Lebanese American University Repository (LAUR)

Post-print version/Author Accepted Manuscript

Publication metadata:

Title: StarD13: a potential star target for tumor therapeutics.

Author(s): Leila Jaafar, Zeinab Chamseddine and Mirvat El-Sibai

Journal: Human Cell

DOI: https://doi.org/10.1007/s13577-020-00358-2

How to cite this post-print from LAUR:

Jaafar, L., Chamseddine, Z., & El-Sibai, M. (2020). StarD13: a potential star target for tumor therapeutics. Human Cell, Doi: https://doi.org/10.1007/s13577-020-003582
Handle: http://hdl.handle.net/10725/11877

C 2020

This Open Access post-print is licensed under a Creative Commons Attribution-Non Commercial-No Derivatives (CC-BY-NC-ND 4.0)

This paper is posted at LAU Repository

For more information, please contact: archives@lau.edu.lb

StarD13: a potential star target for tumor therapeutics

Leila Jaafar, Zeinab Chamseddine & Mirvat El-Sibai

Human Cell

e-ISSN 1749-0774

Human Cell
DOI 10.1007/s13577-020-00358-2

ONLINE FIRST

Springer

Your article is protected by copyright and all rights are held exclusively by Japan Human Cell Society. This e-offprint is for personal use only and shall not be self-archived in electronic repositories. If you wish to self-archive your article, please use the accepted manuscript version for posting on your own website. You may further deposit the accepted manuscript version in any repository, provided it is only made publicly available 12 months after official publication or later and provided acknowledgement is given to the original source of publication and a link is inserted to the published article on Springer's website. The link must be accompanied by the following text: "The final publication is available at link.springer.com”.

Springer

Author's personal copy

Human Cell
https://doi.org/10.1007/s13577-020-00358-2

REVIEW ARTICLE

StarD13: a potential star target for tumor therapeutics

Leila Jaafar[1] · Zeinab Chamseddine[1] · Mirvat El-Sibai[1]

Received: 27 March 2020 / Accepted: 3 April 2020
© Japan Human Cell Society 2020

Abstract
StarD13 is a tumor suppressor and a GTPase activating protein (GAP) for Rho GTPases. Thus, StarD13 regulates cell survival pathways and induces apoptosis in a p53-dependent and independent manners. In tumors, StarD13 is either downregulated or completely inhibited, depending on the tumor type. As such, and through the dysregulation of Rho GTPases, this affects adhesion dynamics, actin dynamics, and leads to an increase or a decrease in tumor metastasis depending on the tumor grade and type. Being a key regulatory protein, StarD13 is a potential promising candidate for therapeutic approaches. This paper reviews the key characteristics of this protein and its role in tumor malignancies.

Keywords StarD13 · RhoGAP · Rho GTPases · RhoA · Cdc42

Introduction

Steroidogenic acute regulatory (StAR)-related lipid transfer domain containing 13 protein, StarD13, also known as deleted in liver cancer-2 (DLC2) is a tumor suppressor encoded by the DLC2 gene and located at chromosome 13q12.3 [1]. Along with DLC1 and DLC3, StarD13 is part of the Deleted in Liver Cancer family of proteins [1–3]. This protein, first discovered by Ching et al. in 2003, is characterized by four main domains involved in different functions [1]. StarD13 is a regulator of many cell events, including cell proliferation, polarity, and migration, and hence, it plays a role in embryogenesis and carcinogenesis [4, 5]. More specifically, StarD13 is a GTPase activating protein (GAP) for the Rho GTPases, RhoA, and Cdc42 [1]. In tumors, StarD13 is commonly downregulated or completely inhibited [6–11]. This leads to the dysregulation of RhoA and Cdc42, which activity is otherwise tightly regulated for normal functioning of the cell [4]. The lack of this regulation is one of the tumorigenic hallmarks of cells [12–16]. StarD13 is involved mainly in the third stage of carcinogenesis—considering that the three stages are initiation, promotion, and progression [17–20]. This review focuses on the different domains of StarD13, its tumor suppressor role and its regulation of cancer metastasis through Rho GTPases.

StarD13 domains

StarD13 has an array of functions and specifications that are mainly attributed to its four domains, as shown in Fig. 1 [1, 4, 9, 21]. The domain located at the C-terminus is 202 amino acid long steroidogenic acute regulatory (STAR)-related lipid transfer (START) domain [1, 22]. The START domain localizes the protein to the mitochondria that are proximal to lipid droplets [1, 23]. These lipid droplets stock lipids used for synthesis and maintenance of membranes in cells. This might suggest that StarD13 regulates mitochondrial permeability and mitochondrial apoptotic pathways [9].

StarD13 also has a 149 amino acid long GAP domain that is located towards the C-terminus between amino acids 677 and 826 [1]. The GAP domain of StarD13 allows it to inactivate some members of the Rho family of GTPases [9]. Rho GTPases are important regulators of many cellular activities, like cell dynamics, cell growth, intracellular membrane trafficking, gene transcription, cell-cycle progression, and apoptosis [24–26]. Rho GTPases are active when bound to GTP. They hydrolyze the bound GTP into GDP to revert to the inactive state. This GTP/GDP switch is established by activators and inhibitors. GEFs (Guanine Exchange factors)

Leila Jaafar and Zeinab Chamseddine have equally contributed to this work.

