MEDWIN PUBLISHERS
Committed to Create Value for Researchers

Advances in Clinical Toxicology
ISSN: 2577-4328

The Role of VGLL4 in Development and Progression of Tumors

Zhang H, Zhong Y, Chen H and Yu W*

Key Laboratory of Respiratory Disease, People's Hospital of Yangjiang, China

***Corresponding author:** Wei Yu, Key Laboratory of Respiratory Disease, People's Hospital of Yangjiang, Yangjiang, Guangdong, China, Email: yuwei@sibs.ac.cn

Mini Review

Volume 8 Issue 4

Received Date: November 20, 2023

Published Date: December 12, 2023

DOI: 10.23880/act-16000288

Abstract

The Hippo pathway plays an important role in controlling the size of organs, as well as cell proliferation, apoptosis and tumor formation. VGLL is a recently discovered family of proteins that can interact with TEAD, a transcription factor downstream of the Hippo pathway, and is an important regulatory factor in tumorigenesis. Unlike other members of the VGLL family, VGLL4 contains two TDU domains that can compete with YAP to bind TEADs to inhibit the transcriptional function of YAP. Overexpression of VGLL4 can inhibit malignant transformation of cells and is considered a tumor suppressor. VGLL4, as a transcriptional cofactor of the Hippo pathway, is involved in regulating the occurrence and development of tumors. Further studying the role and mechanism of VGLL4 in Hippo and other tumor-related pathways in the development and progression of cancer will provide new ideas for the prevention and treatment of human tumors.

Keywords: Hippo pathway; VGLL4; Tumor; Cancer

Abbreviations: VGLL: Vestigial-Like; TEAD: Transcriptional Enhanced Associate Domain; YAP: Yes-Associated Protein; MST: Mammalian Sterile 20-like Kinase; LATS: Large Tumor Suppressor Kinases; MOB: Mob Kinase Activator; EMT: Epithelial-Mesenchymal Transition; UTR: Untranslated Region; USCLC: Non-Small Cell Lung Cancer; HCC: Hepatocellular Carcinoma; USP: Ubiquitin Specific Peptidase; CDK: Cyclin Dependent Kinase; TCF: Transcription Factor; NICD: Notch Intracellular Domain.

Introduction

The Hippo signaling pathway controls the size of organ development by regulating cell proliferation and apoptosis, and its activity is strictly controlled under normal conditions. Once the Hippo pathway is deregulated, uncontrolled proliferation and apoptosis inhibition can occur, leading to the development of malignant tumors. Recently, the Hippo pathway maintenance protein VGLL4 has been found to play an important inhibitory role in the occurrence and development of tumors. Many research groups have conducted a series of studies on it as a target for tumor treatment, and have made some progress. This review will focus on the recent progress of tumor research targeting VGLL4 and its related signaling pathway.

The Occurrence of Tumors and the Hippo Signaling Pathway

The Hippo signaling pathway was first discovered in Drosophila melanogaster, and subsequently homologous molecules were also found in mammals [1,2]. In mammals, the Hippo signaling pathway consists of a series of protein kinases MST1/2 (mammalian sterile 20-like kinase 1/2), Salv1 (Salvador homolog 1), LATS1/2 (large tumor suppressor kinases 1/2), MOB1 (Mob kinase activator 1), as well as transcription factors YAP and TAZ. Under conditions of Hippo pathway activation, SAV1 and MOB1 can bind to MST1/2 and

LATS1/2, respectively, and phosphorylate them to activate them [3]. This activation then phosphorylates transcription factors YAP/TAZ. Once YAP/TAZ is phosphorylated, it cannot enter the nucleus and is instead distributed in the cytoplasm and degraded by proteasomes. When Hippo is inactivated, YAP/TAZ is dephosphorylated and enters the nucleus, regulating the expression of genes related to cell proliferation and promoting tumor formation [4]. Therefore, the Hippo signaling pathway negatively regulates YAP activity through this cascade of phosphorylation reactions, playing a role in inhibiting tumors and precisely controlling the normal development of various tissues and organs during development. Transcriptional co-factor YAP is highly expressed in various human tumors, including primary liver cancer, glioma, squamous cell carcinoma, colon cancer, ovarian cancer, lung cancer, and prostate cancer [5]. TAZ, as a co-activator protein, is also associated with the formation of breast cancer and non-small cell lung cancer [6]. The deletion of Sav1 or Mst1/Mst2 will lead to excessive liver growth and the subsequent development of liver tumors [7]. Lats1 and Lats2 inhibit tumor cell growth by preventing G2-M and G1-S transitions [8]. In some tumors, Lats1/2 has been found to be mutated or under expressed as a tumor suppressor gene, such as leukemia, lung cancer, prostate cancer and breast cancer [9].

