①

Syntenin: a novel PDZ domain-containing scaffolding protein associated with human melanoma metastasis

Jian-bo Yang, James B. McCarthy

(*Department of Laboratory Medicine and Pathology and Comprehensive Cancer Center, University of Minnesota, Minneapolis, MN* 55455, *USA*)

Abstract: Syntenin is overexpressed in multiple human cancers and is newly recognized as a novel regulator in melanoma metastasis. It functions as a scaffolding protein, via its two PDZ domains interacting with multiple transmembrane and cytoplasmic partners to regulate many of the major signaling pathways involved in various cellular processes, such as cell surface receptor clustering, protein trafficking, cytoskeleton remodeling, and activation of transcription factor, and results in the increased abilities for tumor cell growth, adhesion, angiogenesis, invasion and metastasis. The present article attempts to review the structure and functions of syntenin by summarizing our current knowledge on the interacting partners and diverse signaling pathways related to syntenin, and highlight the importance of syntenin as a new potential therapeutic target for the aggressive human melanoma.

Key words: syntenin; PDZ domain; cell signaling; melanoma metastasis

[*J Cent South Univ (Med Sci)*, 2007,32(2):0204-09]

调控黑色素瘤转移的新信号蛋白：Syntenin

Jian-bo Yang, James B. McCarthy

(Department of Laboratory Medicine and Pathology and Comprehensive Cancer Center, University of Minnesota, Minneapolis, MN 55455, USA)

[**摘要**] Syntenin 蛋白在多种肿瘤中表达增强,最近被认为是一个新的黑色素瘤转移调节因子。作为一类支架信号蛋白,Syntenin 通过它的两个 PDZ 功能基团可与许多细胞膜受体胞内末端或细胞内的信号分子结合,调控多种重要的细胞生理过程和信号传导途径,包括细胞膜受体的聚集,细胞内蛋白质的转运,细胞骨架的重建,转录因子的激活,以增强肿瘤细胞的生长、黏附以及肿瘤的血管生成、侵袭和转移能力。本文简要综述了 syntenin 的结构和功能,相关的信号途径,及其在黑色素瘤研究领域的最新进展。

[**关键词**] syntenin; PDZ 功能基团; 信号传导; 黑色素瘤转移

[**中图分类号**] R739.5 [**文献标识码**] A [**文章编号**] 1672-7347(2007)02-0204-09

①**Date of reception** 2007-03-04

Biography Jian-bo Yang, Male, M.D, PhD., mainly engaged in the elucidating potential signal transduction mechanisms of extracellular matrix (ECM) components that control tumor cell growth, adhesion, and motility.

Corresponding Author Jian-bo Yang, E-mail: yangx142@umn.edu

Foundation items This work was supported by National Institutes of Health grants RO2CA82295

1 INTRODUCTION

Malignant melanoma is one of the most deadly aggressive human malignancies with 6 ~ 9 months survival median. A major reason is that the patients with advanced invasive melanomas are inevitably resistant to conventional therapeutic agents, including chemotherapy and radiation, thus, a significant research effort to understand the mechanism(s) underlying the progression of melanoma and develop novel therapies is critical[1-2].

In clinical and histopathological aspects, melanoma progression is well defined to discrete but overlapping four major steps including dysplastic nevus, radial growth phase (RGP), invasive vertical growth phase (VGP), and metastasis[3], however, the mechanisms involved in metastatic dissemination of melanoma are only beginning to be defined. The switch from a radial growth phase to a vertical growth phase is a key event[4]. The RGP primary melanoma do not show the capacity for rapid growth or metastasis, while in the VGP primary melanoma lesions, melanoma cells achieve serial invasive properties including increased adhesive, motility, proteolytic and angiogenic capacities that facilitate cells to infiltrate into the dermis and the subcutaneous tissue, giving rise to life threatening metastatic disease. Several oncogenes and tumor suppressors, such as BRAF, RAS, WNT5A, CDKN2A, MYC, Src, Akt, INK4alpha, PTEN, P53, etc., have been involved in these stages of tumor progression[5-6]. Alterations in the expression or function of adhesion molecules, including integrins, Mel-CAM/MUC18, CD44, ICAM-1, cadherins, and cell surface proteoglycans (PGs), are also associated with the progression of primary melanomas[7], implicating that governing and coordinating multi-signaling pathways in melanoma metastatic progression is particularly important.

Syntenin is a novel PDZ domain-containing protein, which is overexpressed in various human cancers and associated with melanoma metastasis[8-9]. The PDZ domain-containing proteins are the most common scaffolding proteins that play a central role in organizing diverse cell signaling assemblies. The scaffolding proteins via its PDZ domains recruit membrane receptors and cytoplasmic signaling proteins into functional complexes, thereby coordinating and guiding the flow of regulatory information, and allow fast and efficient signal transductions and membrane transport processes in responses to external stimuli[10]. In this review, we will summarize the structure and function of syntenin, as well as its interacting partners in diverse signaling pathways. The potential roles of syntenin in human melanoma metastasis will also be discussed.