✉ Mirvat El-Sibai
mirvat.elsibai@lau.edu.lb

[1] Department of Natural Sciences, School of Arts and Sciences, Lebanese American University, Chouran, P.O. Box 13-5053, 1102 2801 Beirut, Lebanon

Published online: 09 April 2020

Author's personal copy

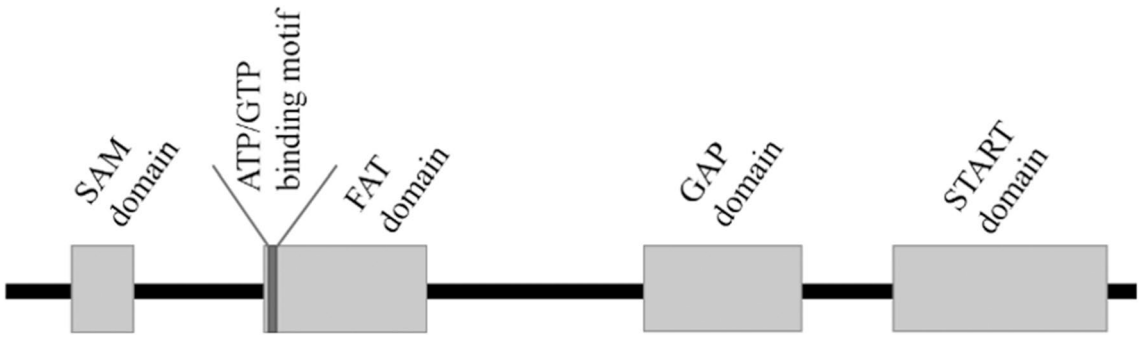

Fig. 1 Representation of the four domains of STARD13 on the amino acid sequence of the protein

remove the GDP through competitive binding, allowing the GTP to then bind to the Rho GTPase and activate it. GAPs stimulate the GTPase activity of the Rho GTPase to hydrolyze its bound GTP, hence inactivating the protein. The Rho GAP domain of StarD13 is accompanied by an ATP/GTP-binding site motif. This is a seven amino acids' long motif, located towards the N-terminus of StarD13 [1].

The third characteristic domain of StarD13 is the Sterile Alpha Motif (SAM) domain [23]. This domain is located at the N-terminus of the protein and consists of 59 amino acids [1]. The SAM domain is a protein–ligand binding motif. It has a hydrophobic cleft lined with aromatic residues that offer a binding site for a unique class of ligands, including proteins and lipids [4, 9]. StarD13 cannot bind nucleic acids, however, for the lack of a positively charged surface [27]. According to Zhong et.al. SAM domains are usually characterized by five α-helices arranged in a globular manner. However, StarD13 has a special SAM domain that is formed of an anti-parallel 4 helix bundle. Consequently, there is no structural homology between the SAM domain of StarD13 and other SAM domains [27, 28]. The SAM domain targets StarD13 to the cell membrane and potentially contributes to its tumor suppressor role. Cheng et.al. observed that xenografts grew faster in mice with SAM domain deletions. Moreover, the deletion of the SAM domain inhibited the increase in pro-apoptotic protein (Caspase-3 and Bax) levels normally observed upon the activation of StarD13 [29]. Based on variations in their SAM domains, four StarD13 isoforms have been identified, DLC2α, DLC2β, DLC2γ (which lacks the SAM domain), and DLC2δ (which consists of only an SAM domain) [4, 9].

A fourth 154 amino acid long domain can be found at the N-terminus of StarD13 (318–472). This domain targets the protein to focal adhesions. Focal adhesions are contractile actin stress fibers that anchor the cell to the extracellular matrix ECM [30]. Thus, the domain was termed the Focal Adhesion Targeting (FAT) domain. It allows StarD13 to bind to tensin2, a component of focal adhesions [31]. The SIYDNV motif of the FAT domain allows it to bind to the SH2 domains of tensin2 and other proteins in a tyrosine phosphorylation independent manner [29].

StarD13 underexpression in tumors

StarD13 is underexpressed in many tumor types such as renal, colon, hepatic, uterine, rectal, gastric, breast, and ovarian cancers [2, 7–9, 11, 32–34]. Lower StarD13 levels were also detected in non-small cell lung cancer cells [23]. A clinicopathological study conducted on 131 breast cancer cases revealed a lower expression of StarD13 in tumor cells when compared to adjacent normal tissues [32]. This decrease significantly correlated with lower cell differentiation, poor prognosis, and metastasis to lymph nodes [32]. A DLC2 gene deletion has been found in glioblastoma patients, explaining the underexpression of StarD13 [35]. However, Wang et al. detected a twofold decrease in the expression of the StarD13 protein in lung squamous cell carcinoma, lung adenocarcinoma, hepatocellular carcinoma, or breast cancer that did not correlate with a loss in the copy number of the DLC2 in a subset of patients [36]. This could be due to epigenetic factors such as DNA methylation, histone post-translational modifications, and non-coding RNA-mediated pathways [37–39]. Indeed, in the case of StarD13, increased promoter methylation at the CpG islands led to the repression of the StarD13 gene and, therefore, to the loss of the relevant protein [2, 3, 40–42].