The Discovery of VGLL and its Protein Structure

In 1919, Morgan discovered a vestigial gene mutant in fruit flies and named it vestigial (vg). Subsequently, Williams pointed out that the protein encoded by the Vestigial gene is a nuclear localization protein that regulates the development of wings and balancers in fruit flies. Further research found that Vg is a transcriptional cofactor that requires interaction with the transcription factor Scalloped (sd) to exert transcriptional activation function. The Vg-Sd complex binds to specific DNA sequences through the TEA domain of the Sd protein to activate the expression of downstream related genes and regulate the development of wings in fruit flies [10]. Until 1999, Vaudin et al. first discovered the homologous gene TONDU (TDU) of vg in the human genome. TONDU is a domain containing 24 amino acids, which is highly homologous to the domain that binds Vg to Sd [11]. The TEAD/TEF transcription factor family (TEAD1-4) in mammals is homologous to the Sd gene in Drosophila. VGLL requires interaction with TEAD to exert its transactivation function. Genes containing the TDU domain have been discovered in mammals, and due to their similarity to Vestigial genes, they are classified as vestigial-like (VGLL) gene family. Currently, it is believed that there are four members of the VGLL gene family in mammals: VGLL1-4. Among them, VGLL1-3 contain a TDU domain consisting of 24 amino acids, which belongs to a subfamily; VGLL4 has two TDU domains consisting of 10 amino acids, with an 18-amino acid linker region between the two domains, thus belonging to another subfamily [12].

Expression and Regulation of VGLL and Interaction with VGLL Protein

VGLL1 is the first VGLL protein discovered and also known as TONDU, mainly expressed in human embryos in the lungs and kidneys [11]. VGLL1 can interact with four TEAD proteins (TEAD1-4) in mammals. The VGLL1-TEAD protein complex is similar to the YAP-TEAD protein complex, which can activate the expression of proliferation-related genes. Recent RNA-Seq studies have shown that VGLL1 is highly expressed in breast cancer, so VGLL1 is thought to be associated with tumor formation [13]. VGLL2, also known as VITO-1, is mainly expressed in skeletal muscle and can not only interact with TEAD but also bind to MEF2 to regulate the proliferation and differentiation of muscle cells [14]. VGLL3, also known as VITO-2, is expressed in placental tissue, skeletal muscle, heart, liver, and brain [15]. In addition, it has been found that VGLL3 is highly expressed in soft tissue sarcomas, and inhibiting the expression of VGLL3 in vitro can slow down the proliferation and migration rates of cells, indicating that VGLL3 can promote tumor formation [16].

VGLL4 is different from VGLL1-3 in that it contains two TDU domains. Studies have found that it can interact with TEAD and MEF2, so VGLL4 is thought to also enhance the binding of TEAD to MEF2 [17]. In addition, VGLL4 competes with YAP to bind to TEAD, and is considered a suppressor of TEAD. Overexpression of VGLL4 in tumors can inhibit tumorigenesis and development [18].

It has been found that the protein level regulation of VGLL4 is related to the deubiquitinating enzyme USP11. The deubiquitination domain of USP11 binds to the N-terminal region of VGLL4, resulting in deubiquitination of VGLL4 for increased stability. Knockdown of USP11 in vitro enhances YAP-TEAD activity, significantly promotes cell proliferation rate and migration invasion ability [19]. The interaction between TEAD and YAP requires TEAD auto-methylation, while the binding between TEAD and VGLL4 does not require this methylation [20]. There are also studies indicating that P300 can methylate the K225 site of VGLL4 to regulate the inhibitory effect of VGLL4 on the YAP-TEAD complex [21].

