 2012) and melanosomes (Basrur et al., 2003). It is also present in cell-released exosomes (Baietti et al., 2012).

Function

SDCBP was identified as melanoma differentiation-associated gene (MDA)-9 (Lin et al., 1998). The same gene was independently cloned and named syntenin, by yeast two hybrid screening. Syntenin interacts through its PDZ domains with the heparan-sulfates syndecans, which are involved in molecular recognition, signaling, and cell trafficking (Grootjans et al., 1997). Through its binding with syndecans and PIP2, syntenin mediates syndecan recycling through endosomal compartments (Zimmermann et al., 2002).

This process modulates the surface availability of growth factor receptors such as FGFR, which follows syndecan in the recycling pathway (Zimmermann et al., 2005). Syntenin binds the C-terminal domain of the pro-transforming growth factor α (proTGF α) (Fernández-Larrea et al., 1999) and to the Delta1 ligand of Notch (Estrach et al., 2007), tethering them to the cell surface.

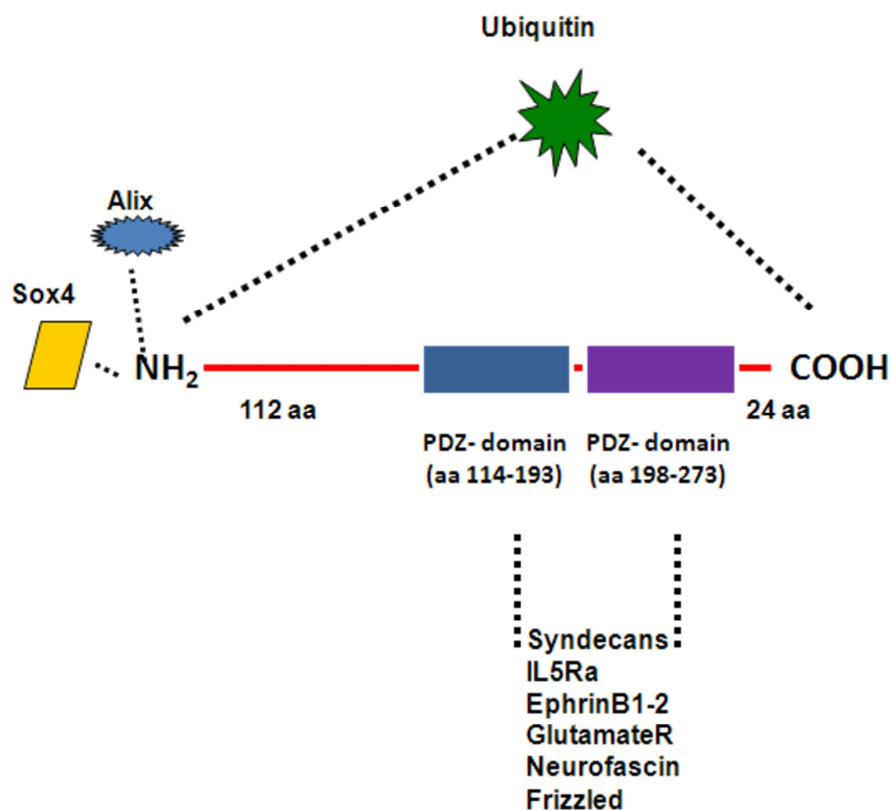
In addition, syntenin directly interacts with the C-terminal of Frizzled 7 and supports non-canonical Wnt signaling (Wawrzak et al., 2009).

Syntenin binds to the cytoplasmic tail of the tetraspanin CD63 at the plasma membrane and is therefore part of the tetraspanin-enriched microdomains (Latysheva et al., 2006).

The over-expression of syntenin can limit internalization of CD63, suggesting a role for syntenin as a regulator of endocytosis.

Syntenin is involved in the establishment and maintenance of synaptic structures through its interaction with several adhesion molecules, such as neurofascin (Koroll et al., 2001).

Presynaptic development also depends upon the interaction of the syntenin PDZ domains with ephrin-B1 and ephrin-B2 (McClelland et al., 2009).



Syntenin protein-protein interactions. Syntenin is an adaptor protein, which interacts with multiple proteins and has several intracellular functions.