Role of StarD13 in cell proliferation

StarD13 controls various proteins involved in different signaling pathways that affect the cell function, such as cell adhesion, polarity, migration, and cell division. The major effectors of StarD13 are RhoA and Cdc42, but not Rac1 [1, 4, 9]. The function of RhoA in cells has been strictly discussed in the context of stress fiber formation and focal adhesion formation, as well as cancer cell invasion [43, 44].

Author's personal copy

This alone, however, does not take into account the indirect effect of such molecular switches on other pathways, due to cross-talk [10, 26]. Indeed, RhoA has been shown to mediate the activation of the mitogen-activated protein kinase kinase (MAPKK) Raf-1 (the Rapidly Accelerated Fibrosarcoma) by the small GTPase Ras, leading to cell proliferation (Fig. 2) [45, 46]. Potentially, StarD13 inhibits cell division through the inhibition of RhoA and the downregulation of the Ras-Raf-1 complex formation [47].

Leung et al. showed that StarD13 inhibits cell growth by blocking the cell cycle at the G1 phase rather than by inducing apoptosis [47]. However, StarD13 3′Untranslated Region (3′UTR) positively regulates apoptosis in hepatocellular carcinomas [48]. The 3′UTR of StarD13 contains necessary elements for the regulation of the gene expression [49]. More specifically, StarD13 3′UTR induces the Bcl-2 modifying factor (BMF) (Fig. 2). BMF releases Blc2 allowing Bax to induce the release of cytochrome c from mitochondria, leading to programmed cell death in solid tumors [50].

Another mechanism through which StarD13 regulates the cell cycle is through the inhibition of RhoA, which leads to the accumulation of the cell-cycle inhibitors, $p27^{kip1}$ and $p21^{waf/cip1}$ (otherwise degraded by active RhoA), leading to cell-cycle arrest [51–53]. In addition, the SAM domain of StarD13 interacts with the Tap73alpha protein through its SAM domain [54]. Tap73alpha and Tap73beta are the products of alternative promotors or alternative splicing of p73, a protein that belongs to the p53 family [55]. While p73 is a tumor suppressor, Tap73alpha is highly expressed in small cell lung carcinoma, where it inhibits induced apoptosis by death stimuli (chemotherapy) [54]. A downside of systemic therapies is being unspecific, affecting all types of cells of a cancer patient, that is why, a new approach to eliminating tumors is targeted therapies [56–64]. In a recent study in glioblastoma, scientists found that StarD13 targets Tap73alpha to degradation by ubiquitination through its SAM domain, leading to p53-dependent cell apoptosis (Fig. 2) [29].

StarD13 is also a Rho GAP for the small GTPase Cdc42 [24]. Cdc42 plays a major role in epithelial tissue formation and homeostasis. The tight regulation of Cdc42 is important for tight and adherent junction formation and maintenance, as well as for mitotic spindle positioning and chromosome attachment during cell division [65–67]. StarD13 also acts upstream from mDia3, a downstream effector of Cdc42 that regulates the organization of microtubules and actin. Along with the new mitotic kinesin Kif1B, it regulates a pathway that controls the cross-talk between the cortical actin cytoskeleton and astral microtubules that are necessary for epithelial integrity, mitotic progression, and spindle positioning [66].

In summary, StarD13 plays a role in cell-cycle regulation by regulating RhoA, thus controlling the G1/S phase progression, and by regulating Cdc42, thereby regulating metaphase/anaphase progression.

Role of StarD13 in cancer metastasis

Metastasis is the spread of cancer cells from their original site to other parts of the organism. It is a complex process that is regulated by many factors. Metastasis starts with the

