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► **To cite this version:**

Marie-Josée Santoni, Rudra Kashyap, Luc Camoin, Jean-Paul Borg. The Scribble family in cancer: twentieth anniversary. *Oncogene*, 2020, 39, pp.7019-7033. 10.1038/s41388-020-01478-7. hal-03087102

**HAL Id: hal-03087102**

**<https://hal.science/hal-03087102>**

Submitted on 23 Dec 2020

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**The Scribble family in cancer:  
twentieth anniversary**

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Running title: The Scribble family in cancer

## **ABSTRACT**

Among the more than 160 PDZ containing proteins described in humans, the cytoplasmic scaffold Scribble stands out because of its essential role in many steps of cancer development and dissemination. Its fame has somehow blurred the importance of homologous proteins, Erbin and Lano, all belonging to the LRR and PDZ (LAP) protein family first described twenty years ago. In this review, we will retrace the history of LAP family protein research and draw attention to their contribution in cancer by detailing the features of its members at the structural and functional levels, and highlighting their shared - but also different - implication in the tumoral process.

**Keywords:** Scribble, Erbin, Lano, LRR, PDZ, LAP family, polarity, signaling.

Abstract: 106 words

Text: 6526 words

## **Introduction**

Cytoplasmic scaffold proteins shape the organization of macromolecular complexes involved in multiple cellular functions including cell proliferation, differentiation, signaling, death, tissue formation and homeostasis. As an example, organism models as 'simple' as yeast *Saccharomyces cerevisiae* rely on the Ste5 scaffold protein to assemble into a functional MAPK signaling complex containing the Ste11, Ste7, and Fus3 protein kinases which is important for mating (Printen and Sprague 1994). The human genome encodes a repertoire of hundreds scaffold proteins classified according to their composition into protein-protein or protein-lipid interactions, a few of them bearing enzymatic domains. Their mosaic composition allows each scaffold protein to interact with itself or with other proteins at the plasma membrane or inside the cell, and to act as building blocks for macromolecular assemblies which localize in specific subcellular compartments and coordinate cell functions.

The Scribble PDZ scaffold protein was first identified in 2000 in *Drosophila melanogaster* (Bilder and Perrimon 2000) and subsequently in humans (Dow et al 2003, Nakagawa and Huibregtse 2000, Navarro et al 2005). Based on a genetic screen aimed at revealing new factors involved in epithelial cell polarity, Bilder and Perrimon cloned the *Drosophila scribble* gene encoding a protein with sixteen amino-terminal LRR and four carboxy-terminal PDZ domains. Loss of function of *scribble* results in a striking mislocalization of apical proteins and adherens junctions in polarized structures, and disruption of the monolayer organization of embryonic epithelia. The same year, our lab and the team of Michel Labouesse published two papers back-to-back revealing the existence of epithelial Scribble homologues named Erbin (ERBB2 Interacting Protein, ERBB2IP) and Let-413 in humans and *Caenorhabditis elegans*, respectively (Borg, et al. 2000; Legouis et al 2000). These homologues have sixteen LRRs but only one PDZ domain, much like Densin-180/LRRC7 previously characterized in neurons (Apperson et al 1996). A collective nomenclature for this

group of novel PDZ proteins was soon proposed in reference to the presence of LRR and PDZ domains (LAP protein family, from the initials of the protein domain names) (Bilder et al 2000). Two years later, we extracted from Metazoan genomes additional *lap* gene sequences and proposed a phylogenetic interpretation of their diversity (Santoni et al 2002) (**Figure 1**).

Whereas Let-413 and Scribble were identified through genetic screens for loss-of-function alleles altering invertebrate epithelial morphogenesis, Erbin was characterized as a binding partner of the PDZ binding motif (PDZBM) found in ERBB2/HER2, a tyrosine kinase receptor with crucial roles in development and oncogenesis (Rubin and Yarden 2001). Human Erbin is a large 180kDa protein which, like its homologue Let-413, localizes at the basolateral membrane of polarized epithelial cells, as well as at post-synaptic densities where it binds to cell surface receptors (Borg et al 2000, Huang et al 2001). In addition to mammalian Scribble, Erbin and Densin-180, we identified a fourth LAP family member, Lano/LRRC1 (hereafter named Lano) which, despite the lack of PDZ domain, is a paralogue of Scribble and similarly localizes at the basolateral side of epithelial cells (Saito et al 2001) (**Figure 1**).

