BBA - Reviews on Cancer 1878 (2023) 188892

Contents lists available at ScienceDirect

BBA - Reviews on Cancer

journal homepage: www.elsevier.com/locate/bbacan

Review

Vestigial-like 1 (VGLL1): An ancient co-transcriptional activator linking wing, placenta, and tumor development

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ARTICLE INFO

Keywords:
Cancer
Placenta
Transcriptional activation
Proliferation
Hippo pathway

ABSTRACT

Vestigial-like 1 (VGLL1) is a recently discovered driver of proliferation and invasion that is expressed in many aggressive human malignancies and is strongly associated with poor prognosis. The VGLL1 gene encodes for a co-transcriptional activator that shows intriguing structural similarity to key activators in the *hippo* pathway, providing important clues to its functional role. VGLL1 binds to TEAD transcription factors in an analogous fashion to YAP1 but appears to activate a distinct set of downstream gene targets. In mammals, VGLL1 expression is found almost exclusively in placental trophoblasts, cells that share many hallmarks of cancer. Due to its role as a driver of tumor progression, VGLL1 has become a target of interest for potential anticancer therapies. In this review, we discuss VGLL1 from an evolutionary perspective, contrast its role in placental and tumor development, summarize the current knowledge of how signaling pathways can modulate VGLL1 function, and discuss potential approaches for targeting VGLL1 therapeutically.

1. Introduction

The Vestigial-like gene family encodes four co-transcriptional activators (VGLL1–4), named after the Vestigial (*vg*) gene in *Drosophila* with which they all show significant homology. VGLL1, the first isolated mammalian Vestigial-like protein with recognized structural and functional similarity to the known promotor of insect wing development Vg [1], has been shown in recent years to play a previously underappreciated role in the tumorigenesis of multiple cancer types, including pancreatic and basal-like breast cancers. Interestingly, VGLL1 tissue expression in mammals is limited mostly to cells within the placenta that are highly proliferative and invasive, suggesting that some tumors actively co-opt this normal developmental pathway to promote their progression. Although VGLL1 studies are still in their relative infancy, VGLL1 appears to bind members of the TEA domain family of transcription factor members (TEADs) in analogous fashion to co-transcriptional activators yes-associated protein 1 (YAP1) and WW Domain-containing transcription regulator 1 (WWTR1/TAZ), which are well known to play crucial roles in the *hippo* pathway of tumor development. This review aims to provide a comprehensive overview of VGLL1, bridging the current knowledge as selected from a wide variety of fields, including evolutionary, structural, developmental, and cancer biology, in addition to discussing critical therapeutic implications for patients with VGLL1-positive cancers.

2. VGLL1 evolution

Evolutionary biology can provide important information regarding gene origin and conservation over millions of years of evolution and comparison of protein sequences between divergent species can identify conserved regions that are most likely to be critical for protein function. VGLL1 is a highly conserved transcriptional coactivator that originated 400–450 million years ago, dating back to the Devonian period of bony fish and tetrapod divergence in which lobed-fin fish evolved to crawl on land, giving rise to all four-limbed vertebrates including amphibians, birds, reptiles, and mammals [2]. According to National Center for Biotechnology Information (NCBI) protein database, there are 326 organisms that have sequenced orthologs to human VGLL1. Unlike its

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https://doi.org/10.1016/j.bbcan.2023.188892
Received 4 February 2023; Accepted 27 March 2023
Available online 31 March 2023

chromosomal location in amphibians, fish, birds, and reptiles, the *VGLL1* gene in mammals resides on the X chromosome. To examine the protein homology between 42 organisms sampled from all vertebrate animal groups, a constraint-based multiple alignment tool (COBALT) was used to generate a phylogenetic tree with the parameters of fast minimum evolution (Fig. 1a) [3]. Although VGLL1 demonstrates 32% to 97% overall protein homology between vertebrate species, the most highly conserved sequences are found within an approximately 23 amino acid region containing a VxxHF motif (where x represents any amino acid) that is known to facilitate binding to families of transcription factors that also show a remarkable degree of conservation (Fig. 1b, c) [4,5].

3. Vestigial in *Drosophila*

In 1910, Thomas Hunt Morgan first noted a phenotype of impaired wing development in strains of *Drosophila* that later became known as wingless [6]. Several decades later, mutations in the *vg* gene were demonstrated to be responsible for this phenotype, revealing the critical role of this gene in wing development [7,8]. Vg protein was subsequently shown to be a transcriptional coactivator which interacts with the scalloped (Sd) protein to drive the transcription of genes involved in wing morphogenesis [2,7]. The first human homolog of Vg reported in 1999 was initially designated as TONDU (TDU), later to be re-named *Vestigial-like 1* (*VGLL1*) as one of four members of a family of homologous mammalian Vg-like genes designated *VGLL1* to *VGLL4*. The TDU domain now refers to the conserved approximately 23 amino acid VxxHF motif-containing region of Vg that interacts with Sd in *Drosophila,* and mediates in an analogous fashion the interaction of VGLL1 with TEAD transcription factors in mammals to activate transcription of specific genes (Fig. 1b, c 1d) [1]. Two co-transcriptional activators, Vg and Yorkie, play major roles during *Drosophila* development. Evidence supports that *vg* acts as a selector gene for wing development, with its expression being restricted to the imaginal wing disc [1,9]. Absence of either *vg* or *sd* gene expression within the imaginal disc results in impaired wing blade formation. Remarkably, the wing blade phenotype could be rescued using gene complementation with human orthologs. For example, ectopic human VGLL1 expression was shown to restore normal wing development in *vg* mutant *Drosophila,* and TEAD1 expression rescued the wingless phenotype in *sd* mutants [1,10,11]. In addition, ectopic expression of Vg converted antenna, eye, and leg discs to wing-like fates [12]. These studies established that tissue expression of *vg* needs to be highly restricted and tightly regulated for normal development in *Drosophila*.