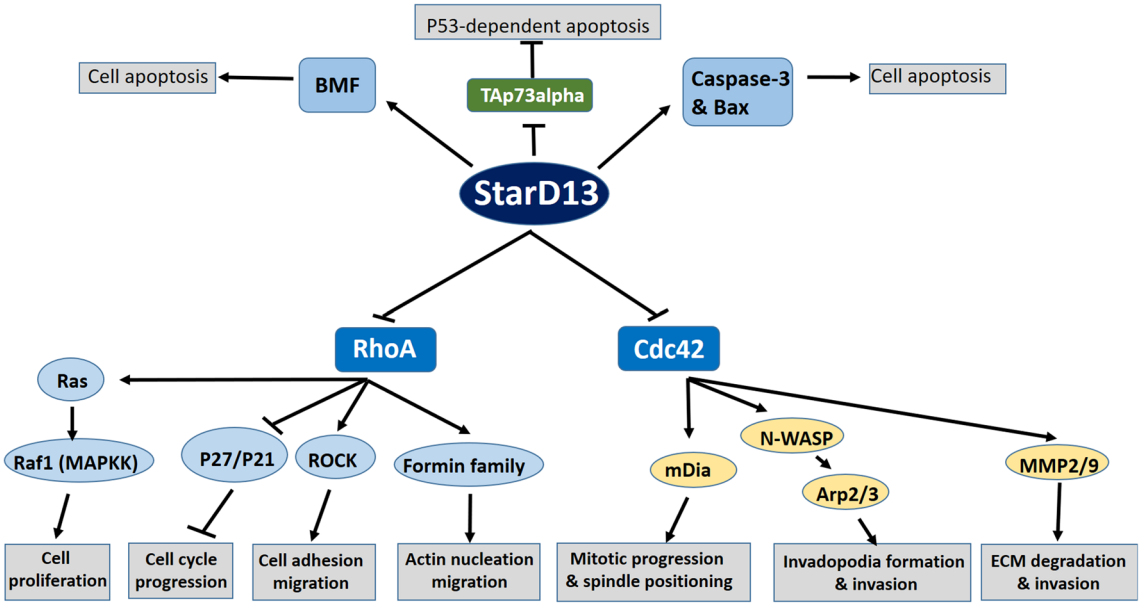

Fig. 2 Downstream effectors from StarD13 involved in cancer survival proliferation and metastasis

Author's personal copy

detachment of the cell from its original locus, surviving in circulation, adhering to a distant site, invading new tissues, and, finally, proliferating to form a new tumor [68–71].

In melanoma and prostate cancer cells, where StarD13 is highly expressed, the formation of actin stress fibers is significantly inhibited [72]. Actin stress fiber formation, actomyosin complex assembly, and contractive processes are all events downstream from RhoA and its effector, the RhoA-associated coiled-coil forming protein kinase (ROCK) [73, 74]. These structures indeed play a crucial role in cell migration, invasion, and metastasis [75, 76]. RhoA also regulates cell migration through positively regulating members of the formin family of actin nucleators [49]. In addition to RhoA, Cdc42 plays a crucial role in cancer metastasis [77, 78]. Cdc42 leads to the activation of the N-WASP and ARP complexes, leading the induction of actin nucleation and the subsequent assembly of invadopodia [79]. In addition, Cdc42 promotes the activation and production of metalloproteinases that degrade the extracellular matrix components facilitating the process of invasion [80]. Given its role in the regulation of RhoA and Cdc42, StarD13 is directly involved in cancer cell migration and metastasis, as was reported in several tumor models (Fig. 2) [2, 7, 8, 81].

Downregulation of StarD13 is a typical characteristic of metastatic tumors [2, 7–9, 11, 32–34]. Many studies support the hypothesis that StarD13 is a metastasis suppressor in solid tumors. A study conducted by Yang et al. on the role of StarD13 in breast cancer cell lines showed that knocking down StarD13 enhances cell migration and invasion in a transwell membrane, through Rho GTPases [32]. This was confirmed in another study where miR-125b microRNA was found to target StarD13 directly, silencing its expression (being complementary to StarD13's 3′UTR) and improving the migration profile of breast cancer cell lines [82]. In addition, the physiologically expressed miR-125b leads to an increase in the metastatic ability of gastric cancer [82, 83]. This emphasizes the negative effect of StarD13 on migration of tumor cells. Furthermore, a recent study shows that StarD13 and its competing endogenous RNA, ceRNAs-3′UTRs inhibit breast cancer metastasis by inhibiting epithelial to mesenchymal transition (EMT) [84–86]. StarD13 knock out mice showed enhanced angiogenesis in response vascular endothelial growth factors, which further proves the metastatic inhibitory effect of StarD13 [81, 87, 88]. A homozygote or heterozygote loss of StarD13 in mammary tumors linked to ErbB2 (tyrosine phosphate—receptor), resulted in increased lung metastasis in in vivo models [74]. Also, according to Hu et al., ectopic expression of CCR2 3′UTR leads to a significant upregulation of StarD13 expression in breast cancer cell lines, which in turn leads to the decrease in the formation of stress fibers and a reduction in metastasis in xenograft models, further demonstrating that StarD13 is an invasion and metastasis suppressor [89].

However, other studies showed that StarD13 is essential for metastasis in solid tumors. A study conducted by Hanna et al. in breast cancer cell lines showed that the depletion of StarD13 by siRNA decreased cellular motility. Breast cancer cells exhibited a dramatic loss in their migration due to their inability to detach their tails to propel forward [8]. This was due to the constitutive activation of RhoA, downstream from StarD13 [8]. Indeed, RhoA goes through cycles of activity and inactivity, which enables the cells to attach and detach to the extracellular matrix during the cell motility cycle [7]. These results indicate that the knockdown of StarD13 suppresses cellular motility, meaning that StarD13 is a cell motility regulator in breast cancer, at least in part through the regulation of RhoA activity [8]. Moreover, a study conducted on DLC1, a homologous of DLC2, concluded that DLC1 is a motility inducer. Deleted in Liver Cancer 1 was established as a tumor suppressor in many studies [3, 8, 90]. Through its GAP activity, DLC1 downregulates RhoA, upregulating cellular motility [8, 28, 91]. This ambiguity between the role as tumor suppressor and the role as metastasis inducer of DLC1 was explained by the interaction between the protein and tensins [8, 92]. These findings together support an earlier study done by El Sitt et al. showing an upregulation in the levels of StarD13 in grade III solid breast tumors [8, 11]. In fact, grade III tumors are cancerous cells who metastasized to new sites [11]. Consequently, StarD13 was needed for this metastatic characteristic of the tumor [8]. As such, this can be reconciled by hypothesizing that StarD13 is a tumor suppressor that can have pro-metastatic roles in advanced grades of tumors.