Scribble is, by far, the most studied LAP protein over the past two decades. The literature describes its essential role in embryonic development in vertebrates, its role in apico-basal and planar cell polarities (PCP) and its important contribution to cancer development (Bonello and Peifer 2019, Stephens et al 2018). Role for Erbin and Lano have also been reported in cancer. We will now detail the shared features as well as the differences of these LAP proteins at the structural, functional and physiopathological levels.

### **Structural organization of LAP family members**

To fully understand the normal and pathological functions of scaffolds such as LAP proteins, it is necessary to dissect the role of each protein interaction domain (LRR, LAPSD and PDZ) that build these proteins.

### *Leucine Rich Repeats*

LRRs are structural motives of 20-30 amino acids which fold into  $\alpha/\beta$  horseshoe-like ternary structures (Kobe and Deisenhofer 1994) (**Figure 2A**). The role of the LRR domains of Scribble, Erbin and their invertebrate homologues was investigated through structure-function studies *in cellulo* and *in vivo* (Dow et al 2007, Legouis et al 2003, Navarro et al 2005, Zeitler et al 2004). These experiments originally showed that the LRRs are both necessary and sufficient to localize LAP proteins to the plasma membrane, and mandatory for LAP functions (Navarro et al 2005, Zeitler et al 2004). However, other recent studies stated that the covalent and reversible N-terminal palmitoylation of LAP proteins is responsible for their membrane localization. Indeed, the N-terminal terminus of LAP family members contains two conserved S-palmitoylable cysteine residues which were shown to be post-translationally modified (Chen et al 2016, Izawa et al 2008, Strassburger et al 2019) (**Figure 1**). According to SwissPalm (<https://swisspalm.org/>), a database that compiles several palmitoyl-proteome studies, Lano is palmitoylated as is the case for other LAPs. Dynamic membrane anchoring of LAP proteins is regulated by palmitoylation/depalmitoylation cycles which were best documented for Scribble. Indeed, ZDHHC7 (Zinc finger DHHC-type palmitoyl Acyltransferase 7) and APT2 (Acyl Protein Thioesterase 2) were identified as enzymes involved in the reversible palmitoylation of Scribble (Chen et al 2016, Hernandez et al 2017). Interestingly, ZDHHC7-mediated palmitoylation is critical for membrane targeting, cell polarity and tumor suppression in a LRR-dependent manner (Chen et al 2016). Although this has not been proven experimentally yet, it is likely that Erbin and Lano are substrates of the same group of enzymes, as this sequence is conserved at their N-terminus. However, the role of palmitoylation in membrane anchoring of LAP proteins has been questioned in some studies (Izawa et al 2008, Khoury and Bilder 2020).

### *LAPSDs*

The LAP LRRs are followed by two LAP specific domains (LAPSDa and b) which are the signature of the LAP family proteins (Santoni et al 2002) (**Figure 1**). LAPSDa consists in a 38-amino acid LRR-like domain adjacent to a second 24-residue conserved region (LAPSDb) unrelated to LRR motifs. It was only recently shown that LAPSDb is essential for basolateral localization of LAP proteins and LAPSDa for basolateral identity and interaction with the Lgl tumor suppressor (Choi et al 2019) (**Figure 1**).

### *PDZ domains*

PDZ domains were originally classified into three classes according to their binding specificity towards carboxy-terminal PDZ binding motives (PDZBM) (Nourry et al 2003). However, ligand selectivity of PDZ domains is far more complex (Liu and Fuentes 2019). The Scribble, Erbin and Densin-180 PDZ domains display a class I binding specificity with affinity to X-T/S-X  $\Phi$  PDZBMs (where T is threonine, S is serine, X is any amino acid, and  $\Phi$  is a hydrophobic residue). However, the Erbin PDZ domain has a dual ligand specificity and also binds to class II X- $\Phi$ -X- $\Phi$  PDZBMs (Ivarsson et al 2014). The PDZ domains of Scribble follow the PDZ class I canonical structure (**Figure 2B**) (Lim et al 2017). In contrast, Erbin contains an atypical class I PDZ domain that lacks the short  $\alpha$ -helix (called  $\alpha 1$  in other PDZs such as those of Scribble) present between the  $\beta 3$  and  $\beta 4$  strands (**Figure 2C**) and seems to have an intrinsic flexibility that enables it to bind to class I or II PDZBMs such as those found in p0071/delta-catenin and ERBB2, respectively (Birrane et al 2003, Borg et al 2000, Laura et al 2002). Structural analysis has allowed to unravel the molecular basis of class II ligand recognition by the class I Erbin PDZ. The side chain of valine at position -2 of the ERBB2 PDZBM (-V<sup>-2</sup>PV) interacts with valine<sup>1351</sup> of Erbin and displaces the peptide