SDCBP participates in the formation and maturation of synapses and colocalizes with Glutamate receptors at growth cones (Hirbec et al., 2005). Outgrowth of developing axon is also regulated by syntenin, which provides a scaffold for the serine/threonine kinase Unc51.1 and for Rab5 GTPase (Tomoda et al., 2004).

Syntenin participates in B cell development and differentiation by interacting with interleukin-5 (IL-5) receptor α and the transcription factor Sox4 and mediates IL-5-induced Sox4 activation (Geijsen et al., 2001). Proteosomal degradation of Sox4 is prevented by the binding of its C-terminal domain with SDCBP, which contributes to its localization into the nucleus (Beekman et al., 2012).

Syntenin mediates the generation of functional asymmetry in T cells during the cellular response to polarized extracellular cues, through the generation of polarized actin structures (Sala-Valdés et al., 2012).

Syntenin interacts with Ubiquitin through its C- and N-terminal regions and facilitates the recruitment of ubiquitinated proteins to its transmembrane partners. The process is facilitated by syntenin dimerization and is inhibited by phosphorylation of its serin in the N-terminal domain mediated by Ulk1 (Rajesh et al., 2011).

Syntenin has a key role in exosome formation through the binding of syndecan 1, syndecan 2, syndecan 3, syndecan 4 with the PDZ domains and ALIX with the N-terminal domain (Baietti et al., 2012).

Homology

The SDCBP gene is conserved in chimpanzee, Rhesus monkey, dog, cow, mouse, rat, chicken, zebrafish, and mosquito (NCBI).

Paralog: SDCBP2.

SDCBP is highly related to SDCBP2 at the amino acid level (70% over the PDZ domains) and in the domains organization (Koroll et al., 2001).

Mutations

Note

Not yet described. Genetic polymorphisms of SDCBP (561 SNPs) have been reported (NCBI) but their relationship to disease is unknown.

Implicated in

Cutaneous melanoma

Note

SDCBP gene was identified as an interferon-inducible gene in melanoma cells (Lin et al., 1998). A subtractive library approach of candidate metastasis genes identified the syntenin gene, which was overexpressed in cutaneous melanoma specimens relative to melanocytic nevi (Helmke et al., 2004). Altering syntenin expression by gene transduction modulates the metastatic ability of human melanoma cells (Boukerche

et al., 2005). Syntenin over-expression increased phosphorylation of focal adhesion kinase, c-Jun-NH2-kinase, p38, and nuclear factor-kappaB (NF-kappaB) in human melanoma cells. As a consequence tumor cell growth and motility are enhanced. The induction of membrane-type matrix metalloproteinase (MMP)-1 and MMP-2 promotes extracellular matrix invasion (Boukerche et al., 2007). Syntenin binds c-Src and mediates the formation of an active FAK/c-Src complex, increasing melanoma cell invasive properties (Boukerche et al., 2008). In addition, src kinase activation is required for syntenin-mediated activation of NF-kappaB (Boukerche et al., 2010). Further studies indicated that syntenin acts as a molecular adaptor linking PKCalpha and FAK activation during human breast cancer and melanoma cell adhesion to fibronectin (Hwangbo et al., 2010).

The Raf kinase inhibitor RKIP, is downregulated in metastatic melanoma cells. The study of melanoma arrays and cell lines showed an inverse relationship between syntenin and RKIP expression during melanoma progression. Syntenin transcriptionally downregulated RKIP and also physically interacted with RKIP protein. Ectopic RKIP expression in melanoma cells inhibited syntenin signaling, cell invasion and growth and in vivo dissemination of melanoma cells. Therefore RKIP acts as an inhibitor of syntenin-dependent melanoma metastasis (Das et al., 2012b).

Disease

Metastatic melanoma.

Uveal melanoma

Note

Uveal melanoma is a rare tumor of the eye, distinct from cutaneous melanoma on the basis of genetic alterations and clinical behavior. High expression of SDCBP gene correlated with metastatic progression in three gene expression profile datasets of primary uveal melanomas. High expression of syntenin protein in primary tumors was also related to metastatic recurrence. Syntenin was also highly expressed in liver metastases from patients and from xenografted mice. Silencing of syntenin inhibited uveal melanoma cell migration and hepatocyte growth factor (HGF)-triggered invasion, activation of FAK, AKT and Src. Conversely syntenin overexpression mediated opposite effects (Gangemi et al., 2012).