In conclusion, StarD13 exerts its anti-tumor activity through its GAP and SAM domains. StarD13 downregulates Rho GTPases promoting cell adhesion and apoptosis through several pathways, preventing the progression of cancer. StarD13 may be metastatic and invasion suppressor or inducer, perhaps depending of the tumor grade and type.

Acknowledgements The authors thank the Lebanese American University. The authors were supported by the Lebanese American University, Department of Natural science.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Ching YP, Wong CM, Chan SF, et al. Deleted in liver cancer (DLC) 2 encodes a RhoGAP protein with growth suppressor function and is underexpressed in hepatocellular carcinoma. J Biol Chem. 2003;278:10824–30.

Author's personal copy

2. Lukasik D, Wilczek E, Wasiutynski A, Gornicka B. Deleted in liver cancer protein family in human malignancies (Review). Oncol Lett. 2011;2:763–8.
3. Durkin ME, Yuan BZ, Zhou X, et al. DLC-1: a Rho GTPase-activating protein and tumour suppressor. J Cell Mol Med. 2007;11:1185–207.
4. Kwan JJ, Donaldson LW. The NMR structure of the murine DLC2 SAM domain reveals a variant fold that is similar to a four-helix bundle. BMC Struct Biol. 2007;7:34.
5. Ullmannova V, Popescu NC. Expression profile of the tumor suppressor genes DLC-1 and DLC-2 in solid tumors. Int J Oncol. 2006;29:1127–32.
6. Bocanegra V, Gil Lorenzo AF, Cacciamani V, Benardon ME, Costantino VV, Valles PG. RhoA and MAPK signal transduction pathways regulate NHE1-dependent proximal tubule cell apoptosis after mechanical stretch. Am J Physiol Renal Physiol. 2014;307:F881–F88989.
7. Khalil BD, Hanna S, Saykali BA, et al. The regulation of RhoA at focal adhesions by StarD13 is important for astrocytoma cell motility. Exp Cell Res. 2014;321:109–22.
8. Hanna S, Khalil B, Nasrallah A, et al. StarD13 is a tumor suppressor in breast cancer that regulates cell motility and invasion. Int J Oncol. 2014;44:1499–511.
9. El-Sitt S, El-Sibai M. The STAR of the DLC family. J Recept Signal Transduct Res. 2013;33:10–3.
10. El Atat O, Fakih A, El-Sibai M. RHOG activates RAC1 through CDC42 leading to tube formation in vascular endothelial cells. Cells. 2019;8:171.
11. El-Sitt S, Khalil BD, Hanna S, El-Sabban M, Fakhreddine N, El-Sibai M. DLC2/StarD13 plays a role of a tumor suppressor in astrocytoma. Oncol Rep. 2012;28:511–8.
12. Vigil D, Cherfils J, Rossman KL, Der CJ. Ras superfamily GEFs and GAPs: validated and tractable targets for cancer therapy? Nat Rev Cancer. 2010;10:842–57.
13. Srivastava SK, Wheelock RH, Aaronson SA, Eva A. Identification of the protein encoded by the human diffuse B-cell lymphoma (dbl) oncogene. Proc Natl Acad Sci USA. 1986;83:8868–72.
14. Katzav S, Martin-Zanca D, Barbacid M. vav, a novel human oncogene derived from a locus ubiquitously expressed in hematopoietic cells. Embo J. 1989;8:2283–90.
15. Miki T, Smith CL, Long JE, Eva A, Fleming TP. Oncogene ect2 is related to regulators of small GTP-binding proteins. Nature. 1993;362:462–5.
16. Whitehead I, Kirk H, Kay R. Expression cloning of oncogenes by retroviral transfer of cDNA libraries. Mol Cell Biol. 1995;15:704–10.
17. Shebaby WN, Mroueh MA, Boukamp P, et al. Wild carrot pentane-based fractions suppress proliferation of human HaCaT keratinocytes and protect against chemically-induced skin cancer. BMC Complement Altern Med. 2017;17:36.
18. Singletary K, MacDonald C. Inhibition of benzo[a]pyrene- and 1,6-dinitropyrene-DNA adduct formation in human mammary epithelial cells bydibenzoylmethane and sulforaphane. Cancer Lett. 2000;155:47–544.
19. Khor TO, Hu R, Shen G, et al. Pharmacogenomics of cancer chemopreventive isothiocyanate compound sulforaphane in the intestinal polyps of ApcMin/+ mice. Biopharm Drug Dispos. 2006;27:407–20.
20. Zeinab RA, Mroueh M, Diab-Assaf M, et al. Chemopreventive effects of wild carrot oil against 7,12-dimethyl benz(a)anthracene-induced squamous cell carcinoma in mice. Pharm Biol. 2011;49:955–61.