2 DISCOVERY AND STRUCTURE OF SYNTENIN

Syntenin was originally described as melanoma differentiation associated gene-9 (mda-9)[8]. Treatment of metastatic human melanoma cells with the combination of IFN-β and the antileukemic compound mezerein (MEZ) causes an irreversible loss of proliferative ability and induction of terminal cell differentiation. This experimental protocol also results in profound changes in biochemical programs and gene expression[11], therefore, subtraction hybridization approach was used to define the molecular basis of these wide-ranging changes in the course of melanoma cell growth inhibition and terminal differentiation. The cDNA libraries were prepared from actively growing melanoma cells and melanoma cells treated with IFN-β + MEZ, and then subtraction was performed between these two temporally spaced libraries to display differential gene expressions. The mda-9/syntenin was one of the genes that were down regulated during terminal differentiation[9]. Subsequently, in a search for any genes associated with melanoma metastasis, Helmke, et al.[12] examined the differential gene expression profiles between primary cutaneous melanomas and melanoma metastases using subtractive suppression hybridization, and confirmed that mda-9/syntenin was an overexpressed gene in metastatic melanomas, suggesting a potential role of syntenin during tumor progression.

The message RNA of syntenin (2.4 kb) was widely and abundantly expressed in fetal tissues (kid-

ney, liver, lung and brain); in normal adult tissues, higher expression levels of syntenin were detected in heart and placenta, much lower expression levels were found in all other tissues, including brain, kidney, liver, lung, skeleton muscle and pancreas[13]. The physiological significance of unique expression pattern of syntenin in adult tissues need be further investigated. The cDNA of syntenin consists of 2 084 nucleotides, and encodes a protein of 298 amino acids. Two isoforms of syntenin, termed as syntenin-2α and syntenin-2β, were cloned by PCR from a fetal human brain cDNA library.

A noticeable structure feature of syntenin is the presence of a tandem two PDZ domains (PDZ-1 and PDZ-2) with an N-terminal domain and a C-terminal domain[14]. Syntenin-2α shares highly similar as syntenin and 70% identity over the PDZ domains. Syntenin-2 β, which lacks 85 amino acid residues at NH_2-terminal segment, is a shorter isoform of syntenin-2α[15]. Syntenin is highly conserved in mammalian. The deduced amino acid sequences of both mouse and rat syntenin are highly similar to human syntenin: The PDZ-1 and COOH-terminal domains are nearly completely identical, and PDZ-2 domains are 90% homologous to each other. The N-terminal domain of human syntenin is 81% and 77% identical to the mouse and rat domains, respectively[16].

The PDZ domains are structurally conserved motifs of about 80 to 90 amino acids that were initially found in the post synaptic density-95, disc-large, and zonulin-1 proteins but occur in a large variety of proteins. They represent one category of the most common modular protein-interaction domains in eukaryotic signal transduction systems. Similar to SH2 domains, PDZ domains might have evolved in response to the increased signaling needs of multi-cellular organisms since they are rare in non-metazoans, in contrast, multiple copies of PDZ domains are often present in the same protein in metazoans. Typically, the PDZ domains bind to target proteins via recognizing the specific C-terminal PDZ binding motifs that are usually 3 5-residues in length; on the basis of target peptides, PDZ domains are divided into 3 main classes: Class I PDZ domains recognize the motif (S/T-X-Φ-COOH), Class II motif (Φ-X-Φ-COOH) and Class III (X-X-C-COOH), where Φ is a hydrophobic residue and is the most critical for recognition. In adaptor proteins, one PDZ domain can interact with several targets, and a given PDZ binding motif can also adapt to several PDZ domains, with these properties, PDZ domains normally bind to many of receptors, channels and adhesion molecules. However, within a complex cellular environment, PDZ domains have been illustrated to be extremely selective and specific for recognition of target proteins by mutagenic studies[17-18]. Therefore, PDZ-domain proteins are critical for the organization and maintenance of large dynamic multi-protein signaling complexes.

3 SYNTENIN REGULATES MELANOMA METASTASIS

The molecular changes associated with the transition of melanoma cells from radial growth phase (RGP) to vertical growth phase (VGP, metastatic phenotype) are not yet well defined. Recent immunohistochemical studies support that syntenin expression was related to acquisition of an aggressive phenotype in the transition of melanoma cells.

Several pieces of evidence from Fisher PB lab showed that syntenin expression was significantly reduced in normal melanocytes FM516-SV, a nonmetastatic radial growth phase (RGP) primary melanoma cell line, WM35, and a weakly metastatic human melanoma cell line, M4Beu[11]. In contrast, expression was significantly enhanced in metastatic cells, including vertical growth phase (VGP) primary melanoma (WM278) and highly metastatic melanoma variants (T1P26, 7GP) as well as cell lines derived from patients with metastatic melanomas; immunoperoxidase staining also showed that VGP melanoma cells and metastatic melanoma cells stained strongly positive with anti-mda-9/syntenin antibody compared to cells from nevi and RGP lesions[18]. The similar results was obtained from Helmke's group, they analyzed syntenin

expression in 28 primary skin melanomas, 23 melanoma metastases and 17 acquired melanocytic nevi. The proportion of syntenin expressing tumor cells in melanoma metastases was higher when compared with non-metastasizing primary melanomas and acquired melaocytic nevi[13]. These data further supporting an association between mda-9/syntenin expression and melanoma progression.