The Role of VGLL4 in Tumors

In 2012, Mann and others first proposed that VGLL4 is a potential tumor suppressor in human pancreatic cancer [22]. Subsequently, Pan et al. further overexpressed VGLL4 in a transgenic mouse model of liver-specific overexpression of YAP-induced liver tumors, and found that it could

significantly inhibit tumor formation, confirming for the first time the inhibitory role of VGLL4 in tumor formation [23]. Since then, research on VGLL4 in tumors has been carried out one after another.

Cai et al. generated a conditional VGLL4 knockout mouse model to investigate the functional relationship between VGLL4 and YAP. It was found that the deletion of VGLL4 completely rescued the developmental defects of Yap mutant liver and lung, greatly enhanced the occurrence of intrahepatic cholangiocarcinoma formation in Nf2-deficient liver, and improved CCl4-induced liver injury. The results showed that the main function of YAP in normal tissue development is to antagonize the default inhibition mediated by VGLL4. The YAP-VGLL4 antagonistic effect also regulates the Hippo signaling output and regeneration in tumorigenesis [24]. IRF2BP2 is directly inhibited by the YAP/TEAD4 transcription complex and can inhibit YAP activity through a feedback loop. Liver-specific IRF2BP2 overexpression inhibits tumor formation induced by Hippo pathway inactivation [25]. Zhang et al. found that the expression of VGLL4 was down-regulated in mouse lung cancer cells, and in a novel mouse lung cancer model, overexpressed VGLL4 using lentiviral vectors. They found that VGLL4 could inhibit the progression of lung cancer, and proposed that this inhibitory effect of VGLL4 was achieved by competing with YAP to bind TEAD4, reducing the transcriptional activity of TEAD4, thereby inhibiting the proliferation of tumor cells [26]. Wu et al. targeted immune checkpoints, opening up a new avenue for treating cancer. VGLL4 is an important regulator of cancer immune checkpoint PD-L1. VGLL4 deficiency reduces PD-L1 expression in tumor cells, and YAP inhibits PD-L1 expression, enabling tumor cells to evade immune cell attacks [27].

Zhou et al. proposed that the inhibitory effect of VGLL4 on YAP is achieved by competing with YAP for TEAD binding through its TDU domain. They synthesized a TDU analog short peptide “Super-TDU” to inhibit the formation of the YAP-TEAD complex. In a mouse model of gastric cancer, intravenous injection of Super-TDU short peptides effectively reduced tumor size and weight. In vitro experiments using human gastric primary cells also showed that this short peptide effectively inhibited cell proliferation and provided a theoretical basis for clinical application [28]. In gastric cancer, downregulation of VGLL4 is associated with microRNA (miR-222). miR-222 directly targets VGLL4 to reduce its protein expression. Meanwhile, activation of YAP-TEAD1 can further upregulate miR-222 expression, forming a regulatory chain of miR-222/VGLL4/YAP-TEAD1 that maintains low VGLL4 expression in tumor cells [29]. Other studies have knocked down or overexpressed VGLL4 in human gastric cancer cell lines and transplanted them into mice, finding that VGLL4 overexpression slowed tumor growth while VGLL4 knockdown led to faster tumor growth. This again demonstrates the inhibitory effect of VGLL4 in gastric cancer progression. It has also been proposed that VGLL4 can inhibit the epithelial-mesenchymal transition (EMT) process of tumor cells by inhibiting the Wnt/b-catenin signaling pathway [30]. Geng et al. found that HOXB13 expression is significantly reduced in human gastric cancer cells. They also found that HOXB13 overexpression can transcriptionally activate VGLL4 to inhibit TEAD4 participation in the Hippo signaling pathway, thereby inhibiting gastric cancer cell proliferation, migration, and invasion while promoting apoptosis [31]. VGLL4 can bind to IRF2BP2, increasing the interaction between TEAD4 and YAP1 and leading to coactivation of YAP1 downstream target gene CTGF transcription [32].