21. Wolosz D, Walczak A, Szparecki G, et al. Deleted in Liver Cancer 2 (DLC2) protein expression in hepatocellular carcinoma. Eur J Histochem. 2019;63:2981.
22. Satheesh V, Chidambaranathan P, Jagannadham PT, et al. Transmembrane START domain proteins: in silico identification, characterization and expression analysis under stress conditions in chickpea (*Cicer arietinum* L.). Plant Signal Behav. 2016;11:e992698.
23. Sun L, Sun J, Song JD. High expression of DLC family proteins predicts better prognosis and inhibits tumor progression in NSCLC. Mol Med Rep. 2019;19:4881–9.
24. Tcherkezian J, Lamarche-Vane N. Current knowledge of the large RhoGAP family of proteins. Biol Cell. 2007;99:67–866.
25. Hall A, Nobes CD. Rho GTPases: molecular switches that control the organization and dynamics of the actin cytoskeleton. Philos Trans R Soc Lond B Biol Sci. 2000;355:965–70.
26. Hanna S, El-Sibai M. Signaling networks of Rho GTPases in cell motility. Cell Signal. 2013;25:1955–61.
27. Li H, Fung KL, Jin DY, et al. Solution structures, dynamics, and lipid-binding of the sterile alpha-motif domain of the deleted in liver cancer 2. Proteins. 2007;67:1154–66.
28. Zhong D, Zhang J, Yang S, et al. The SAM domain of the RhoGAP DLC1 binds EF1A1 to regulate cell migration. J Cell Sci. 2009;122:414–24.
29. Cheng C, Feng S, Jiao J, et al. DLC2 inhibits development of glioma through regulating the expression ratio of TAp73alpha/TAp73beta. Am J Cancer Res. 2018;8:1200–13.
30. Malik-Sheriff RS, Imtiaz S, Grecco HE, Zamir E. Diverse patterns of molecular changes in the mechano-responsiveness of focal adhesions. Sci Rep. 2018;8:2187.
31. Kawai K, Seike J, Iino T, et al. START-GAP2/DLC2 is localized in focal adhesions via its N-terminal region. Biochem Biophys Res Commun. 2009;380:736–41.
32. Yang Z, Chen H, Shu M, Zhang Y, Xue L, Lin Y. DLC2 operates as a tumor suppressor gene in breast cancer via the RhoGTPase pathway. Oncol Lett. 2019;17:2107–16.
33. Salem C, Atallah D, Safi J, et al. Breast density and breast cancer incidence in the Lebanese population: results from a retrospective multicenter study. Biomed Res Int. 2017;2017:7594953.
34. Nasreddine G, El-Sibai M, Abi-Habib RJ. Cytotoxicity of [HuArgI (co)-PEG5000]-induced arginine deprivation to ovarian cancer cells is autophagy dependent. Investig New Drugs. 2019;38:10–9.
35. de Tayrac M, Etcheverry A, Aubry M, et al. Integrative genome-wide analysis reveals a robust genomic glioblastoma signature associated with copy number driving changes in gene expression. Genes Chromosom Cancer. 2009;48:55–68.
36. Wang D, Qian X, Rajaram M, Durkin ME, Lowy DR. DLC1 is the principal biologically-relevant down-regulated DLC family member in several cancers. Oncotarget. 2016;7:45144–57.
37. Al-Haddad R, Karnib N, Assaad RA, et al. Epigenetic changes in diabetes. Neurosci Lett. 2016;625:64–9.
38. Sharma A, Kaut O, Pavlova A, et al. Skewed X-chromosome inactivation and XIST locus methylation levels do not contribute to the lower prevalence of Parkinson's disease in females. Neurobiol Aging. 2017;57:248.e1–48.e5.
39. Shammas H, Kuech E-M, Rizk S, Das AM, Naim HY. Different Niemann-Pick C1 genotypes generate protein phenotypes that vary in their intracellular processing, trafficking and localization. Sci Rep. 2019;9:5292.
40. Hankins GR, Sasaki T, Lieu AS, et al. Identification of the deleted in liver cancer 1 gene, DLC1, as a candidate meningioma tumor suppressor. Neurosurgery. 2008;63:771–80 **(discussion 80-1)**.
41. Harden SV, Tokumaru Y, Westra WH, et al. Gene promoter hypermethylation in tumors and lymph nodes of stage I lung cancer patients. Clin Cancer Res. 2003;9:1370–5.
42. Peng H, Long F, Wu Z, et al. Downregulation of DLC-1 gene by promoter methylation during primary colorectal cancer progression. Biomed Res Int. 2013;2013:181384.