backbone away from the helix  $\alpha$  (Birrane et al 2003). In addition, Erbin presents an unusually long loop between  $\beta 2$  and  $\beta 3$  strands ( $\beta 2:\beta 3$  loop) compared to canonical PDZ domains (Appleton et al 2006, Birrane et al 2003) (**Figures 2C**). Co-crystallization analysis shows that this  $\beta 2:\beta 3$  loop is able to interact with tyrosine<sup>1248</sup> at position -7 of the ERBB2 PDZBM which plays a crucial role in ERBB2 signaling. The PDZ domain of Erbin binds to the native ERBB2 peptide with good affinity but not with the phosphorylated version on tyrosine 1248, suggesting the regulation of the Erbin-ERBB2 interaction by the active state of the receptor (Birrane et al 2003, Borg et al 2000).

Finally, whereas Lano lacks a PDZ domain, it carries a *bona fide* carboxy-terminal PDZBM (-TTSV) (**Figure 1**) which recognizes class I PDZ domains such as those found in PSD-95. Interestingly, Lano interacts with Erbin indirectly through PSD-95, and with Scribble most probably through a PDZ domain interaction (Daulat et al 2019, Saito et al 2001).

### **Protein networks associated with LAP proteins**

The role of scaffold proteins is to organize macromolecular complexes into functional units at proper sites in cells. Before describing the functions of LAP proteins, we will give an overview of what is known about the interactions involving LAP proteins, from the simple (binary) interactions to the most complex interactions.

#### *LRR interactions*

At the moment, very few partners have been described for LAP LRR domains. Notably, the Ser/Thr protein kinase PHLPP1 which functions as a tumour suppressor binds to the LRR domain of Scribble through its carboxy-terminus. Knockdown of Scribble delocalizes PHLPP1 from the membrane to the cytoplasm and increases AKT phosphorylation (Li et al 2011). Scribble and the cell polarity and tumor suppressor protein Lethal giant larvae 2 (Lgl2)



were previously shown to interact via the LRR domains of Scribble (Kallay et al 2006). Similarly, Lano interacts in the same way with Lgl2 *in vitro* (unpublished data). The scaffold LRR protein SHOC2/SUR8 was also demonstrated to bind Scribble and Erbin LRR domains forming an inhibitory complex for ERK signaling (Dai et al 2006, Young et al 2013). It is less clear how Erbin interacts with and regulates Nod2 stimulation by a component of the bacterial wall muramyl dipeptide, leading to NF- $\kappa$ B activation and an inflammatory response. However, this interaction seems to require the LRR domains of Erbin and the Nod2 CARD domain (McDonald et al 2005).

#### *PDZ interactions*

A long list of studies have revealed numerous binding partners for Scribble and Erbin PDZ domains using various techniques, mainly yeast two hybrid screens, peptide pull-downs coupled to mass spectrometry, and peptide arrays (**Table 1**).

Work from several labs has shown that Scribble directly interacts through its PDZ domains with proteins playing a role in different steps of cancer development and dissemination. Direct interactions have been reported with tumor suppressors mutated in cancer, Adenomatous polyposis coli (APC), a major component of Wnt signaling (How et al 2019), the lipid phosphatase PTEN (Feigin et al 2014), MCC (Mutated Colorectal Cancer) (Arnaud et al 2009), and with ZO-2, a junctional protein downregulated during cancer progression (Metais et al 2005). The Scribble PDZ domains also tightly bind to the PDZBM of the Guanine Exchange Factor (GEF)  $\beta$ -PIX/ARHGEF7 which promotes cancer cell migration (Audebert et al 2004, Nola et al 2008). Crystal structure and quantitative binding data revealed that Scribble PDZ1 and PDZ3 domains display the highest affinity for the  $\beta$ -PIX PDZBM, whereas PDZ2 displays a 20-fold weaker affinity, and PDZ4 none (Lim et al 2017). Scribble also forms a ternary complex with Dlg1 and SGEF, a RhoG-specific GEF, at cell-cell

junctions through the PDZ1 of Scribble and an atypical internal PDZBM in SGEF (Awadia et al 2019).