During the formation of tumors, several microRNAs have been studied for their regulatory effects on VGLL4, including miR-130a, miR-130b, miR-346 and miR-301a-3p. It has been shown that miR-130a is a target gene of YAP-TEAD, which can activate the expression of miR-130a. miR-130a then binds to the 3’UTR of VGLL4, inhibiting the translation of VGLL4 and reducing its protein level. When miR-130a is specifically suppressed by anti-sense oligonucleotides, the protein level of VGLL4 significantly increases [33]. In bladder cancer, VGLL4 is a direct target of miR-130b, which plays an important role in regulating the translation of VGLL4. Overexpression of miR-130b can reduce the protein level of VGLL4, while knockout of miR-130b can increase the protein level of VGLL4, but there is no significant change in the mRNA level of VGLL4. VGLL4 inhibition is crucial for miR-130b-induced proliferation, migration, and invasion of BCa cells [34]. In non-small cell lung cancer (NSCLC), VGLL4 is a target gene of miR-346, and the formed miR-346/VGLL4 axis is regulated by Circular RNA Circ_ 0006427. Circ_0006427 competes with VGLL4 for miR-346 binding, inhibiting the proliferation, migration, and invasion of NSCLC cells. Liu et al. found that the expression of LINC00641 and VGLL4 decreased, while the expression of miR-365a-3p increased in human prostate cancer (PCa) samples. In addition, it was also found that overexpression of LINC00641 inhibited the growth and invasion of prostate cancer cells, while overexpression of miR-365a-3p promoted the growth and invasion of prostate cancer cells. Molecular mechanism studies found that miR-365a-3p/VGLL4 is a downstream target of LINC00641. miR-365a-3p is up-regulated in PCa and can directly bind to LINC00641. LINC00641 can regulate the expression of VGLL4 through miR-365a-3p. In summary, LINC00641 can act as a tumor suppressor lncRNA in PCa, affecting the growth and invasion of PCa cells through the MIR-365a-3p/VGLL4 axis [35]. miR-301a-3p is upregulated in hepatocellular carcinoma (HCC) tissues and cell lines, and high miR-301a-3p expression predicts poor prognosis in HCC patients. miR-301a-3p overexpression enhances the proliferation, invasion, and chemotherapy resistance of HCC

cell lines. VGLL4 is a direct target of miR-301a-3p, which targets VGLL4 to upregulate TEAD transcriptional activity and VGLL4 expression, thereby reducing the promotion effect of miR-301a-3p on tumor cells [36].

In a study using human esophageal squamous cell carcinoma primary cells to overexpress VGLL4 in vitro, it was found that Ctgf was downregulated, effectively inhibiting the proliferation and migration of cancer cells [37]. In epidermal squamous cell carcinoma, VGLL4 inhibits YAP1/TEAD dependent transcription, thereby reducing the expression of YAP1 target genes (CCND1, CYR61, and CTGF) and pro-oncogenic collagen genes (COL1A2 and COL3A1). The loss of these YAP1-regulated genes is necessary for VGLL4 to inhibit the phenotype of cancer cells, as forced expression of CCND1 or COL1A2 partially restores the invasive cancer phenotype in VGLL4-expressing cells. Consistent with these findings, decreased VGLL4 expression is associated with reduced tumor formation, which is associated with reduced mRNA and protein levels of CCND1, CYR61, CTGF, COL1A2, and COL1A3, as well as reduced expression of EMT markers [38].

In human colon cancer samples, the expression level of VGLL4 was also significantly inhibited. The study pointed out that the level of tumor VGLL4 was also positively correlated with patient survival rate. At the same time, it was also found that the expression level of VGLL4 was negatively correlated with Wnt downstream genes. Further injection of TDU analog short peptide Super-TDU in mouse colon cancer model could effectively inhibit the progression of colon cancer [39]. Molecular mechanism research found that TEAD4 could interact with TCF4 to regulate the downstream target genes of Wnt signaling pathway. On the other hand, VGLL4 could compete with TCF4 to bind to TEAD4, thereby inhibiting the transcriptional function of TCF4. VGLL4 could regulate the binding of TEAD4-TCF4 to jointly regulate the Hippo and Wnt signaling pathways [39]. In colorectal cancer patients, VGLL4-positive and low-expression YAP are significantly positively correlated with good prognosis. It is proposed that VGLL4 inhibits the development of colorectal cancer by competitively binding to TEAD4 with YAP, leading to good prognosis [40].