For metastasis, the prerequisites of primary tumor cells are abilities to migrate and invade to surrounding tissue. Expression of syntenin seems to contribute melanoma cells for these capacities. Forced expression or inhibition of expression of syntenin can regulate invasiveness and motility of human melanoma cells. Increasing exogenous syntenin expression levels 2 ~ 3 folds in melanocytes or poorly metastatic parental human melanoma cell line M4Beu causes them significantly increased in migration/invasion up to approximately 4- and 8-fold; in contrast, reducing endogenous syntenin expression 3 folds by antisense in highly metastatic melanoma cell line T1P26, decreased migration/invasion by almost 85% relative to controls[18]. These findings consist with our recent results that knock-down syntenin expression using SiRAN in WM1341D melanoma cells (VGP) significantly inhibited them migration, invasion and anchorage-independent growth (Yang, et al., unpublished).

More strong evidence comes from in vivo melanoma metastasis experiment that confirmed a direct involvement of syntenin in the metastatic process. When M4Beu. cells were infected with Ad. syntenin/sense, the cells acquired an enhanced ability to spontaneously metastasize to the lungs after 3 weeks. Immunohistochemical staining confirmed positive mda-9/syntenin staining was distributed over the entire tumor lung nodules. In contrast, Ad. syntenin-/antisense-infected T1P26 cells displayed a significant decrease in the average number of metastatic surface tumor nodules per lung lobe. These results indicate that the expression of Syntenin protein is a key component of melanoma metastasis[18].

Syntenin expression regulating melanoma metastasis is involved in focal adhesion kinase activity, p38, c-JNK, NF-κB and MT1-MMP pathways. Over-expressed syntenin in melanoma cells also altered their morphology. The cells infected with Ad. syntenin/sense developed well-organized actin stress fiber network. In contrast, in T1P26-cells infected with Ad. syntenin/anti-sense decreased actin microfilament and focal adhesion formation, implicating altering cytoskeletal organization and cell shape by syntenin expression may be via focal adhesion kinase (FAK). FAK is a key component of integrin-mediated signaling pathways and is critical for regulating cell motility and invasion. Overexpression of syntenin displayed greater FAK phosphorylation in poorly metastatic M4Beu cell, and decreased expression of syntenin in T1P26 cells displayed a significant reduction in FAK phosphorylation[18]. Expression of syntenin correlating with FAK was further confirmed by a significant colocalization of syntenin with focal adhesion phospho-FAK protein in WM1341D melanoma cells (Figure 1A, 1B, and 1C). Activation of FAK by syntenin could up-regulate c-JNK and p38 activity, but not ERK and AKT activity (Yang, et al., unpublished). Recently Fisher PB group found that syntenin initiated a signaling cascade that activates nuclear factor-kappaB and MT1-MMP in human melanoma cells, so the hypothetical model of syntenin leading to enhanced tumor metastasis as following: tumor cells on interacting with the ECM, FAK is phosphorylated by mda-9/syntenin, which results in phosphorylation and activation of p38 MAPK. This results in degradation of IκB and movement of p65 from the cytoplasm where interaction with p50 results in binding to target genes (MT1-MMP), resulting in enhanced production of MT1-MMP, which interacts with TIMP-2 activating pro-MMP-2 to produce active MMP-2. This product then enhances cell motility, invasion, and cancer cell growth[19].

These observations highlight the importance of syntenin as a key component of melanoma metastasis providing a rational molecular target for potentially intervening in the metastatic process.

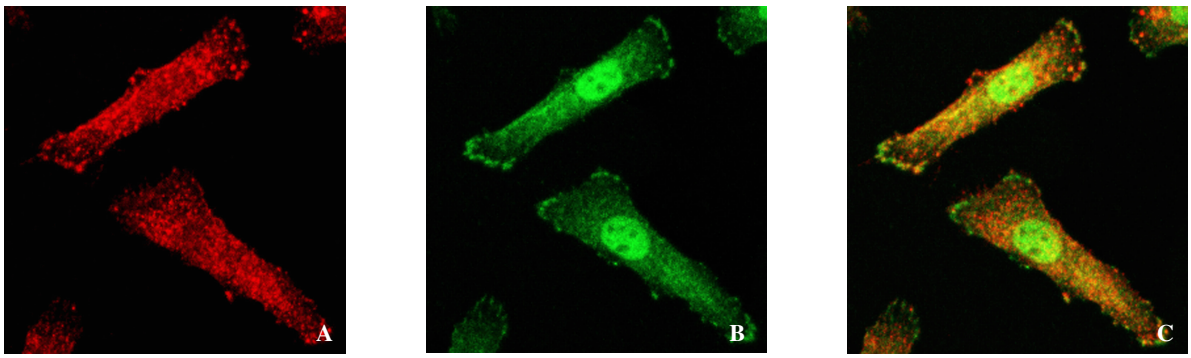

Fig. 1 Fluorescent confocal micrographs of the metastatic melanoma WM1341D cells show co-localization of focal adhesion phospho-FAK protein and syntenin A: Syntenin; B: Phospho-FAK; C: Merged