Erbin was originally identified through its PDZ interaction with the carboxy-terminal sequence of ERBB2 (Borg et al 2000) and has since then been shown to bind other PDZBMs such as those found in members of the p120 catenin family (ARVCF, p0071/PKP4/Plakophilin 4) (Jaulin-Bastard et al 2002, Laura et al 2002) (Jaulin-Bastard et al 2002, Laura et al 2002) (Jaulin-Bastard et al 2002, Laura et al 2002) (Jaulin-Bastard et al 2002, Laura et al 2002) and  $\beta$ -catenin (Ress and Moelling 2008) (**Table 1**).

DSG1/Desmoglein1, an adhesion membrane protein located in epidermal desmosomes, interacts through a cytoplasmic region with the Erbin carboxy-terminus encompassing the PDZ domain. Although mapping of this atypical interaction has not clearly demonstrated the implication of the PDZ domain, DSG1 which directs stratification and differentiation of epidermis may recruit Erbin and negatively regulate the RAS/RAF pathway triggered by EGFR/ERBB2 (Harmon et al 2013).

Scribble has a strong propensity to bind PDZBMs present in oncoviral proteins such as E6 encoded by the high-risk subgroup of human papillomaviruses (HPV-16, HPV-18) causally linked to uterine cervical carcinomas, a major cause of death in women worldwide. It is noteworthy that human Scribble (named at this time VARTUL) was first identified by affinity purification followed by mass spectrometry analysis using GST-E6AP-E6 complex as a bait (Nakagawa and Huibregtse 2000). It has indeed been suggested that the E6-E6AP complex recruits and ubiquitinylates p53 and cell polarity proteins such as Scribble in HPV infected cells, promoting their destruction and switching off their tumor suppressing functions (Thomas et al 2005). Moreover, another proteomic approach demonstrated that Scribble recognition is a conserved feature in all cancer-causing HPV E6 oncoproteins and correlates directly with their increased oncogenic potential (Thomas et al 2016).

Intriguingly, in cooperation with E6, Scribble plays also a role in protein translation through the S6 kinase signaling pathway and potentially increases progression of HPV-induced malignancies (Kranjec et al 2016).

Using a powerful proteomic peptide-phage display approach, Ivarsson et al. discovered previously uncharacterized viral PDZBMs binding to LAPs, among others, rabies virus glycoprotein G for Scribble and Bat coronavirus envelope small membrane protein for Erbin (Ivarsson et al 2014). The Scribble PDZ domains were also shown to interact with other viral PDZBMs found in the NS1 protein of influenza virus (Liu et al 2010) and in the Tax protein of Human T-cell leukemia virus type 1 (HTLV-1) (Okajima et al 2008). A recent study attributed to the Scribble-Tax interaction a prominent role in immortalization of HTLV-1 infected T-cells, as found in human adult T-cell leukemia/lymphoma (Peres et al 2018).

#### *Regions between LRRs and PDZs*

Sequences outside the LRR, LAPSD and PDZ domains of LAP proteins are also the sites of interactions with partners, especially for Erbin. Regions in Erbin indeed interact with bullous pemphigoid antigen 1 (eBPAG1) and Integrin  $\beta$ 4 subunit, two components of hemidesmosomes involved in cell-substrate attachment in the skin (Favre et al 2001), as well as with other PDZ proteins. The postsynaptic density protein-95 (PSD-95) interacts simultaneously with Erbin and with ERBB4, allowing the localization of the ERBB family members to synapses through this PDZ network (Huang et al 2001, Saito et al 2001). Erbin also interacts with the carboxy-terminus of NHERF1 (sodium/hydrogen exchanger regulatory factor1)/EBP50, which harbors two PDZ domains, thus linking Merlin/NF2 to adherens junctions (Rangwala et al 2005).

An interacting motif of about 60 amino acids located close to the Erbin PDZ domain binds to SMAD2/3 and SARA (SMAD anchor for receptor activation) which are regulators of the

TGF $\beta$ /Activin pathway involved in embryonic development and diseases such as cancer (Dai et al 2007, Sflomos et al 2011, Warner et al 2003). Erbin is targeted to early endosomes by SARA and, interestingly, other LAP proteins have been involved in membrane vesicle trafficking (Audebert et al 2004, Liu et al 2018). The SMAD2/3 and SARA common motif is partially shared with another partner of Erbin: MUSK (MUScle associated Receptor Tyrosine Kinase). At the neuromuscular junction, ERBB2, Erbin and MUSK negatively modulate SMAD3-mediated transcriptional activation of TGF $\beta$  target genes (Simeone et al 2010). Finally, Erbin is able to self-associate thanks to its intermediary region and PDZ domain, and therefore enhance its efficiency of signaling (Jaulin-Bastard et al 2001).