In breast cancer samples, the low expression level of VGLL4 was also found to be positively correlated with the survival rate of patients. Overexpression of VGLL4 in breast cancer cell lines in vitro and transplanted tumors in mice can effectively inhibit the proliferation and migration of breast cancer cells [18]. VGLL4 interacts with the core component of the JAK-STAT pathway, STAT3, resulting in STAT3 inactivation and inhibition of downstream transcription of STAT3. VGLL4 acts as a tumor suppressor in TNBC by interacting with STAT3, subsequently inhibiting the STAT3 signaling axis, providing potential biomarkers and therapeutic methods for this deadly disease [41].

The study found that USP11, a deubiquitinating enzyme, was identified as a new VGLL4 interactant. USP11 controls the stability of VGLL4 protein by promoting its deubiquitination. Knocking down USP11 promotes cell growth, migration, and invasion in a YAP-dependent manner [22]. VGLL4 interacts with cIAP1, cIAP2, and XIAP. VGLL4 is mainly expressed in the nucleus and triggers the relocation of IAP from the cytoplasm to the nucleus, inhibiting the ability of IAP to prevent cell apoptosis [42]. In the process of cell mitosis, Ser-58, -155, -280 and Thr-159 of VGLL4 can be phosphorylated by CDK1. After the mutation of the four phosphorylation sites, VGLL4 cannot be phosphorylated and has higher affinity with TEAD, which can effectively inhibit the generation of pancreatic cancer tumors, suggesting that its tumor inhibitory function will be blocked after VGLL4 phosphorylation [43].

Communication between Tumor-Related Signaling Pathways and Prospects

Hippo and Wnt signaling pathways regulate biological individual development and maintain tissue homeostasis. In recent years, advances in the study of the mechanisms of tumorigenesis and development have also attracted increasing attention. The β-Catenin of the Wnt pathway is associated with the occurrence of malignant tumors [44]. In human colon cancer tissues, more than 90% have abnormal activation of β-Catenin, while the activity of YAP/TAZ in the Hippo pathway also significantly increases during the progression of colon cancer [45]. Both Hippo and Wnt signaling pathways require the activity regulation of phosphorylation-dependent core transcriptional co-factors. Some studies have found that the transcriptional activators YAP/TAZ of Hippo and Wnt signaling pathways can interact with β-Catenin. In addition, the downstream transcription factor TEAD4 of the Hippo pathway and the downstream transcription factor TCF4 of the Wnt pathway can directly interact with each other to regulate the expression of target gene promoters, thus affecting the growth of tumor cells. The latest research indicates that VGLL4 can target the TEAD4-TCF4 complex and simultaneously inhibit the TEAD4-TCF4 transcriptional activity, thereby playing a role in inhibiting tumor growth [39].

TGF-β Signal pathway plays an important role in the pathogenesis of breast cancer. During tumor formation, TGF-β, the growth factor of the family can bind to the receptors on the surface of cells, and bind to and phosphorylate the Smad family proteins. The Smad proteins in the cytoplasm then enter the nucleus to regulate the transcription of downstream target genes, activating the EMT process to promote tumor migration and deterioration [46]. The pathways communicate with each other, some studies have

found that Hippo can also interact with TGF- β, YAP1 can bind to Smad2 and is regulated by a tumor suppressor factor RASSF1A in the Hippo pathway [47]. In addition, YAP/TAZ in the Hippo pathway can also form a Smad2/3/YAP/TEAD protein complex, enhancing CTGF expression, promoting cancer cell proliferation and extracellular matrix secretion [48].

The inactivation of the Hippo signaling pathway is the main cause of liver cancer. Inhibition of the Hippo signaling pathway in the liver by knocking out Mst1 and Mst2 leads to the activation of genes related to the Wnt and Notch signaling pathways. The NICD protein of the Notch pathway further interacts with TAP/TAZ and enhances the transcriptional activity and stability of YAP/TAZ, ultimately inducing liver cancer. In this process, the further knockdown of β-Catenin in the Wnt signaling pathway will further accelerate the formation of liver tumors in situ [44].

VGLL4 plays an important inhibitory role in tumor formation through multiple mechanisms, providing new technological tools for cancer treatment. It remains to be further investigated whether VGLL4, as a tumor suppressor, plays a role in the formation of transcription factor protein complexes between related signaling pathways. In addition to its tumor-suppressing role, VGLL4 also plays an important role in cardiac growth, valve development, muscle regeneration, and bone development. Further research to explore the genetic function of VGLL4 remains a hot topic [21,49-51].