Author's personal copy

43. El-Sibai M, Pertz O, Pang H, et al. RhoA/ROCK-mediated switching between Cdc42- and Rac1-dependent protrusion in MTLn3 carcinoma cells. Exp Cell Res. 2008;314:1540–52.
44. Fagan-Solis KD, Schneider SS, Pentecost BT, et al. The RhoA pathway mediates MMP-2 and MMP-9-independent invasive behavior in a triple-negative breast cancer cell line. J Cell Biochem. 2013;114:1385–94.
45. Li W, Chong H, Guan KL. Function of the Rho family GTPases in Ras-stimulated Raf activation. J Biol Chem. 2001;276:34728–37.
46. Morrison DK, Cutler RE. The complexity of Raf-1 regulation. Curr Opin Cell Biol. 1997;9:174–9.
47. Leung TH, Yam JW, Chan LK, Ching YP, Ng IO. Deleted in liver cancer 2 suppresses cell growth via the regulation of the Raf-1-ERK1/2-p70S6K signalling pathway. Liver Int. 2010;30:1315–23.
48. Zhang H, Wang F, Hu Y. STARD13 promotes hepatocellular carcinoma apoptosis by acting as a ceRNA for Fas. Biotechnol Lett. 2017;39:207–17.
49. Pezeshkpoor B, Berkemeier AC, Czogalla KJ, Oldenburg J, El-Maarri O. Evidence of pathogenicity of a mutation in 3′ untranslated region causing mild haemophilia A. Haemophilia. 2016;22:598–603.
50. Guo X, Xiang C, Zhang Z, Zhang F, Xi T, Zheng L. Displacement of Bax by BMF Mediates STARD13 3′UTR-Induced Breast Cancer Cells Apoptosis in an miRNA-Depedent Manner. Mol Pharm. 2018;15:63–71.
51. Laufs U, Marra D, Node K, Liao JK. 3-Hydroxy-3-methylglutaryl-CoA reductase inhibitors attenuate vascular smooth muscle proliferation by preventing rho GTPase-induced down-regulation of p27(Kip1). J Biol Chem. 1999;274:21926–31.
52. Mammoto A, Huang S, Moore K, Oh P, Ingber DE. Role of RhoA, mDia, and ROCK in cell shape-dependent control of the Skp2-p27kip1 pathway and the G1/S transition. J Biol Chem. 2004;279:26323–30.
53. Seasholtz TM, Zhang T, Morissette MR, Howes AL, Yang AH, Brown JH. Increased expression and activity of RhoA are associated with increased DNA synthesis and reduced p27(Kip1) expression in the vasculature of hypertensive rats. Circ Res. 2001;89:488–95.
54. Muppani N, Nyman U, Joseph B. TAp73alpha protects small cell lung carcinoma cells from caspase-2 induced mitochondrial mediated apoptotic cell death. Oncotarget. 2011;2:1145–54.
55. Vikhreva P, Melino G, Amelio I. p73 alternative splicing: exploring a biological role for the C-terminal isoforms. J Mol Biol. 2018;430:1829–38.
56. El-Amm J, Aragon-Ching JB. Targeting bone metastases in metastatic castration-resistant prostate cancer. Clin Med Insights Oncol. 2016;10:11–9.
57. Daaboul HE, Dagher C, Taleb RI, et al. The chemotherapeutic effect of beta-2-himachalen-6-ol in chemically induced skin tumorigenesis. Biomed Pharmacother. 2018;103:443–52.
58. Nader R, El Amm J, Aragon-Ching JB. Role of chemotherapy in prostate cancer. Asian J Androl. 2018;20:221–9.
59. Audi H, Azar DF, Mahjoub F, et al. Cytotoxicity modulation of ruthenium(II) tris-bathophenanthroline complexes with systematically varied charge. J Photochem Photobiol A. 2018;351:59–68.
60. Abou-Antoun TJ, Hale JS, Lathia JD, Dombrowski SM. Brain cancer stem cells in adults and children: cell biology and therapeutic implications. Neurotherapeutics. 2017;14:372–84.
61. Abou-Antoun TJ, Nazarian J, Ghanem A, Vukmanovic S, Sandler AD. Molecular and functional analysis of anchorage independent, treatment-evasive neuroblastoma tumorspheres with enhanced malignant properties: a possible explanation for radio-therapy resistance. PLoS One. 2018;13:e0189711.
62. Khalife R, Hodroj MH, Fakhoury R, Rizk S. Thymoquinone from Nigella sativa seeds promotes the antitumor activity of noncytotoxic doses of topotecan in human colorectal cancer cells in vitro. Planta Med. 2016;82:312–21.
63. Najar M, Fayyad-Kazan H, Faour WH, et al. Human hepatic stellate cells and inflammation: a regulated cytokine network balance. Cytokine. 2017;90:130–4.
64. Al-Dimassi S, Salloum G, Saykali B, et al. Targeting the MAP kinase pathway in astrocytoma cells using a recombinant anthrax lethal toxin as a way to inhibit cell motility and invasion. Int J Oncol. 2016;48:1913–20.
65. Braun AC, Olayioye MA. Rho regulation: DLC proteins in space and time. Cell Signal. 2015;27:1643–51.
66. Vitiello E, Ferreira JG, Maiato H, Balda MS, Matter K. The tumour suppressor DLC2 ensures mitotic fidelity by coordinating spindle positioning and cell-cell adhesion. Nat Commun. 2014;5:5826.
67. Faour WH, Fayyad-Kazan H, El Zein N. fMLP-dependent activation of Akt and ERK1/2 through ROS/Rho A pathways is mediated through restricted activation of the FPRL1 (FPR2) receptor. Inflamm Res. 2018;67:711–22.
68. Al Hassan M, Fakhoury I, El Masri Z, et al. Metformin treatment inhibits motility and invasion of glioblastoma cancer cells. Anal Cell Pathol (Amst). 2018;2018:5917470.
69. Jin X, Zhu Z, Shi Y. Metastasis mechanism and gene/protein expression in gastric cancer with distant organs metastasis. Bull Cancer. 2014;101:E1–.
70. Fayyad-Kazan H, Faour WH, Badran B, Lagneaux L, Najar M. The immunomodulatory properties of human bone marrow-derived mesenchymal stromal cells are defined according to multiple immunobiological criteria. Inflamm Res. 2016;65:501–10.
71. Zaatiti H, Abdallah J, Nasr Z, Khazen G, Sandler A, Abou-Antoun TJ. Tumorigenic proteins upregulated in the MYCN-amplified IMR-32 human neuroblastoma cells promote proliferation and migration. Int J Oncol. 2018;52:787–803.
72. Takaoka M, Ito S, Miki Y, Nakanishi A. FKBP51 regulates cell motility and invasion via RhoA signaling. Cancer Sci. 2017;108:380–9.
73. Worthylake RA, Lemoine S, Watson JM, Burridge K. RhoA is required for monocyte tail retraction during transendothelial migration. J Cell Biol. 2001;154:147–60.
74. Basak P, Leslie H, Dillon RL, Muller WJ, Raouf A, Mowat MRA. In vivo evidence supporting a metastasis suppressor role for Stard13 (Dlc2) in ErbB2 (Neu) oncogene induced mouse mammary tumors. Genes Chromosomes Cancer. 2018;57:182–91.
75. Prudnikova TY, Rawat SJ, Chernoff J. Molecular pathways: targeting the kinase effectors of RHO-family GTPases. Clin Cancer Res. 2015;21:24–9.
76. Zhou FQ, Snider WD. Intracellular control of developmental and regenerative axon growth. Philos Trans R Soc Lond B Biol Sci. 2006;361:1575–92.
77. El-Sibai M, Nalbant P, Pang H, et al. Cdc42 is required for EGF-stimulated protrusion and motility in MTLn3 carcinoma cells. J Cell Sci. 2007;120:3465–74.
78. Fostok SF, El-Sibai M, El-Sabban M, Talhouk RS. Gap junctions and Wnt signaling in the mammary gland: a cross-talk? J Mammary Gland Biol Neoplasia. 2019;24:17–38.
79. Stengel K, Zheng Y. Cdc42 in oncogenic transformation, invasion, and tumorigenesis. Cell Signal. 2011;23:1415–23.
80. Yamaguchi H, Pixley F, Condeelis J. Invadopodia and podosomes in tumor invasion. Eur J Cell Biol. 2006;85:213–8.
81. Lin Y, Chen NT, Shih YP, Liao YC, Xue L, Lo SH. DLC2 modulates angiogenic responses in vascular endothelial cells by regulating cell attachment and migration. Oncogene. 2010;29:3010–6.
82. Tang F, Zhang R, He Y, Zou M, Guo L, Xi T. MicroRNA-125b induces metastasis by targeting STARD13 in MCF-7 and MDA-MB-231 breast cancer cells. PLoS ONE. 2012;7:e35435.