#### *Large scale networks associated to LAP proteins*

The first attempt to identify endogenous interactors of Scribble was performed in our team using specific anti-Scribble antibodies (Audebert et al 2004). Although the in-depth identification of protein complexes was limited at that time, our strategy led to the discovery of the  $\beta$ PIX/ARGHEF7-GIT1 complex which binds to Scribble PDZ1 and PDZ3 through a PDZBM found in  $\beta$ PIX. Later on, we identified the Ser/Thr protein kinase PAK1 as another component of the complex (Nola et al 2008). By a single-step method or a TAP-tag purification of Scribble using epitope-tagged constructs, a more extensive network was discovered which comprises additional signaling and polarity proteins including VANGL1, VANGL2, SHOC2/SUR-8, M-RAS,.... (Anastas et al 2012, Young et al 2013). We recently provided a comprehensive map of the partners of Scribble and Lano and confirmed interactions between these LAPs and previously described binding partners ( $\beta$ PIX/GIT, PP1, p0071 among others) (Daulat et al 2019). Around 199 proteins are common to the Scribble and Lano networks, whereas 191 and 275 proteins including many PDZ domain containing

proteins are specifically associated with Scribble and Lano, respectively. Interestingly, the associated network can be regulated by pharmacological inhibition of the proteasome activity. In a recent study aiming to assess the composition of integrin-associated complexes (IACs) in pancreatic fibroblasts using proximity biotinylation (Chastney et al 2020), Scribble and Erbin were identified by mass spectrometry in these cellular structures, together with already known partners including  $\beta$ PIX/GIT for Scribble and  $\beta$ 4-integrin for Erbin. This confirms previous studies demonstrating their presence in phosphoproteomic analysis of IACs and at the leading edge of migratory cells (Horton et al 2015, Robertson et al 2015), and their implication in cell migration (Nola et al 2008, Osmani et al 2006, Stevens et al 2018).

#### *Post-translational modifications of LAP family members*

At the moment, very few studies have described the role of post-translational modifications in LAP functions besides the ones describing the reversible N-terminal dual palmitoylation of LAP proteins (see above and **Figure 1**). However, multiple phosphosites in Erbin, Scribble and Lano are found in databases with no assigned functions for most of them (**Figure 3**). Three phosphorylation sites (S1378, S1508, S1601) in Scribble were shown to contribute to localization at adherens junctions and to cell contractility (Yoshihara et al 2011). The lab of Lawrence Banks also showed that Scribble binds to ERK through two kinase interaction motif (KIM) docking sites, both of which are also required for ERK or PKA-induced phosphorylation of Scribble on S853 (Nagasaka et al 2010). Finally, as demonstrated in the context of HPV infection, Scribble is ubiquitinated and sensitive to proteasomal degradation triggered by E6AP (Nakagawa and Huibregtse 2000) (**Figure 3**). Of note, the intermediate filament protein Vimentin interacts with and protects Scribble from proteasomal degradation (Phua et al 2009).

## **Role of LAP proteins in cancer**

In *Drosophila*, *scribble* plays a major role in the control of epithelial apico-basal polarity and cell proliferation. It belongs to the same tumor suppressing genetic pathway as *discs large* (*dlg*) and *lethal giant larvae* (*lgl*). The *scribble-dlg-lgl* complex genetically interacts with two other sets of cell polarity genes (*bazooka-apkc-par6* and *stardust-crumbs-patj*) in a complex manner to establish and maintain the epithelial phenotype (Bonello and Peifer 2019, Stephens et al 2018).

The most spectacular phenotype of mouse *lap* gene mutants is observed in *scribble*-deficient embryos which have a completely open neural tube and abnormalities in cochlea stereocilia alignments, axonal guidance, heart formation and lung development, all linked to PCP defects (Murdoch et al 2001). Conditional knock-out mouse models revealed other defects in synapse plasticity (Moreau et al 2010), myelination in the central nervous system (Jarjour et al 2015), muscle regeneration (Ono et al 2015) and mammary alveogenesis (Baker et al 2016). *ErbB* knock-out mice are viable and fertile although to a lesser extent than their wild-type counterparts, and display defects of myelination of the peripheral nervous system (Tao et al 2009) and cardiac hypertrophy (Rachmin et al 2014). *Densin-180/LRRC7* was identified as a candidate gene in severe childhood emotional dysregulation. This finding is consistent with the phenotype of *lrrc7* mutant mice which present juvenile aggressive and anxiety-like behaviors and social dysfunction in adulthood (Chong et al 2019). To our knowledge, no implication of *Densin-180/LRRC7* in cancer has been reported yet. Finally, *lano* knock-out mice are viable and fertile with a normal Mendelian distribution (Lopez Almeida et al 2018). However, as in *scribble* and *erbin*-deficient mice (Baker et al 2016, Godde et al 2014, Zhan et al 2008), we observed a delay in the development of the mammary epithelium in these animals (unpublished observations).