4 SYNTENIN ORGANIZES MULTIPLE SIGNALING COMPLEXES

Immunofluorescence microscopy localizes endogenous syntenin to cell adhesion sites, microfilaments, and the nucleus, suggesting a role for syntenin in the composition of adherens junctions and the regulation of plasma membrane dynamics, correct subcellular localization of receptors and imply a potential role for syntenin in nuclear processes. The studies have showed that the specific and flexible interacting partners allows syntenin to selectively bind to many cell surface membrane proteins, including class B ephrins, pro-transforming growth factor-α, PTP-η, phosphatidylinositol 4,5-biphosphate, neurofaschin, neurexin, schwannomin, interleukin-5 receptor α, lymphocyte receptor CD63, various glutamate receptor subtypes, and the syndecan family of heparan sulfate proteoglycans[14,18,20]. Below, we discuss some specific examples of syntenin regulating several tumor-associated proteins and tumor suppressor proteins.

4.1 SYNTENIN AND TUMOR-ASSOCIATED PROTEINS

4.1.1 Syntenin regulates syndcan recycling

The syndecans (syndecan1-4), a family of Type I transmembrane heparan sulfate proteoglycan (HSPG), function as co-receptors through their versatile heparan sulfate moieties attracting and concentrating various growth, scatter factors and adhesion molecules to their receptors; the heparan sulfate chains also bind to multiple matrix ligands, including fibronectin, vitronectin, laminins and the fibrillar collagens. As such, the syndecans are believed to be involved in the organization of the actin cytoskeleton and have important roles as cell surface receptors during cell-matrix interactions, signaling, and endocytosis trafficking[21-22].

In some human cancers, syndecans have been shown to regulate tumor cell proliferation, adhesion, motility, and serve as a prognostic marker for tumor progression and patient survival. Syndecan-1 is required for Wnt-1 induced tumorigenesis of the mouse mammary gland[23] and promotes the formation of metastases in mouse lung squamous carcinoma cells[24]. Enhanced syndecan-1 expression has also been observed in pancreatic, gastric[25], breast carcinomas[26] and melanoma (Yang, et al., unpublished); upregulation of syndecan-4 has been noted in hepatocellular carcinomas and malignant mesotheliomas[27] and such overexpression may correlate with increased tumor cell proliferation. Studies using Lewis lung cancer and mesothelioma cells have shown that syndecan-2 is upregulated in these cells compared to normal tissues[28], and, in colon carcinoma, syndecan-2 is often overexpressed by 2 to 5 fold and is required for both cell cycle progression and cell matrix interactions[23].

Syntenin was originally identified as a syndecan-binding protein in yeast two-hybrid screens by using the cytoplasmic domains of the syndecans as bait[14]. The structures of ectodomains of four known syndecans have not been evolutionary conserved; in contrast, the membrane proximal and the small cytoplasmic domains of the syndecans (C1 and C2, respectively), show extensive structural similarity and have been highly conserved during evolution, suggesting these moieties are essential for syndecan function. The PDZ domains of

syntenin react with the syndecans via the FYA C-terminal amino acid sequence, and syntenin deletion mutants suggests that the two PDZ domains together are required for the interaction with the syndecans, whereas the N-terminal region is dispensable[14]. Syntenin colocalizes with syndecans at the plasmamembrane and intracellular vesicles. Further studies show that the syntenin PDZ domain-PIP_2 interaction controls syndecan recycling back to the plasma membrane through endosomal compartments. Both PDZ domains of syntenin can bind to either syndecan or PIP_2, while, PIP_2 has higher affinity for PDZ1 than for PDZ2. The high levels of PIP_2 on the plasma membrean may completely replace the syndecans, liberating them from syntenin and allowing them return to the cell surface. Syndecans defective for PDZ interaction that cannot recycle via this pathway become trapped intracellularly in endosomes and perinuclear compartment, leading to rapid degradation by of the ER system. Importantly, multiple adhesion and signaling molecules that bind to the HS chains of the syndecans (e. g. FGF receptors and integrins) are likely to be trapped in these endosomes, which ultimately resulting in inhibiting cell spreading, adhesion, and motility due to imbalance of receptor densities at cell surfaces[13].