Disease

Metastatic uveal melanoma.

Gastric and breast cancers

Note

The expression level of syntenin was related with invasive potential in human breast and gastric cancer cells in vitro. Syntenin gene was highly expressed in gastric cancer tissues. Syntenin overexpression in human gastric or breast cancer cells increased their

migration in vitro and induced pseudopodia formation on collagen I. Mutation studies suggested that the PDZ2 domain of syntenin is involved in the stimulatory effect on cell migration (Koo et al., 2002).

Colon cancer

Note

The proteoglycan syndecan-2 is involved in tumorigenicity of colon cancer cells. Syndecan-2-induced migration requires the EFYA motif in its C-terminal region as its deletion inhibited cell migration and interaction with syntenin. In addition, overexpression of syntenin in colon cancer cells enhanced their migratory capacity, while syntenin silencing had opposite effects. Syntenin interaction with syndecan-2 mediates Rac activation, and colon cancer cell migration (Lee et al., 2011).

HIV infection

Note

Syntenin is recruited to the plasma membrane during HIV-1 attachment and associates with CD4. Syntenin overexpression inhibits HIV-1 production and HIV-mediated cell fusion, while syntenin depletion increases HIV-1 entry, suggesting a regulatory role of syntenin in HIV-1 entry (Gordón-Alonso et al., 2012).

Disease

AIDS.

References

- Grootjans JJ, Zimmermann P, Reekmans G, Smets A, Degeest G, Dürr J, David G. Syntenin, a PDZ protein that binds syndecan cytoplasmic domains. *Proc Natl Acad Sci U S A*. 1997 Dec 9;94(25):13683-8
- Lin JJ, Jiang H, Fisher PB. Melanoma differentiation associated gene-9, mda-9, is a human gamma interferon responsive gene. *Gene*. 1998 Jan 30;207(2):105-10
- Fernández-Larrea J, Merlos-Suárez A, Ureña JM, Baselga J, Arribas J. A role for a PDZ protein in the early secretory pathway for the targeting of proTGF-alpha to the cell surface. *Mol Cell*. 1999 Apr;3(4):423-33
- Stier S, Totzke G, Grünewald E, Neuhaus T, Fronhoffs S, Sachinidis A, Vetter H, Schulze-Osthoff K, Ko Y. Identification of syntenin and other TNF-inducible genes in human umbilical arterial endothelial cells by suppression subtractive hybridization. *FEBS Lett*. 2000 Feb 11;467(2-3):299-304
- Geijsen N, Uings IJ, Pals C, Armstrong J, McKinnon M, Raaijmakers JA, Lammers JW, Koenderman L, Coffey PJ. Cytokine-specific transcriptional regulation through an IL-5Ralpha interacting protein. *Science*. 2001 Aug 10;293(5532):1136-8
- Koroll M, Rathjen FG, Volkmer H. The neural cell recognition molecule neurofascin interacts with syntenin-1 but not with syntenin-2, both of which reveal self-associating activity. *J Biol Chem*. 2001 Apr 6;276(14):10646-54
- Zimmermann P, Tomatis D, Rosas M, Grootjans J, Leenaerts I, Degeest G, Reekmans G, Coomans C, David G. Characterization of syntenin, a syndecan-binding PDZ protein, as a component of cell adhesion sites and microfilaments. *Mol Biol Cell*. 2001 Feb;12(2):339-50