4. VGLL1: structural and functional similarity to YAP1

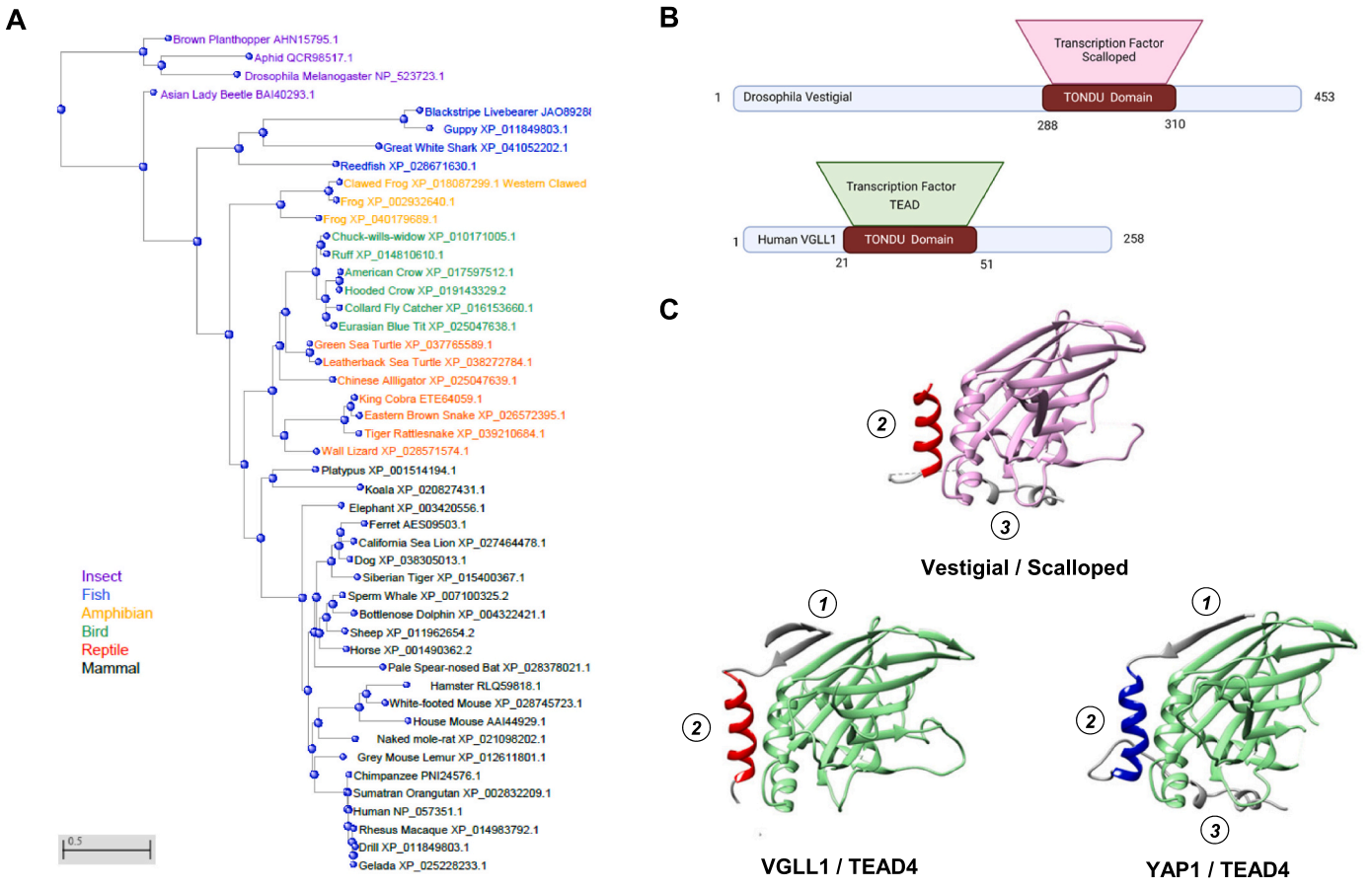
Yorkie and its mammalian homologs YAP1 and TAZ are co-transcriptional activators in the hippo pathway that control the expression of genes critical for organ development, cell growth and proliferation, and wound healing [13,14]. Dysregulation of the hippo pathway can facilitate cancer development by a number of mechanisms, such as targeting of hippo pathway components for degradation, accumulation of somatic inactivating mutations, or through upregulation of YAP1 or TAZ expression [15–18]. Over the past several years, YAP1 and TAZ have been shown to play crucial roles in cancer biology and have been linked to a variety of cancer types, including esophageal, sarcoma, pancreatic, liver, glioma, gastric, melanoma, colorectal, head and neck, non-small cell lung, prostate, ovarian, breast, uterine, colorectal and bladder cancers [19]. YAP1 and TAZ promote cell proliferation and metastasis, induce chemoresistance and facilitate low levels of autophagy to avoid senescence and cell death [19]. In addition, they may play a negative role in tumor immunity by upregulating transcription of PD-L1 in cancer cells and recruiting immune suppressive cells, such as myeloid-derived suppressor cells, and polarizing monocytes into M2 macrophages [20–23]. Over the years, many researchers have aimed to inhibit YAP and TAZ signaling by preventing their interaction with TEADs using molecules like Super-TDU (a VGLL4 peptide), verteporfin, or flufenamic acid and its derivatives [24–26]. Other studies have demonstrated inhibition of YAP and TAZ phosphorylation and nuclear trafficking by Src family kinase inhibitors or PI3K inhibitors, suggesting involvement of these signaling pathways in the regulation of YAP and TAZ activation [24,27,28]. However, to date there is no FDA-approved therapy that has effectively inhibited YAP or TAZ, or disrupted their ability to bind to TEADs, without causing toxicity [29].