4.1.2 Syntenin and proTGF-α transport

Transforming growth factor alpha (TGFalpha), as a functional EGFR ligand, is widely expressed in malignant as well as normal cells and is involved in regulating cell growth and differentiation. Transmembrane molecule proTGF-α is a precursor of TGF-α that transduces a mitogenic signal to adjacent cells by juxtacrine fashion. Its ectodomain can also be shed from the cell surface to generate an autocrine or paracrine signal[29]. Early reports showed that proTGF-α expressed by certain malignant cells apparently induced a higher phosphorylation of EGFR than equivalent levels of TGF-α[30]. On human colon carcinoma cells, the interaction of membrane proTGF-α with the EGFR caused a slower internalization of activated EGFR relative to the soluble TGFalpha/EGFR complexes, and more resistant to the protein-tyrosine phosphatases (PTPs) to reduce EGFR tyrosine phosphorylation. The higher activation of EGFR by proTGF-α accumulation on the cell surface indicates that defective TGFalpha processing provides a mechanism whereby malignant cells can obtain an autonomous growth advantage over normal cells[30-31]. Unlike proteins of the ER or Golgi compartments, which normally need specific signals and mechanisms to be targeted to and maintained in their proper locations, transmembrane proteins are frequently assumed to be delivered to the plasma membrane via a nonregulated default pathway. However, several reports indicate that some plasma membrane proteins need specific mechanisms to be transported to the cell surface[32-33]. Commonly, mutations and truncations of the cytoplasmic domain of transmembrane proteins induce ER retention[34]. For proTGF-α, the cytoplasmic tail has been also shown to control its subcellular distribution. Through mutational analysis, the C-terminal amino acid valine (V159) has been mapped to be necessary for the normal trafficking of proTGF-α to the cell surface[35]. One possible explanation for these results is the requirement of the C-terminal valine (V159) for correct folding, and therefore exiting of the ER; or, alternatively, necessary for interaction with a factor leading to the normal transport of proTGF-α to the cell surface.

Yeast two-hybrid assays with the C-terminal of proTGF-α as bait have identified syntenin as a proTGF-α cytoplasmic domain-binding protein and both PDZ domains of syntenin were required for this interaction[20]. Conservative mutation of V159 to a leucine (V159L) had no effect on the trafficking of proTGF-α; however, mutations of V159 to G, K, or M disrupts the binding of the cytoplasmic domain of proTGF-α to syntenin, and also caused retention of these mutants in intracellular ER compartments. These results were further strengthened by making a chimeric protein, composed of the extracellular and transmembrane domains of proTGF-α fused to the cytoplasmic domain of syndecan-2 that was identified to interact with syntenin PDZ domains. The results showed that the cytoplasmic tail of syndecan-2 could functionally replace that of proTGF-α mediate intracellular trafficking; in contrast, the trafficking of a control chimeric protein containing the cytoplasmic tail of Betaglycan (BG), a transmembrane protein whose transport to the cell surface is independent of its cytoplasmic tail, was severely impaired. These findings indicated that interaction of proTGF-α

with syntenin is necessary for correct targeting of proTGF-α to the cell surface[20].

4.2 SYNTENIN AND TUMOR SUPPRESSOR PROTEINS

4.2.1 Syntenin and r-PTPη Syntenin has been found to interact with tumor suppressor protein r-PTPη, a receptor-type tyrosine phosphatase in rat, by a yeast two-hybrid screening using the cytoplasmic region of r-PTPη as bait[36].

The r-PTPη gene expression is reduced in several thyroid oncogene-transformed cells, and absent in highly malignant thyroid cells[37]. The human homolog of r-PTPη, HPTPη/DEP-1, is drastically reduced in human thyroid carcinomas. Loss of heterozygosity at the locus of this gene is frequent in human colon, lung, breast and thyroid cancers[38-40]. Restoration of r-PTP expression-in malignant rat thyroid cells and in human thyroid carcinoma cell lines inhibits their growth and tumorigenicity. The tumor suppressor activity of r-PTPη is mediated by p27Kip1 protein stabilization, through the inhibition of mitogen-activated protein kinase activation[38-39]. The growth inhibition properties of HPTP/DEP-1 are related to dephosphorylation of the PDGF , HGF and VEGF receptors at specific cell-cell adhesion sites[41-42].

Both PDZ domains of syntenin are demonstrated to be required for the interaction with r-PTPη, and syntenin interacts with the C-terminal region but not with the juxtamembrane region of r-PTPη, suggesting that the carboxy-terminal region of r-PTPη contains a PDZ binding peptide. The mutant bait, containing the cytoplasmic r-PTPη region deleted four amino acids at the C-terminal, fails to interact with syntenin in a two-hybrid assay. Although interaction each other, syntenin seems not a substrate of r-PTPη. In the amino-terminal region of syntenin, has five tyrosines that may represent a potential target for tyrosine kinases. The expression-of r-PTPη is not able to reduce tyrosine phosphorylation levels of syntenin; moreover, r-PTPη binds preferentially the unphosphorylated form of syntenin, and this could explain the inability of r-PTPη to decrease the phosphorylation level of syntenin. Since syntenin is not a substrate of r-PTPη, the functional significance of this interaction was unknown. However, an involvement of syntenin in the trafficking of r-PTPη is possible[36].