- Koo TH, Lee JJ, Kim EM, Kim KW, Kim HD, Lee JH. Syntenin is overexpressed and promotes cell migration in metastatic human breast and gastric cancer cell lines. *Oncogene*. 2002 Jun 13;21(26):4080-8
- Zimmermann P, Meerschaert K, Reekmans G, Leenaerts I, Small JV, Vandekerckhove J, David G, Gettemans J. PIP(2)-PDZ domain binding controls the association of syntenin with the plasma membrane. *Mol Cell*. 2002 Jun;9(6):1215-25
- Basrur V, Yang F, Kushimoto T, Higashimoto Y, Yasumoto K, Valencia J, Muller J, Vieira WD, Watabe H, Shabanowitz J, Hearing VJ, Hunt DF, Appella E. Proteomic analysis of early melanosomes: identification of novel melanosomal proteins. *J Proteome Res*. 2003 Jan-Feb;2(1):69-79
- Helmke BM, Polychronidis M, Benner A, Thome M, Arribas J, Deichmann M. Melanoma metastasis is associated with enhanced expression of the syntenin gene. *Oncol Rep*. 2004 Aug;12(2):221-8
- Kang BS, Devedjiev Y, Derewenda U, Derewenda ZS. The PDZ2 domain of syntenin at ultra-high resolution: bridging the gap between macromolecular and small molecule crystallography. *J Mol Biol*. 2004 Apr 30;338(3):483-93
- Tomoda T, Kim JH, Zhan C, Hatten ME. Role of Unc51.1 and its binding partners in CNS axon outgrowth. *Genes Dev*. 2004 Mar 1;18(5):541-58
- Boukerche H, Su ZZ, Emdad L, Baril P, Balme B, Thomas L, Randolph A, Valerie K, Sarkar D, Fisher PB. mda-9/Syntenin: a positive regulator of melanoma metastasis. *Cancer Res*. 2005 Dec 1;65(23):10901-11
- Cierpicki T, Bushweller JH, Derewenda ZS. Probing the supramodular architecture of a multidomain protein: the structure of syntenin in solution. *Structure*. 2005 Feb;13(2):319-27
- Hirbec H, Martin S, Henley JM. Syntenin is involved in the developmental regulation of neuronal membrane architecture. *Mol Cell Neurosci*. 2005 Apr;28(4):737-46
- Zimmermann P, Zhang Z, Degeest G, Mortier E, Leenaerts I, Coomans C, Schulz J, N'Kuli F, Courtoy PJ, David G. Syndecan recycling [corrected] is controlled by syntenin-PIP2 interaction and Arf6. *Dev Cell*. 2005 Sep;9(3):377-88
- Latysheva N, Muratov G, Rajesh S, Padgett M, Hotchin NA, Overduin M, Berditchevski F. Syntenin-1 is a new component of tetraspanin-enriched microdomains: mechanisms and consequences of the interaction of syntenin-1 with CD63. *Mol Cell Biol*. 2006 Oct;26(20):7707-18
- Boukerche H, Su ZZ, Emdad L, Sarkar D, Fisher PB. mda-9/Syntenin regulates the metastatic phenotype in human melanoma cells by activating nuclear factor-kappaB. *Cancer Res*. 2007 Feb 15;67(4):1812-22
- Estrach S, Legg J, Watt FM. Syntenin mediates Delta1-induced cohesiveness of epidermal stem cells in culture. *J Cell Sci*. 2007 Aug 15;120(Pt 16):2944-52
- Boukerche H, Su ZZ, Prévot C, Sarkar D, Fisher PB. mda-9/Syntenin promotes metastasis in human melanoma cells by activating c-Src. *Proc Natl Acad Sci U S A*. 2008 Oct 14;105(41):15914-9
- McClelland AC, Sheffler-Collins SI, Kayser MS, Dalva MB. Ephrin-B1 and ephrin-B2 mediate EphB-dependent presynaptic development via syntenin-1. *Proc Natl Acad Sci U S A*. 2009 Dec 1;106(48):20487-92
- Sulka B, Lortat-Jacob H, Terreux R, Letourneur F, Rousselle P. Tyrosine dephosphorylation of the syndecan-1 PDZ binding domain regulates syntenin-1 recruitment. *J Biol Chem*. 2009 Apr 17;284(16):10659-71