The roles played by YAP1 and TAZ in TEAD transcription factor activation, the hippo tumor suppressor pathway, and cancer development have been extensively reviewed elsewhere [14,19,20,24,29,30]. Fortunately, these prior studies shed valuable light on the potential functional role of VGLL1 in tumor development, for which comparatively little is known. An important clue was revealed by crystal structure studies demonstrating that VGLL1 and YAP1 exhibit intriguing structural similarity in their modes of binding to the TEAD4 transcription factor, despite sharing little overall amino acid sequence homology [4]. This data suggests that VGLL1 may function analogously to YAP1 as a coactivator of TEADs. YAP1 binding to TEAD4 involves three primary interfaces. Interface 1 consists of two antiparallel β sheets held together by defined hydrogen bond interactions also observed in VGLL1-TEAD4 complexes (Figs. 1c) [4]. By contrast, Interface 2 is formed by the interaction of YAP1 α helix containing a highly conserved LxxLF motif to a hydrophobic groove between two α helixes of TEAD4 (Fig. 1c, d). As shown in Fig. 1d, this motif is analogous to the VxxHF motif found at the core of the TDU domain in both Vg and VGLL1. Furthermore, this motif is critical for stabilizing interactions of VGLL1-TEAD4 since mutations in this motif prevented the binding of VGLL1 to this transcription factor [4,5]. YAP1 also interacts with TEAD4 at a third interface mediated by a proline-rich region containing a PxxxR motif (Fig. 1c, d). The same PxxxR motif is also found in *Drosophila* Vg which appears to stabilize its binding to Sd (Fig. 1c). Although Interface 3 of mouse VGLL1-TEAD4 binding could not be crystallized [4], sequence analysis shows that mammalian VGLL1 also contains a proline-rich region with a PxxxR motif (Figs. 1d). The striking structural similarities with YAP1 provide intriguing clues to better understanding the role of VGLL1 in human physiology and tumorigenesis.

5. VGLL1 in human development

The precise role that VGLL1 plays in mammalian development remains largely unknown but based on its normal tissue expression potential clues can be inferred. Human transcriptome analyses demonstrated very high expression of VGLL1 within the placenta (>200 transcripts per million, TPM), with moderate expression in the bladder (~20 TPM) and low expression within salivary gland, breast, pituitary and lung tissue (1 to 5 TPM) (Fig. 2a) [31–35]. The restricted expression of VGLL1 in human tissues is a critical point because inappropriate induction of this co-transcriptional activator in other tissues may promote the development of cancer. Furthermore, it also provides insights into potential therapeutic safety concerns of targeting VGLL1 therapeutically.

During pregnancy, the placenta provides for the exchange of oxygen, nutrients, metabolites and other molecules by acting as an interface between the bloodstream of the mother and the developing fetus [36,37]. The placenta is comprised of the trophoblast and mesodermal cell lineages, which come together in the process of chorio-allantoic fusion [37]. The mesodermal lineage forms the fetal portion of the placenta vasculature and the umbilical cord, while the trophoblast lineage gives rise to specialized placental cell types which provide nutrient and gas exchange [36,37]. Within the placenta, VGLL1 expression is most highly enriched in trophoblast-derived cells, including syncytiotrophoblasts (~1300 TPM), proliferative cytotrophoblasts (~1000 TPM), and extravillous cytotrophoblasts (~500 TPM) [32,38,39]. Extravillous cytotrophoblast cells have highly



D

			Interface 1		Interface 2				Interface 3	
VGLL1	Human	27	CVLFT	YFQG	DISSVVDEHFSRAL	49	---	77	PNQWRYSSPWTKPQP	91
	Chimpanzee	27	CVLFT	YFQF	DISSVVDEHFSRAL	49	---	77	PNQWRYSSPWTKPQP	91
	Mouse	27	SVIFT	YGEG	DINSMVDEHFSRAL	49	---	116	PPNQRHLSSWTIAQP	129
	Horse	23	CVLFT	YFQG	DISSVVDEHFSRAL	45	---	73	PNQWRFSPQWTKPEP	87
	Dog	23	CVLFT	YFQG	DIGSVVDEHFSRAL	45	---	73	PNQWRFSSQWTKPEP	87
	Common Frog	26	CVVFT	YYQG	DINSVVDEHFSRAL	48	---	73	GNVLVEDYTWTKPYQ	87
	Blue Tilapia	19	FVILT	YFQG	DINSMVDAHFNRAL	41	---	156	SSKPELLPSWTIPQG	170
	Tiger Rattlesnake	26	YMVLT	YFQG	DTNSMVDEHFSRAL	48	---	75	PSHEWGLPPHWTKTY	89
	American Crow	26	SVVFT	YFQG	DINSMVDEHFSRAL	48	---	76	PHQWNFSSHCYRPYP	90
Vestigial	Drosophila	288	CVVFT	NYSG	DTASQVDEHFSRAL	310	---	323	PMSNRNFPPSFWNSN	337
	Aphid	157	CVVFT	HYTG	DVATVVDEHFSRAL	179	---	198	PMSSRNFPASFWNSN	212
YAP1	Human	52	HQIVHV	RG	DSETDLEALFNAVM	73	---	85	PMRLRKLPDSFFKPP	99
	Mouse	37	HQVVHV	RG	DSETDLEALFNAVM	58	---	70	PMRLRKLPDSFFKPP	84
Yorkie	Drosophila	55	NLVVRV	NQ	DTDDNLQALFDSVL	76	---	88	PLRMRKLPNSFFTPP	102

Fig. 1. Overview of *VGLL1* gene evolution and conserved structural features. (A) Phylogenetic tree for VGLL1 constructed by COBALT [3] with parameters of maximum sequence difference of 0.85 and distance Grishin (protein). (B) Schematic depiction of *Drosophila* Vestigial and human VGLL1 proteins interacting with their respective transcription factors Scalloped and TEAD via conserved TONDU domains. (C) Visualizations of crystal structure complexes of Vestigial-Scalloped (PDBID: 6Y20), VGLL1-TEAD4 (PDBID: 5Z2Q), and YAP1-TEAD4 (PDBID: 3KYS), highlighting transcription factor and co-activator binding interaction Interfaces 1 to 3. (D) Amino acid sequence alignments of VGLL1, Vestigial, YAP1, and Yorkie from different species. The highly conserved TONDU domain encompasses Interfaces 1 and 2. Interface 3 of VGLL1 was inferred from crystal structures of Vestigial-Scalloped and YAP1-TEAD4 shown in (C) and from amino acid sequence homology (red). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