Author's personal copy

83. Chang S, He S, Qiu G, et al. MicroRNA-125b promotes invasion and metastasis of gastric cancer by targeting STARD13 and NEU1. Tumour Biol. 2016;37:12141–51.
84. Li X, Zheng L, Zhang F, et al. STARD13-correlated ceRNA network inhibits EMT and metastasis of breast cancer. Oncotarget. 2016;7:23197–211.
85. Najar M, Fayyad-Kazan H, Faour WH, Badran B, Journe F, Lagneaux L. Breast cancer cells and bone marrow mesenchymal stromal cells: a regulated modulation of the breast tumor in the context of immune response. Inflamm Res. 2017;66:129–39.
86. Najar M, Fayyad-Kazan H, Faour WH, et al. Immunological modulation following bone marrow-derived mesenchymal stromal cells and Th17 lymphocyte co-cultures. Inflamm Res. 2019;68:203–13.
87. Neufeld G, Cohen T, Gengrinovitch S, Poltorak Z. Vascular endothelial growth factor (VEGF) and its receptors. Faseb J. 1999;13:9–22.
88. Sellami N, Lamine LB, Turki A, et al. Association of VEGFA variants with altered VEGF secretion and type 2 diabetes: a case–control study. Cytokine. 2018;106:29–34.
89. Hu J, Li X, Guo X, et al. The CCR2 3'UTR functions as a competing endogenous RNA to inhibit breast cancer metastasis. J Cell Sci. 2017;130:3399–413.
90. Yuan BZ, Miller MJ, Keck CL, Zimonjic DB, Thorgeirsson SS, Popescu NC. Cloning, characterization, and chromosomal localization of a gene frequently deleted in human liver cancer (DLC-1) homologous to rat RhoGAP. Cancer Res. 1998;58:2196–9.
91. Kim TY, Vigil D, Der CJ, Juliano RL. Role of DLC-1, a tumor suppressor protein with RhoGAP activity, in regulation of the cytoskeleton and cell motility. Cancer Metastasis Rev. 2009;28:77–83.
92. Cao X, Voss C, Zhao B, Kaneko T, Li SS. Differential regulation of the activity of deleted in liver cancer 1 (DLC1) by tensins controls cell migration and transformation. Proc Natl Acad Sci USA. 2012;109:1455–60.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.