- Wawrzak D, Luyten A, Lambaerts K, Zimmermann P. Frizzled-PDZ scaffold interactions in the control of Wnt signaling. *Adv Enzyme Regul*. 2009;49(1):98-106
- Boukerche H, Aissaoui H, Prévost C, Hirbec H, Das SK, Su ZZ, Sarkar D, Fisher PB. Src kinase activation is mandatory for MDA-9/syntenin-mediated activation of nuclear factor-kappaB. *Oncogene*. 2010 May 27;29(21):3054-66
- Hwangbo C, Kim J, Lee JJ, Lee JH. Activation of the integrin effector kinase focal adhesion kinase in cancer cells is regulated by crosstalk between protein kinase Calpha and the PDZ adapter protein mda-9/Syntenin. *Cancer Res*. 2010 Feb 15;70(4):1645-55
- Lee H, Kim Y, Choi Y, Choi S, Hong E, Oh ES. Syndecan-2 cytoplasmic domain regulates colon cancer cell migration via interaction with syntenin-1. *Biochem Biophys Res Commun*. 2011 May 27;409(1):148-53
- Rajesh S, Bago R, Odintsova E, Muratov G, Baldwin G, Sridhar P, Rajesh S, Overduin M, Berditchevski F. Binding to syntenin-1 protein defines a new mode of ubiquitin-based interactions regulated by phosphorylation. *J Biol Chem*. 2011 Nov 11;286(45):39606-14
- Baietti MF, Zhang Z, Mortier E, Melchior A, Degeest G, Geeraerts A, Ivarsson Y, Depoortere F, Coomans C, Vermeiren E, Zimmermann P, David G. Syndecan-syntenin-ALIX regulates the biogenesis of exosomes. *Nat Cell Biol*. 2012 Jun 3;14(7):677-85
- Beekman JM, Vervoort SJ, Dekkers F, van Vessem ME, Vendelbosch S, Brugulat-Panès A, van Loosdregt J, Braat AK, Coffey PJ. Syntenin-mediated regulation of Sox4 proteasomal degradation modulates transcriptional output. *Oncogene*. 2012 May 24;31(21):2668-79
- Das SK, Bhutia SK, Kegelman TP, Peachy L, Oyesanya RA, Dasgupta S, Sokhi UK, Azab B, Dash R, Quinn BA, Kim K, Barral PM, Su ZZ, Boukerche H, Sarkar D, Fisher PB. MDA-9/syntenin: a positive gatekeeper of melanoma metastasis. *Front Biosci*. 2012a Jan 1;17:1-15
- Das SK, Bhutia SK, Sokhi UK, Azab B, Su ZZ, Boukerche H, Anwar T, Moen EL, Chatterjee D, Pellicchia M, Sarkar D, Fisher PB. Raf kinase inhibitor RKIP inhibits MDA-9/syntenin-mediated metastasis in melanoma. *Cancer Res*. 2012b Dec 1;72(23):6217-26
- Gangemi R, Mirisola V, Barisione G, Fabbi M, Brizzolara A, Lanza F, Mosci C, Salvi S, Gualco M, Truini M, Angelini G, Boccardo S, Cilli M, Airolidi I, Queirolo P, Jager MJ, Daga A, Pfeffer U, Ferrini S. Mda-9/syntenin is expressed in uveal melanoma and correlates with metastatic progression. *PLoS One*. 2012;7(1):e29989
- Gordón-Alonso M, Rocha-Perugini V, Álvarez S, Moreno-Gonzalo O, Ursa A, López-Martín S, Izquierdo-Useros N, Martínez-Picado J, Muñoz-Fernández MÁ, Yáñez-Mó M, Sánchez-Madrid F. The PDZ-adaptor protein syntenin-1 regulates HIV-1 entry. *Mol Biol Cell*. 2012 Jun;23(12):2253-63
- Sala-Valdés M, Gordón-Alonso M, Tejera E, Ibáñez A, Cabrero JR, Ursa A, Mittelbrunn M, Lozano F, Sánchez-Madrid F, Yáñez-Mó M. Association of syntenin-1 with M-RIP polarizes Rac-1 activation during chemotaxis and immune interactions. *J Cell Sci*. 2012 Mar 1;125(Pt 5):1235-46

This article should be referenced as such:

Gangemi R, Pfeffer U, Ferrini S. SDCBP (syndecan binding protein (syntenin)). *Atlas Genet Cytogenet Oncol Haematol*. 2013; 17(4):240-244.