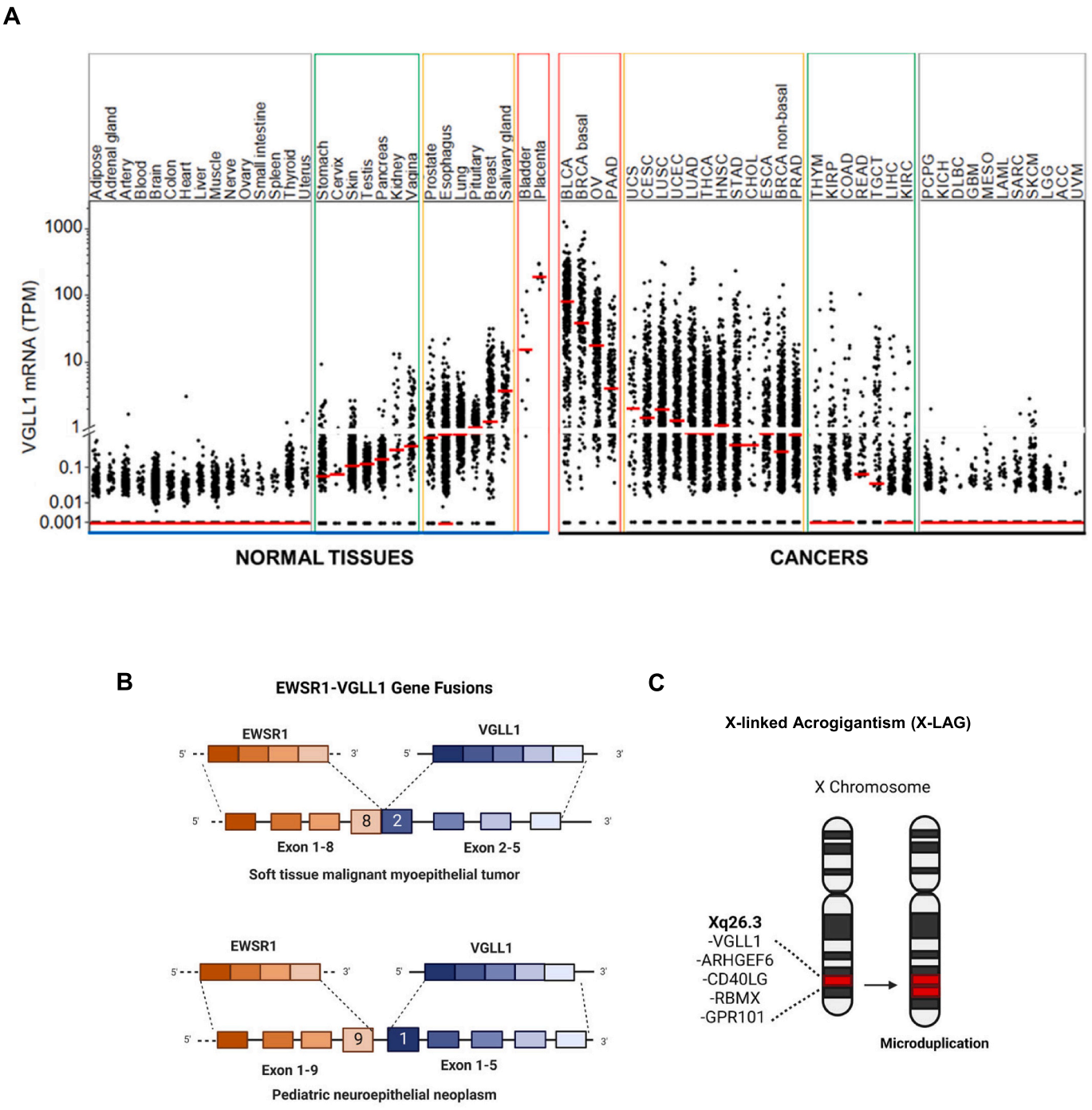


Fig. 2. Human VGLL1 tissue expression and known genetic alterations. (A) Human RNA sequencing data showing VGLL1 transcript expression levels in different normal tissues (left, GTex Portal) and cancer tissues (right, TCGA), with median value indicated in red. Relative transcript expression levels are indicated with boxes: red, high expression; orange, moderate expression; green, low expression; grey, no expression. Genetic alterations involving *VGLL1* include (B) *EWSR1-VGLL1* gene fusions detected in myoepithelial and neuroepithelial cancers and (C) X chromosome-linked microduplications as described in X-LAG patients. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

invasive and proliferative properties that allow for the implantation of the embryo into the uterine wall [39]. For a viable pregnancy the mother's immune system must enter a state of immune tolerance to prevent attack of the developing fetus [40]. In order to maintain this tolerance the trophoblast cells induce homeostatic T regulatory cells and M2 macrophages, which are also known to play an immunosuppressive role in the tumor microenvironment [40–42]. Based on this, it is tempting to speculate that VGLL1 may be involved in regulating cell proliferation, invasion, migration, and/or immune tolerance during normal fetal development. Conversely, dysregulated VGLL1 expression might contribute to complications associated with placental dysfunction such as miscarriage and preeclampsia, or the development of trophoblastic cancers such as choriocarcinoma [43,44]. Consistent with its potential roles in human development, VGLL1 has also been shown to play key roles in placental development in horses, ovary development in chickens and embryogenesis in frogs [2,45,46].