4.2.2 Syntenin and a novel type of tumor suppressor NF2 /Schwannomin/Merlin The patients with familial cancer syndrome neurofibromatosis Type 2 (NF2) are predisposed to schwannomas, meningiomas and gliomas[44-45]. The NF2 tumor suppressor gene on chromosome 22q12 encodes a widely expressed protein, named NF2 protein, also known as Schwannomin-1 (sch-1) or merlin, and is inactivated in virtually all schwannomas and meningiomas. More recently, NF2 mutations have been reported in some sporadic thyroid carcinomas, hepatocellular carcinoma cell lines, and perineurial tumors, revealing additional cell types affected by NF2 loss[46-47]. Overexpression of NF2 can block both cell proliferation and oncogene-induced transformation by negatively regulating cyclin D1 levels[48-50].

NF2 protein is a member of the ERM (ezrin, radixin, and moesin) super family proteins, which is predominantly localized to actin-rich plasma membrane processes and also binds to microtubules[51-52]. Unlikely "classic" tumor suppressor p53 or Rb directly controlling the cell cycle machinery in the nucleus, NF2, like the ERM proteins, appears to provide regulated linkage between membrane-associated proteins and the actin cytoskeleton and function in membrane organization. Therefore, NF2 is a novel type of tumor suppressor by modulating signals from the extracellular milieu to cytoskeletal linkage critical for cell growth and adhesion pathways[53].

Using the yeast two-hybrid system, syntenin has been identified as a binding partner for schwannomin isoform-1 (sch-1). There are two isoforms of the NF2 protein, sch-1 and sch-2, which differ in the C-terminal 16 amino acids[54]. More importantly, only sch-1 has been shown to suppress cell growth suggesting that the last 16 amino acids of sch-1 are essential for its tumor suppressor function[55]. The C terminus 25 amino acids of sch-1 and the two PDZ domains of syntenin mediate their binding, and mutations introduced within the VAFFEEL region of sch-1 defined a sequence crucial for syntenin recognition. The two proteins interacted in vitro and in vivo and co-localized underneath the plasma membrane and also in punctate intracellular vesicular structures. Fibroblast cells expressing heterolo-

gous antisense syntenin display alterations in the subcellular distribution of sch-1, indicating that syntenin/sch-1 interaction plays a role in the subcellular trafficking and targeting of sch-1 to the plasma membrane[56].

These observations of syntenin interaction with some tumor suppressor proteins indicate that syntenin is potentially facilitating the activity of tumor suppressor proteins, which making a contrast with the phenomenon that syntenin overexpression is associated with a metastatic cancer phenotype. Recent studies showed that the interaction of eukaryotic translation initiation factor 5A (eIF5A) with syntenin could collaboratively regulate p53 activity, possibly unraveling a novel pathways for p53 network to be more selective and sensitive manner to manipulate cell apoptosis[57]. This raises the intriguing possibility of tissue specific action of syntenin and emphasizes the complexity of the putative involvement of syntenin in modulating the balance that how cells organize their interface with the extracellular environment to control proliferation, and how disorganization of this interface contributes to tumorigenesis and metastasis.

ACKNOWLEDGEMENTS

This work was supported by National Institutes of Health grants RO2 CA82295.

References:

[1] Chin Lynda, Garraway L A, Fisher D E. Malignant melanoma: genetics and therapeutics in the genomic era[J]. Genes Dev, 2006, 20 (16):2149-2182.

[2] La Porta C A. Drug resistance in melanoma: new perspectives[J]. Curr Med Chem, 2007, 14 (4):387-391. (Review)

[3] Clark W H. Tumour progression and the nature of cancer[J]. Br J Cancer, 1991, 64(4):631-644. (Review)

[4] Leslie M C, Bar-Eli M. Regulation of gene expression in melanoma: new approaches for treatment[J]. J Cell Biochem, 2005,94 (1):25-38.

[5] Pons M, Quintanilla M. Molecular biology of malignant melanoma and other cutaneous tumors[J]. Clin Transl Oncol, 2006,8(7): 466-474.

[6] Dhomen N, Marais R. New insight into BRAF mutations in cancer [J]. Curr Opin Genet Dev, 2007,17(1):31-39.

[7] Yang J, Price M A, Neudauer C L, et al. Melanoma chondroitin sulfate proteoglycan enhances FAK and ERK activation by distinct mechanisms[J]. J Cell Biol, 2004, 165(6):881-891.

[8] Lin J J, Jiang H, Fisher P B. The melanoma differentiation associated gene-6 (mda-9), which the enocdes cyclin-dependent kinase inhibitor p21, may function as a negative regulator of human melanoma growth and progression[J]. Mol Cell Differ, 1996, 4(1): 67-89.

[9] Lin J J, Jiang H, Fisher P B. Melanoma differentiation associated gene-9, mda-9, is a human gamma interferon responsive gene[J]. Gene, 1998, 207(2):105-110.

[10] Brone B, Eggermont J. PDZ proteins retain and regulate membrane transporters in polarized epithelial cell membranes[J]. Am J Physiol Cell Physiol, 2005,288(1):C20-29. (Review)

[11] Fisher P B, Prignoli D R, Hermo H Jr, et al. Effects of combined treatment with interferon and mezerein on melanogenesis and growth in human melanoma cells[J]. J Interferon Res,1985,5(1):11-22.