References

1. Justice RW, Zilian O, Woods DF, Noll M, Bryant PJ (1995) The Drosophila tumor suppressor gene warts encodes a homolog of human myotonic dystrophy kinase and is required for the control of cell shape and proliferation. Genes Dev 9(5): 534-546.

2. Xu T, Wang W, Zhang S, Stewart RA, Yu W (1995) Identifying tumor suppressors in genetic mosaics: the Drosophila lats gene encodes a putative protein kinase. Development 121(4): 1053-1063.

3. Praskova M, Xia F, Avruch J (2008) MOBKL1A/MOBKL1B phosphorylation by MST1 and MST2 inhibits cell proliferation. Curr Biol 18(5): 311-21.

4. Zanconato F, Cordenonsi M, Piccolo S (2016) YAP/TAZ at the Roots of Cancer. Cancer Cell 29(6): 783-803.

5. Zanconato F (2016) YAP/TAZ as therapeutic targets in cancer. Curr Opin Pharmacol 29: 26-33.

6. Zhou Z, Hao Y, Liu N, Raptis L, Tsao MS, et al. (2011) TAZ is a novel oncogene in non-small cell lung cancer. Oncogene 30(18): 2181-2186.

7. Zhang X, Guo C, Wu X, Li XA, Liu L, et al. (2016) Analysis of Liver Tumor-Prone Mouse Models of the Hippo Kinase Scaffold Proteins RASSF1A and SAV1. Cancer Res 76(9): 2824-2835.

8. Hori T, Takaori-Kondo A, Kamikubo Y, Uchiyama T (2000) Molecular cloning of a novel human protein kinase, kpm, that is homologous to warts/lats, a Drosophila tumor suppressor. Oncogene 19(27): 3101-3109.

9. Visser S, Yang X (2010) Identification of LATS transcriptional targets in HeLa cells using whole human genome oligonucleotide microarray. Gene 449(1-2): 22-29.

10. Kim J, Sebring A, Esch JJ, Kraus ME, Vorwerk K, et al. (1996) Integration of positional signals and regulation of wing formation and identity by Drosophila vestigial gene. Nature 382(6587): 133-138.

11. Vaudin P, Delanoue R, Davidson I, Silber J, Zider A (1999) TONDU (TDU), a novel human protein related to the product of vestigial (vg) gene of Drosophila melanogaster interacts with vertebrate TEF factors and substitutes for Vg function in wing formation. Development 126(21): 4807-4816.

12. Yamaguchi N (2020) Multiple Roles of Vestigial-Like Family Members in Tumor Development. Front Oncol 10: 1266.

13. Castilla MA, López-García MA, Atienza MR, Rosa-Rosa JM, Díaz-Martín J (2014) VGLL1 expression is associated with a triple-negative basal-like phenotype in breast cancer. Endocr Relat Cancer 21(4): 587-599.

14. Maeda T, Chapman DL Stewart AF (2002) Mammalian vestigial-like 2, a cofactor of TEF-1 and MEF2 transcription factors that promotes skeletal muscle differentiation. J Biol Chem 277(50): 48889-48898.

15. Mielcarek M, Piotrowska I, Schneider A, Günther S, Braunet T (2009) VITO-2, a new SID domain protein, is expressed in the myogenic lineage during early mouse embryonic development. Gene Expr Patterns 9(3): 129-137.

16. Helias-Rodzewicz Z, Pérot G, Chibon F, Ferreira C, Lagarde P, et al (2010) YAP1 and VGLL3, encoding two cofactors of TEAD transcription factors, are amplified and overexpressed in a subset of soft tissue sarcomas. Genes Chromosomes Cancer 49(12): 1161-1171.

17. Chen HH, Mullett SJ, Stewart AF (2004) Vgl-4, a novel

member of the vestigial-like family of transcription cofactors, regulates alpha1-adrenergic activation of gene expression in cardiac myocytes. J Biol Chem 279(29): 30800-30806.

18. Zhang Y, Shen H, Withers HG, Yang N, Denson KE, et al. (2017) VGLL4 Selectively Represses YAP-Dependent Gene Induction and Tumorigenic Phenotypes in Breast Cancer. Sci Rep 7(1): 6190.