6. Genetic alterations of *VGLL1*

VGLL1 overexpression is a hallmark of a significant number of human malignancies, as demonstrated by transcriptome analysis of a variety of tumors (Fig. 2a). By contrast, tumor-associated VGLL1 mutations are relatively uncommon as shown in the cBioPortal and COSMIC databases, which both reported <1% incidence in >100,000 human cancer specimens analyzed [47–49]. Interestingly, two separate case studies have reported tumor-associated gene fusions between *VGLL1* and the Ewing's Sarcoma RNA binding Protein 1 (*EWSR1*) gene, which is known to be involved in multiple cancer types through fusions with the *CREB1, ATF1, PATZ1* or *FLI1* genes [50,51]. The first report described a soft tissue malignant myoepithelial tumor in which exon 8 of *EWSR1* was fused with exon 2 of *VGLL1* [52]. The other fusion was described in a pediatric neuroepithelial neoplasm in which the intron following exon 9 of *EWSR1* was fused to the region immediately upstream of exon 1 of *VGLL1* (Fig. 2b) [53]. Both are predicted to leave the entire VGLL1 protein sequence intact, but with expression of the fusion protein presumably under the control of the *EWSR1* promoter. Further studies will be required to show how frequently *VGLL1* gene fusions occur in human cancer and to determine the functional consequences of these events.

Intriguingly, *VGLL1* has also been shown to be one of five neighboring genes along with *CD40LG, ARHGEF6, RBMX,* and *GPR101* that are microduplicated in the Xq26.3 region of the X chromosome (Fig. 2c), directly leading to development of the rare genetic disorder X-linked acrogigantism (X-LAG) [54,55]. X-LAG patients are characterized by significant enlargement of their pituitary gland, which in turn drives excessive growth hormone (GH) production leading to gigantism [54,55]. Subsequent studies have implicated the overexpression of GPR101, an orphaned G-coupled protein, to hypersecretion of GH driving excessive growth in mouse and zebrafish models [56,57]. However, GPR101 did not appear to have any clear impact on cell proliferation or tumorigenesis within the pituitary gland, leaving open the possibility that dysregulated expression of *VGLL1* may play a role in the development of X-LAG. Although *VGLL1* transcript expression in X-LAG hyperplasia is higher than that of normal pituitary, it remains relatively low compared to its expression in placenta [58]. However, following microduplication the additional copy of *VGLL1* ends up in a novel chromosomal location immediately downstream and adjacent to the *GRP101* gene and contains putative cis-regulatory elements (CRE) that have been proposed to drive GRP101 overexpression and GH overproduction in the pituitary glands of X-LAG patients [58].

7. VGLL1 in cancer

Lines of evidence derived from a variety of cancer types supports the notion that VGLL1 expression endows cancer cells with several attributes found in placental trophoblasts, including rapid cell proliferation, tissue invasion, and the induction of immune tolerance. VGLL1 has also been shown to be a negative prognostic factor, with high expression levels correlating with lower overall survival in patients with pancreatic adenocarcinoma, triple negative breast cancer, estrogen receptor (ER) positive breast cancer, gastric cancer, endometrial cancer, and HPV-related cancers [31,32,59–62]. Furthermore, multiple studies have demonstrated that ectopic overexpression of VGLL1 stimulates cancer cell proliferation, migration, and invasion *in vitro* and promotes formation of metastasis *in vivo* [4,59–62]. The following section will review the current knowledge about the mechanisms by which VGLL1 contributes to the development of different human cancers.

7.1. Gastric cancer

Gastric cancer is the fifth most diagnosed and third most deadly cancer worldwide, with a 5-year survival of 31% at the metastatic stage [63]. Immunohistochemistry and RNAseq analyses have revealed elevated levels of VGLL1 expression in half of gastric cancer specimens, and higher VGLL1 expression was associated with lower overall patient survival [31,60]. To explore potential clinical relevance, microarray analysis performed on 556 gastric tumors demonstrated that VGLL1 positively correlates with expression of PIK3CA and PIK3CB [60]. The PI3K inhibitor LY294002 reduced VGLL1 mRNA and protein expression in a dose-dependent manner but had no discernable impact on the level of YAP1 expression [60] (Fig. 3). Interestingly, gastric cancer cells harboring activating AKT mutations were resistant to PI3K inhibitor-induced VGLL1 downregulation [60]. In addition, ChIP-PCR assays revealed that β-catenin binds to TCF4- and LEF1-binding regions within the VGLL1 promoter and activates its transcription [60]. In mouse xenograft models, overexpression of VGLL1 in gastric cancer cells increased tumor burden as well as metastasis to the lung and liver [60]. Interestingly, this study also demonstrated that expression of matrix metalloprotease-9 (MMP9), a known driver of invasion and metastasis, directly correlated with VGLL1 expression. Furthermore, VGLL1 was shown to interact with TEAD4 and was found to be localized within TEAD4-binding regions of the MMP9 promoter [60]. Similar to YAP1/TAZ, VGLL1 activity might be controlled through phosphorylation of serine (S) residues [64,65]. For example, it was shown that TGFβ stimulation of gastric cancer cells promoted the phosphorylation of VGLL1 at S84 [61]. This phosphorylation of VGLL1 was directly mediated by RSK2 kinase through stimulation of ERK signaling pathway in response to TGFβ. Importantly, this study also confirmed that VGLL1 phosphorylation increases its binding to TEAD4 and activates the transcription of its target gene *MMP9* (Fig. 3) [64]. In contrast, preventing VGLL1 phosphorylation using a thirteen amino acid VGLL1 decoy peptide containing S84 resulted in attenuation of complex formation between VGLL1 and TEAD4 and was associated with decreased MMP9 expression as well as suppression of cancer cell invasion and proliferation [64]. Thus, this study clearly demonstrated a link between TGFβ signaling and VGLL1-dependent transcription of genes such as MMP9 to promote gastric cancer invasion and metastasis (Fig. 3).