[12] Helmke B M, Polychronidis M, Benner A, et al. Melanoma metastasis is associated with enhanced expression of the syntenin gene [J]. Oncol Rep, 2004, 12(2): 221-228.

[13] Zimmermann P, Tomatis D, Rosas M, et al. Characterization of syntenin, a syndecan-binding PDZ protein, as a component of cell adhesion sites and microfilaments[J]. Mol Biol Cell, 2001, 12 (2):339-350.

[14] Grootjans J J, Zimmermann P, Reekmans G, et al. Syntenin, a PDZ protein that binds syndecan cytoplasmic domains[J]. Proc Natl Acad Sci USA, 1997, 94(25):13683-13688.

[15] Koroll M, Rathjen F G, 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]. J Biol chem, 2001, 276 (14):10646-10654.

[16] Sarkar D, Boukerche H, Su Z Z, et al. mda-9/syntenin: recent insights into a novel cell signaling and metastasis-associated gene [J]. Pharmacol Ther, 2004, 104 (2): 101-115.

[17] Harris B Z, Hillier B J, Lim W A. Energetic determinants of internal motif recognition by PDZ domains[J]. Biochemistry, 2001, 40 (20): 5921-5930.

[18] Boukerche H, Su Z Z, Emdad L. mda-9/Syntenin: a positive regulator of melanoma metastasis[J]. Cancer Res, 65(23):10901-10911.

[19] Li A L, Li H Y, Jin B F, et al. A novel eIF5A complex functions as a regulator of p53 and p53-dependent apoptosis[J]. J Biol Chem, 2004,279(47): 49251-49258.

[20] Fernandez-Larrea J, Merlos-Suarez A, Urena J M, et al. A role for a PDZ protein in the early secretory pathway for the targeting of proTGF-alpha to the cell surface[J]. Mol Cell, 1999, 3(4):423-433.

[21] Bernfield M, Gotte M, Park P W. Functions of cell surface heparan sulfate proteoglycans[J]. Annu Rev Biochem, 1999, 68:729-777.

[22] Carey D J. Syndecans: multifunctional cell-surface co-receptors [J]. Biochem J, 1997, 327 (Pt 1):1-16. 327.

[23] Han I, Park H, Oh E S. New insights into syndecan-2 expression and tumourigenic activity in colon carcinoma cells[J]. J Mol Histol, 2004,35(5):319-326.

[24] Alexander C M, Reichsman F, Hinkes M T, et al. Syndecan-1 is required for Wnt-1-induced mammary tumorigenesis in mice[J]. Nat Genet, 2000,25(3):329-332.

[25] Burbach B J, Friedl A, Mundhenke C, et al. Syndecan-1 accumu-

lates in lysosomes of poorly differentiated breast carcinoma cells [J]. Matrix Biol, 2003, 22(2):163-177.

[26] Hirabayashi K, Numa F, Suminami Y, et al. Altered proliferative and metastatic potential associated with increased expression of syndecan-1[J]. Tumour Biol, 1998,19(6):454-463.

[27] Wiksten J P, Lundin J, Nordling S, et al. Epithelial and stromal syndecan-1 expression as predictor of outcome in patients with gastric cancer[J]. Int J Cancer, 2001,95 (1):1-6.

[28] Gulyas M, Hjerpe A. Proteoglycans and WT1 as markers for distinguishing adenocarcinoma, epithelioid mesothelioma, and benign mesothelium[J]. J Pathol, 2003,1999(4): 479-487.

[29] Roskams T, De Vos R, David G, et al. Heparan sulphate proteoglycan expression in human primary liver tumours[J]. J Pathol, 1998, 185(3):290-297.

[30] Bringman T S, Lindquist P B, Derynck R. Different transforming growth factor-alpha species are derived from a glycosylated and palmitoylated transmembrane precursor[J]. Cell, 1987, 48(3): 429-440.

[31] Yang H, Jiang D, Li W, et al. Defective cleavage of membrane bound TGFα leads to enhanced activation of the EGF receptor in malignant cells[J]. Oncogene, 2000, 19(15) 1901-1914.

[32] Wong S T, Winchell L F, McCune B K, et al. The TGF-alpha precursor expressed on the cell surface binds to the EGF receptor on adjacent cells, leading to signal transduction[J]. Cell, 1989, 56(3): 495-506.

[33] McLatchie L M, Fraser N J, Main M J, et al. RAMPs regulate the transport and ligand specificity of the calcitonin-receptor-like receptor[J]. Nature,1998, 393(6683):333-339.

[34] Meyer-Franke A, Wilkinson G A, Kruttgen A, et al. Depolarization and cAMP elevation rapidly recruit TrkB to the plasma membrane of CNS neurons[J]. Neuron,1998, 21(4): 681-693.

[35] Hammond C, Helenius A. Quality control in the secretory pathway [J]. Curr Opin Cell Biol, 1995, 7(4):523-529.

[36] Briley G P, Hissong M A, Chiu M L, et al. The carboxyl-terminal valine residues of proTGF alpha are required for its efficient maturation and intracellular routing[J]. Mol Biol Cell, 1997, 8(8): 1619-1631.