19. Zhang E, Shen B, Mu X, Qin Y, Zhang F, et al (2016) Ubiquitin-specific protease 11 (USP11) functions as a tumor suppressor through deubiquitinating and stabilizing VGLL4 protein. Am J Cancer Res 6(12): 2901-2909.

20. Chan P, Han X, Zheng B, DeRan M, Yu J, et al. (2016) Autopalmitoylation of TEAD proteins regulates transcriptional output of the Hippo pathway. Nat Chem Biol 12(4): 282-289.

21. Lin Z, Guo H, Cao Y, Zohrabian S, Zhou P, Ma Q, et al. (2016) Acetylation of VGLL4 Regulates Hippo-YAP Signaling and Postnatal Cardiac Growth. Dev Cell 39(4): 466-479.

22. Mann KM, Jerrold MW, Christopher CKY, Anne K, David WD, al. (2012) Sleeping Beauty mutagenesis reveals cooperating mutations and pathways in pancreatic adenocarcinoma. Proc Natl Acad Sci U S A 109(16): 5934-5941.

23. Koontz LM, Chittenden YL, Yin F, Zheng Y, Jianzhong Y, et al. (2013) The Hippo effector Yorkie controls normal tissue growth by antagonizing scalloped-mediated default repression. Dev Cell 25(4): 388-401.

24. Cai J, Kyungsuk C, Hongde L, Katiuska DPP, Yonggang Z, et al. (2022) YAP-VGLL4 antagonism defines the major physiological function of the Hippo signaling effector YAP. Genes Dev 36(21-24): 1119-1128.

25. Feng X, Tiantian L, Jinhui L, Ruizeng Y, Liqiao H, et al. (2020) The Tumor Suppressor Interferon Regulatory Factor 2 Binding Protein 2 Regulates Hippo Pathway in Liver Cancer by a Feedback Loop in Mice. Hepatology 71(6): 1988-2004.

26. Zhang W, Yijun G, Peixue L, Zhubing S, Tong G, et al. (2014) VGLL4 functions as a new tumor suppressor in lung cancer by negatively regulating the YAP-TEAD transcriptional complex. Cell Res 24(3): 331-343.

27. Wu A, Qingzhe W, Yujie D, Yuning L, Jinqiu L, et al. (2019) Loss of VGLL4 suppresses tumor PD-L1 expression and immune evasion. EMBO J 38(1): e99506.

28. Jiao, S, Huizhen W, Zhubing S, Aimei D, Wenjing Z, et al. (2014) A peptide mimicking VGLL4 function acts as a YAP antagonist therapy against gastric cancer. Cancer Cell 25(2): 166-180.

29. Li N, Nanrong Y, Jia W, Haofeng X, Weiqun L, et al, (2015) miR-222/VGLL4/YAP-TEAD1 regulatory loop promotes proliferation and invasion of gastric cancer cells. Am J Cancer Res 5(3): 1158-1168.

30. Li H, Ziwei W, Wei Z, Kun Q, Gang L, et al. (2015) VGLL4 inhibits EMT in part through suppressing Wnt/beta-catenin signaling pathway in gastric cancer. Med Oncol 32(3): 83.

31. Geng H, Guangli L, Jiandong H, Jianchao L, Dong W, et al. (2021) HOXB13 suppresses proliferation, migration and invasion, and promotes apoptosis of gastric cancer cells through transcriptional activation of VGLL4 to inhibit the involvement of TEAD4 in the Hippo signaling pathway. Mol Med Rep 24(4).

32. Yao Y, Wang Y, Li L, Xiang X, Li J, et al. (2019) Down-regulation of interferon regulatory factor 2 binding protein 2 suppresses gastric cancer progression by negatively regulating connective tissue growth factor. J Cell Mol Med 23(12): 8076-8089.

33. Shen S, Guo X, Yan H, Yi L, Ji X, et al. (2015) A miR-130a-YAP positive feedback loop promotes organ size and tumorigenesis. Cell Res 25(9): 997-1012.

34. Liu X, Kong C, Zhang Z (2018) miR-130b promotes bladder cancer cell proliferation, migration and invasion by targeting VGLL4. Oncol Rep 39(5): 2324-2332.