7.2. Breast cancer

Basal-like breast cancer, often referred to as triple negative breast cancer (TNBC), accounts for approximately 12% of all breast cancers diagnosed [66]. It is by far the most aggressive breast cancer subtype and is associated with poor prognosis with a 5-year survival of only 8–16% [66,67]. It is classified by the lack of expression of estrogen receptor (ER) and progesterone receptor (PR), as well as lack of HER2 expression [67]. Interestingly, VGLL1 is much more highly expressed in tumors from TNBC patients (>95%) compared with other non-basal breast cancer subtypes (<15%) (Fig. 2a). Furthermore, tumor-associated VGLL1 expression was positively correlated with the cell proliferation marker Ki67 and reduced overall TNBC patient survival [59]. A study analyzing micro-RNA (miRNA) expression patterns in breast cancer revealed that miRNA-934 was highly upregulated in TNBC [59]. Although the function of miRNA-934 remains largely unknown, its sequence is encoded within the 4th intron of the *VGLL1* gene [59].

Hormone receptor-positive breast cancers account for >70% of breast cancers diagnosed [66]. ER^+ tumors are usually diagnosed as low-grade and patients are often treated with estrogen receptor degraders (SERDs) such as fulvestrant [62]. Analysis of tumor biopsies taken before and after fulvestrant administration revealed higher expression levels of VGLL1 in patients that developed resistance to this therapy. ChIP-seq analysis of SERD-resistant cancer cells demonstrated an increase in histone H3 acetylation at K27 (H3K27ac), which was associated with upregulation of VGLL1 mRNA and protein expression but not canonical hippo pathway genes [62]. Since ER1 knockdown in breast cancer cells resulted in a similar phenotype, it was postulated that ER degradation may promote VGLL1 expression which in turn stimulates the transcription of VGLL1 target genes. VGLL1 Chip-seq analysis identified TEAD4-binding motifs to be the most enriched, and VGLL1 binding was associated with intronic and intergenic regions of DNA,

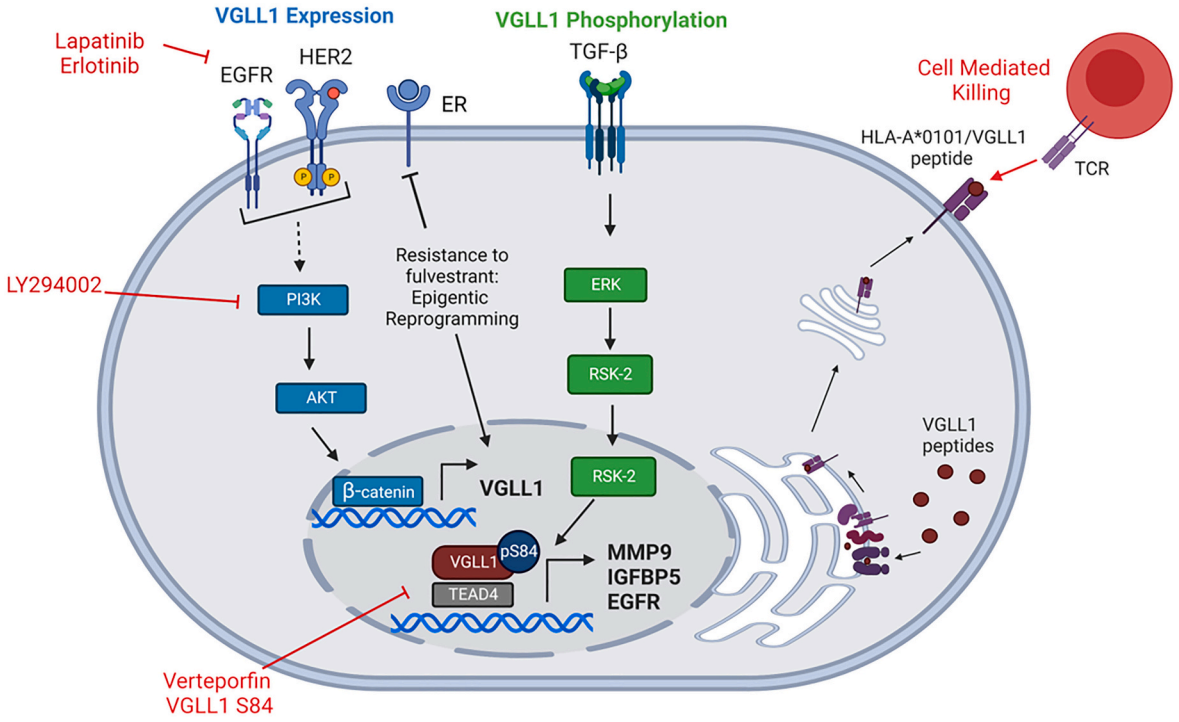


Fig. 3. Overview of VGLL1 regulation, function, and potential therapeutic targeting approaches. Schematic diagram showing regulation of VGLL1 expression via cell surface receptor-mediated signaling through PI3K, AKT, and β-catenin (blue), and phosphorylation-induced activation of VGLL1 through TGF-β, ERK, and RSK-2 (green). Potential therapeutic approaches for targeting VGLL1 in cancer currently include VGLL1-specific T-cell mediated killing of HLA-A*0101-expressing tumor cells, receptor tyrosine kinase inhibitors Lapatinib and Erlotinib, the PI3K inhibitor LY294002, and agents that can disrupt the interaction between VGLL1 and TEAD4 such as Vertporfin and S84-phosphorylated VGLL1 peptide (red). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

suggesting that VGLL1 may function as a distal enhancer similar to YAP1 and TAZ [62]. The list of candidates of VGLL1 target genes included *EGFR*, *MMP9*, *IGFBP5* and *CTGF* [62]. Breast cancer patients demonstrating higher expression of these VGLL1-induced genes experienced poorer overall survival [62]. Moreover, research has shown that ectopic overexpression of VGLL1 stimulates cancer cell proliferation and this effect can be reversed by siRNA or verteporfin that blocks its interaction with TEAD4 [62] (Fig. 3). Importantly, ectopic expression of either *VGLL1* or its target gene *EGFR* in cancer cells led to SERD resistance, suggesting that EGFR inhibitors might be an effective line of therapy for patients that develop SERD-resistant tumors [62].