[37] Iuliano R, Trapasso F, Sama I, et al. Rat protein tyrosine phosphatase eta physically interacts with the PDZ domains of syntenin [J]. FEBS Lett, 2001, 500(1-2):41-44.

[38] Trapasso F, Iuliano R, Boccia A, et al. Rat protein tyrosine phosphatase eta suppresses the neoplastic phenotype of retrovirally transformed thyroid cells through the stabilization of p27(Kip1) [J]. Mol Cell Biol, 2000, 20(24): 9236-9246.

[39] Zhang L, Martelli M L, Battaglia C, et al. Thyroid cell transformation inhibits the expression of a novel rat protein tyrosine phosphatase[J]. Exp Cell Res, 1997, 235(1): 62-70.

[40] Iuliano R, Trapasso F, Le Pera I, et al. An adenovirus carrying the rat protein tyrosine phosphatase eta suppresses the growth of human thyroid carcinoma cell lines in vitro and in vivo[J]. Cancer Res, 2003,63(4): 882-886.

[41] Iuliano R, Le Pera I, Cristofaro C, et al. The tyrosine phosphatase PTPRJ? DEP-1 genotype affects thyroid carcinogenesis[J]. Oncogene, 2004, 23(52): 8432-8438.

[42] Ruivenkamp C, Hermsen M, Postma C, et al. LOH of PTPRJ occurs early in colorectal cancer and is associated with chromosomal loss of 18q1221[J]. Oncogene, 2003,22(22): 3472-3474.

[43] Palka H L, Park M, Tonks N K. Hepatocyte growth factor receptor tyrosine kinase met is a substrate of the receptor protein-tyrosine phosphatase DEP-1 [J]. J Biol Chem, 2003, 278 (8): 5728-5735.

[44] Lampugnani M G, Zanetti A, Corada M, et al. Contact inhibition of VEGF-induced proliferation requires vascular endothelial cadherin, beta-catenin, and the phosphatase DEP-1/CD148[J]. J Cell Biol, 2003,161(4): 793-804.

[45] Louis D N, Ramesh V, Gusella J F. Neuropathology and molecular genetics of neurofibromatosis 2 and related tumors [J]. Brain Pathol, 1995, 5(2):163-172.

[46] Lasota J, Fetsch J F, Wozniak A, et al. The neurofibromatosis type 2 gene is mutated in perineurial cell tumors: a molecular genetic study of eight cases[J]. Am J Pathol, 2001, 158 (4): 1223-1229.

[47] Pineau P, Marchio A, Nagamori S, et al. Homozygous deletion scanning in hepatobiliary tumor cell lines reveals alternative pathways for liver carcinogenesis[J]. Hepatology, 2003,37(4): 852-861.

[48] Sheikh H A, Tometsko M, Niehouse L, et al. Molecular genotyping of medullary thyroid carcinoma can predict tumor recurrence [J]. Am J Surg Pathol, 2004, 28(1): 101-106.

[49] Tikoo A, Varga M, Ramesh V, et al. An anti-Ras function of neurofibromatosis type 2 gene product (NF2/Merlin) [J]. J Biol Chem,1994, 269(38): 23387-23390.

[50] Lutchman M, Rouleau G A. The neurofibromatosis type 2 gene product, schwannomin, suppresses growth of NIH 3T3 cells[J]. Cancer Res, 1995, 55(11): 2270-2274.

[51] Xiao G H, Beeser A, Chernoff J, et al. p21-activated kinase links Rac/Cdc42 signaling to merlin[J]. J Biol Chem, 2002, 277(2): 883-886.

[52] Trofatter J A, MacCollin M M, Rutter J L, et al. A novel moesin-, ezrin-, radixin-like gene is a candidate for the neurofibromatosis 2 tumor suppresso[J]. Cell, 1993, 72(5): 791-800.

[53] Xu H M, Gutmann D H. Merlin differentially associates with the microtubule and actin cytoskeleton[J]. Neurosci Res, 1998, 51 (3):403-415.

[54] Tsukita S, Oishi K, Sato N, et al. ERM family members as molecular linkers between the cell surface glycoprotein CD44 and actin-based cytoskeletons[J]. J Cell Biol, 1994, 126(2): 391-401.

[55] Pykett M J, Murphy M, Harnish P R, et al. The neurofibromatosis 2 (NF2) tumor suppressor gene encodes multiple alternatively spliced transcripts[J]. Hum Mol Genet, 1994, 3(4):559-564.

[56] Gutmann D H, Sherman L, Seftor L, et al. Increased expression of the NF2 tumor suppressor gene product, merlin, impairs cell motility, adhesionand spreading[J]. Hum Mol Genet, 1999, 8(2): 267-275.

[57] Jannatipour M, Dion P, Khan S, et al. Schwannomin isoform-1 interacts with syntenin via PDZ domains[J]. J Biol Chem, 2001, 276 (35): 33093-33100.

(Edited by CHEN Li-wen)