35. Liu WH, Lu JJ, Yu RK, Zhou L, Yu Q, et al. (2021) LINC00641 regulates prostate cancer cell growth and apoptosis via the miR-365a-3p/VGLL4 axis. Eur Rev Med Pharmacol Sci 25(1): 108-115.

36. Hu J, Ruan J, Liu X, Xiao C, Xiong J, et al. (2018) MicroRNA-301a-3p suppressed the progression of hepatocellular carcinoma via targeting VGLL4. Pathol Res Pract 214(12): 2039-2045.

37. Jiang W, Yao F, He J, Lv B, Fang W, et al.(2015) Downregulation of VGLL4 in the progression of esophageal squamous cell carcinoma. Tumour Biol 36(2): 1289-1297.

38. Mickle M, Adhikary G, Shrestha S, Xu W, Eckert RL (2021) VGLL4 inhibits YAP1/TEAD signaling to suppress the epidermal squamous cell carcinoma cancer phenotype. Mol Carcinog 60(7): 497-507.

39. Jiao S, Li C, Hao Q, Miao H, Zhang L, et al. (2017) VGLL4 targets a TCF4-TEAD4 complex to coregulate Wnt and

Hippo signalling in colorectal cancer. Nat Commun 8: 14058.

40. Kim JY, Kim EK, Lee WM, Hong YO, Lee H (2020) VGLL4 with low YAP expression is associated with favorable prognosis in colorectal cancer. APMIS 128(10): 543-551.

41. Song H, Luo Q, Deng X, Ji C, Li D, et al. (2019) VGLL4 interacts with STAT3 to function as a tumor suppressor in triple-negative breast cancer. Exp Mol Med 51(11): 1-13.

42. Jin HS, Park HS, Shin JH, Kim DH, Jun SH, et al. (2011) A novel inhibitor of apoptosis protein (IAP)-interacting protein, Vestigial-like (Vgl)-4, counteracts apoptosis-inhibitory function of IAPs by nuclear sequestration. Biochem Biophys Res Commun 412(3): 454-459.

43. Zeng Y, Stauffer S, Zhou J, Chen X, Chen Y, et al. (2017) Cyclin-dependent kinase 1 (CDK1)-mediated mitotic phosphorylation of the transcriptional co-repressor Vgll4 inhibits its tumor-suppressing activity. J Biol Chem 292(36): 15028-15038.

44. Kim W, Khan SK, Gvozdenovic-Jeremic J, Kim Y, Dahlman J, et al. (2017) Hippo signaling interactions with Wnt/beta-catenin and Notch signaling repress liver tumorigenesis. J Clin Invest 127(1): 137-152.

45. Park J, Jeong S (2015) Wnt activated beta-catenin and YAP proteins enhance the expression of non-coding RNA component of RNase MRP in colon cancer cells. Oncotarget 6(33): 34658-34668.

46. Xu J, Acharya S, Sahin O, Zhang Q, Saitoet Y, et al. al. (2015) 14-3-3zeta turns TGF-beta's function from tumor suppressor to metastasis promoter in breast cancer by contextual changes of Smad partners from p53 to Gli2. Cancer Cell 27(2): 177-192.

47. Pefani DE, Pankova D, Abraham AG, Grawenda AM, Pefani NV, et al. (2016) TGF-beta Targets the Hippo Pathway Scaffold RASSF1A to Facilitate YAP/SMAD2 Nuclear Translocation. Mol Cell 63(1): 156-166.

48. Fujii M, Toyoda T, Nakanishi H, Yatabe Y, Sato A, et al. (2012) TGF-beta synergizes with defects in the Hippo pathway to stimulate human malignant mesothelioma growth. J Exp Med 209(3): 479-494.

49. Feng X, Wang Z, Wang F, Lu T, Xu J, et al. (2019) Dual function of VGLL4 in muscle regeneration. EMBO J 38(17): e101051.

50. Yu W, Ma X, Xu J, Heumuller AW, Fei Z, et al. (2019) VGLL4 plays a critical role in heart valve development and homeostasis. PLoS Genet 15(2): e1007977.

51. Suo J, Feng X, Li J, Wang J, Wang Z, et al. (2020) VGLL4 promotes osteoblast differentiation by antagonizing TEADs-inhibited Runx2 transcription. Sci Adv 6(43): eaba4147.