7.3. HPV-related cancers

Human papillomavirus (HPV) infection can be a major risk factor for the development of a variety of cancer types including anal, vulvar, penile, vaginal, oropharyngeal, and oral cancers, and accounts for nearly all cases of cervical cancer [68,69]. HPV infects epithelial cells and uses the host cell machinery for vegetative replication and formation of virion progeny [61,70]. If the infection is not cleared, the virus can integrate into the host cell genome which in turn drives the expression of viral oncoproteins E6 and E7. These oncoproteins have been implicated in contributing to tumorigenesis by degrading the tumor suppressor genes pRB and p53, and controlling signaling pathways that lead to immune evasion, cell proliferation and avoidance of apoptosis [70–73]. E6 and E7 oncoproteins have also been shown to play key roles in regulating the hippo pathway, as reviewed elsewhere [68]. A long control region (LCR) within the viral genome contains binding regions for host transcription factors that activate the promoter regions of these early viral oncogenes [61]. Interestingly, TEAD1 can bind to the HPV16 LCR and mutations to the TEAD-binding motif have been shown to decrease early viral gene promoter activity [61,74]. However, TEADs require co-transcriptional activators in order to induce gene transcription [75]. To identify which epithelial cell-specific coactivators interacted with TEAD1, an siRNA screen was employed in conjunction with a luciferase reporter assay to measure HPV early promoter activity [61]. This screen revealed that VGLL1 knockdown alone or in combination with TEAD1 led to decreased HPV early gene promoter activity, and reduction of mRNA and protein levels of E6 and E7 [61]. Furthermore, ChIP assays confirmed that VGLL1 was indeed enriched within the LCR regions of the viral genome [61]. According to The Cancer Genome Atlas (TCGA), approximately one-third of human cervical cancers demonstrate VGLL1 transcript overexpression [31] (Fig. 2A). Moreover, knockdown of VGLL1 expression in cervical cancer cell lines led to the inhibition of cancer cell proliferation [61].

7.4. BMP4-driven cancers

Bone morphogenetic protein 4 (BMP4) signaling has been implicated in a wide variety of cancers and is associated with increased migration and invasion of breast, colorectal, ovarian, melanoma and pancreatic cancer cells. Many research studies demonstrated that BMP4 is involved in promoting epithelial-mesenchymal transition and metastasis, cancer stem cell self-renewal, and the induction of M2 macrophage polarization in addition to chemotherapy resistance [76–79]. Similarly to BMP4, VGLL1 mRNA is significantly overexpressed in ovarian (>80%), pancreatic cancers (~50%), and TNBC (>95%) [31]. Notably, BMP4 stimulation can differentiate embryonic stem cells or pluripotent stem cells into the placental trophoblast lineage, while also driving VGLL1 mRNA expression up to levels typically observed in placenta tissue [44,80–82]. This data collectively suggests that VGLL1 plays a role in the development of cancers linked to BMP4 signaling, particularly in pancreatic and ovarian cancers where high tumor VGLL1 expression constitutes a negative prognostic factor [31]. Further studies will be

required to determine the precise role that VGLL1 may play in driving these aggressive cancer types.

8. VGLL1 as a potential target for anticancer therapy

VGLL1 has several attributes that make it an attractive potential therapeutic target for treatment of multiple cancers. In addition to its demonstrated role as a driver of tumor cell proliferation and invasion as well as its strong association with reduced overall patient survival, VGLL1 is expressed at low to negligible levels in most normal tissues (Fig. 2a). Although its high expression within the normal placenta would preclude its targeting during pregnancy, VGLL1 demonstrates only moderate RNA transcript levels in bladder and low transcript levels in mammary tissue and salivary gland. Importantly, VGLL1 shows no expression in essential tissues such as brain, heart, colon, pancreas, liver, or hematopoietic tissues (Fig. 2a). This "safe" normal tissue expression profile combined with its propensity for overexpression in tumor cells indicate that VGLL1 is a promising therapeutic target with expected minimal potential toxicity [31,83]. Furthermore, due to its association with tumor cell invasion and metastasis in aggressive cancers, VGLL1 detection using non-invasive liquid biopsy techniques can be used as a prognostic biomarker. The most common objectives of liquid biopsies are detection and quantitation of cell-free tumor DNA and circulating tumor cells. [84,85]. Since the *VGLL1* gene usually shows minimal genetic alterations in cancer, analysis of cell-free tumor DNA would not be useful for early detection of VGLL1-positive tumors. However, detection of circulating tumor cells expressing VGLL1 would be possible with the use of single cell RNA sequencing techniques [86]. Therefore, liquid biopsies might help early detection of VGLL1-positive tumors that often are not diagnosed until they are late-stage cancers. Although there are currently no approved therapies that directly target VGLL1 in cancer, in the following sections we discuss potential approaches that could be employed to achieve this goal.

8.1. Immunotherapeutic targeting of VGLL1

T-cell mediated immunotherapies have shown success in recent years, as underscored by the FDA approvals of checkpoint blockade inhibitors and chimeric antigen receptor T cell (CAR-T) therapies for treatment of several different cancer types [87–89]. In addition to these modalities, cytotoxic T lymphocytes (CTL) can be elicited or engineered to kill tumor cells via T-cell receptor (TCR) recognition of antigenic peptides presented at the tumor cell surface by human leukocyte antigen (HLA) molecules [90,91]. One such tumor-associated antigenic peptide derived from VGLL1 (LSELETPGKY) was identified by our group in multiple pancreatic cancer specimens through mass spectrometry (MS)-based identification of HLA-bound peptides. The VGLL1 peptide was presented by HLA-A*0101, an HLA allotype that is common in Western countries (25 to 30% prevalence) [31]. CTLs demonstrating specificity for the LSELETPGKY peptide were derived from the blood of an A*0101-positive pancreatic cancer patient, expanded to nearly 20 billion cells, and adoptively transferred back to the patient, representing the first effort to target VGLL1 clinically (Fig. 3) [31]. This endogenous T cell therapy (ETC) was well tolerated with no adverse events; however, no clinical response was observed, likely due to VGLL1 antigen loss in the patient's tumor cells in response to prior treatments [83]. Although this patient did not benefit from their own CTLs, these VGLL1-specific T-cells demonstrated robust killing of a large panel of HLA-A*0101-positive tumor cell lines derived from pancreatic, ovarian, breast, bladder, stomach, and lung cancer patients, and showed minimal killing of most human normal primary cells [31].

Taken together, the results of this study suggest that VGLL1 is a promising shared immunotherapeutic target, and that VGLL1-specific CTLs could potentially be utilized for treatment of multiple cancer indications. The unique tissue expression profile of VGLL1 led us to designate it as a prototype "cancer-placenta antigen (CPA)", in order to differentiate it from the cancer-testis antigens (CTA) already shown to be robust targets for T-cell based immunotherapies [31]. Moreover, TCRs generated from the pancreatic patient's VGLL1-specific T cells were expressed in allogeneic peripheral blood T cells, which endowed them with the capacity to kill A*0101/VGLL1-positive tumor cells [31]. These pre-clinical efforts have set the stage for producing engineered VGLL1 TCR-T cells for treatment of cancer patients that express both VGLL1 and A*0101. Identification of VGLL1 peptides presented by other HLA allotypes should allow for expansion of the patient population eligible for VGLL1-directed immunotherapies. One such potential peptide target (SELETPGKYSL) has been reported to be presented by the TNBC cell line HCC1937 in the context of HLA-B*4001, an allotype that is expressed frequently in East Asian populations [92]. Considering the immunogenicity demonstrated by VGLL1 peptides, it is possible that VGLL1 antigen-specific CTLs may be elicited in cancer patients through vaccine-based approaches, but this will require further assessment in the context of a human clinical trial.

8.2. Inhibiting expression or function of VGLL1

Since immunotherapy use is currently limited due to HLA restrictions, development of therapies that could target VGLL1 in all patients would be highly desirable. It is potentially feasible to reduce the impact of VGLL1 using multiple approaches, including preventing its transcription or translation, interfering with its function as a co-transcriptional activator at the protein level, or by inhibiting its downstream target genes (Fig. 3). Currently, no small molecules or drugs have been developed for the purpose of inhibiting VGLL1 expression or function. However, several approaches have been taken to inhibit YAP1 function in cancer which may be informative for VGLL1 targeting due to the structural similarity of the two molecules [4]. Antisense oligonucleotide (ASO)-based approaches for targeting YAP1 have been developed and are currently being tested in clinical trials for patients with multiple solid tumor types [93]. Alternative approaches for inhibiting VGLL1 expression may include administration of siRNA or shRNA. Verteporfin, an inhibitor of YAP1-TEAD protein binding and downstream gene transcription, has been repurposed to inhibit VGLL1-TEAD interactions in VGLL1-dependent endocrine-resistant breast cancer [25,62,94]. Verteporfin demonstrated the capacity to inhibit the transcription of VGLL1 downstream targets, including *MMP9*, *EGFR* and *IGFBP5* (Fig. 3) [62]. This dual capacity of verteporfin could be beneficial for treating pancreatic cancer in which nearly half of patients overexpress VGLL1 and the majority show upregulation of YAP1 upon chemotherapy resistance [30,31,95]. In a phase I/II clinical trial, the use of verteporfin was indeed deemed safe and feasible to treat pancreatic cancer, although future studies will be required to determine its efficacy in this setting [96]. VGLL1 expression could also potentially be reduced by inhibiting its upstream signaling molecules such as PI3K or AKT. For example, treatment of gastric cancer cells with a PI3K inhibitor, Ly294002, led to decreased VGLL1 expression *in vitro* [60]. Targeting posttranslational modifications of VGLL1 represents another potential strategy for restraining its function. This could be accomplished by inhibiting ERK kinase to prevent RSK2-induced phosphorylation of VGLL1, or by administering a VGLL1 competitor peptide to prevent interaction of VGLL1 with TEAD4 (Fig. 3) [64].

9. Summary

Although much remains to be learned about the precise roles played by VGLL1 in normal tissue and tumor development, the basic and translational studies to date have shown that it is an intriguing and promising therapeutic target. Its high degree of evolutionary conservation, its demonstrated role in the induction of cellular proliferation and invasion, and its association with poor prognosis in multiple cancers supports the hypothesis that tumors can co-opt critical VGLL1-driven gene expression programs that are normally only active during

placenta development. It remains to be seen whether VGLL1 expression can also promote immune suppression, another important feature shared by the placenta and tumor microenvironments. The structural and functional similarities of VGLL1 with the much more well-studied YAP1 provide a valuable road map for uncovering the mechanistic attributes of VGLL1 function in addition to potential approaches for its therapeutic targeting. To date, approaches taken to target YAP and TAZ to reduce TEAD binding in cancer have unfortunately been limited by toxicities likely attributable to both co-activators being ubiquitously expressed in normal tissues, necessitating tumor-specific targeting of such agents along with its associated challenges [29,33]. By contrast, the much more limited normal tissue expression profile of VGLL1 suggests that similar therapeutic approaches to target VGLL1 might show significantly reduced toxicity in patients. Further clinical studies will be required to determine whether VGLL1 lives up to its promise as a therapeutic target, but the evidence uncovered so far suggests that such studies could be of significant benefit for patients suffering from VGLL1-positive cancers.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Gregory Lizée has patent #US20200040079A1 ("HLA-restricted VGLL1 peptides and use thereof") pending to University of Texas System.

Gregory Lizée has patent #US2020063028262P ("T cell receptors with VGLL1 specificity and uses thereof") pending to University of Texas System.

Data availability

All research data described in the article were derived from publically available or published sources.

Acknowledgement

Funding for this project was provided by The National Science Foundation (NSF) Graduate Research Fellowship Program (GRFP) Award Number 2043424, and by generous philanthropic contributions to The University of Texas MD Anderson Pancreatic Cancer Moon Shots Program.

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