Loss of cell polarity is one of the hallmarks of cancer of epithelial origin. Considering the prominent role of Scribble in apico-basal polarity and tumor development in *Drosophila*, and its close conservation with its human homologue (Dow et al 2003), it was anticipated that role of LAP proteins in cancer would be mostly due to defects of epithelial architecture and that their downregulation would contribute to human cancer aggressiveness. Mammalian Scribble was indeed reported to be important in many aspects of cancer development (Elsum et al 2013, Ivanov et al 2010, Zhan et al 2008). However, the reality is far more complex, as several studies have shown that Scribble and its homologues can be downregulated or overexpressed in cancer, and that they have a role in cancer beyond their function in loss of cell polarity (**Table 2**).

### *Scribble*

As a review nicely detailing the role of the Scribble polarity complex in tumorigenesis was recently published (Stephens et al 2018), we will only focus here on some aspects of the role of Scribble in cancer. In many tumors, especially breast and prostate cancer, Scribble levels are low and associated with poor prognosis, supporting the notion that Scribble acts as a tumor suppressor (Anastas et al 2012, Navarro et al 2005, Pearson et al 2011). Reports of interactions of Scribble with major actors of tumoral development have led to further explorations of its role in cancer in the context of this downregulation. Functional studies have indeed shown that loss of Scribble affects the subcellular localization of PTEN, activating the AKT-mTOR-S6 kinase signaling pathway and promoting mammary tumorigenesis in basal breast cancer (Feigin et al 2014). The lab of Senthil Muthuswamy also found that the disrupted expression of Scribble in mouse mammary epithelia impairs cell polarity and apoptosis, ultimately leading to mammary tumorigenesis (Zhan et al 2008). In this paper, the authors showed that Scribble cooperates with the Myc oncogene in an

$\beta$ PIX/ARGHEF7- and RAC-JNK-dependent manner. Stefano Piccolo's lab later found that Scribble is associated with the transcriptional coactivator TAZ at the plasma membrane of breast cancer stem cells, keeping the Hippo pathway in check. Mislocalization of Scribble due to induction of epithelial-mesenchymal transition (EMT) or Scribble depletion trigger Hippo signaling activation, thereby promoting aggressive breast cancer development (Cordenonsi et al 2011). Patrick Humbert's lab convincingly demonstrated a role of Scribble in murine prostate homeostasis and cancer (Pearson et al 2011). Loss of Scribble in the prostate promotes MAPK activation, leading to hyperplasia and low grade tumor development. As previously shown in *Drosophila* (Stephens et al 2018), cooperation between Scribble loss and an oncogenic event (such as the expression of mutated K-RAS) accelerates tumor progression and the formation of invasive carcinoma. In human prostate cancers, Scribble mislocalization was found to be associated with poor survival (Pearson et al 2011). One of the important finding of these studies is that Scribble mislocalization, sometimes associated with its overexpression as in breast cancer (Feigin et al 2014) (**Table 2**), is key to its tumor suppressing activity. It is thus important to investigate the mechanism of its membrane localization. Oncogenic properties of Scribble were also described in Myc-driven B-cell lymphomagenesis (Hawkins et al 2016).

### *Erbin*

The tyrosine kinase receptor ERBB2 was the first identified Erbin binding partner. It is an orphan receptor which homodimerizes in a ligand-independent manner when overexpressed or forms heterodimers with other members of the EGFR family (Rubin and Yarden 2001). ERBB2-positive breast cancer patients have a poor clinical outcome and can benefit from specific therapies targeting the extracellular (trastuzumab, a monoclonal antibody) or the tyrosine kinase (for example lapatinib, a tyrosine kinase inhibitor) domains. The Erbin-



ERBB2 interaction is highly specific as Erbin has no affinity for other EGFR family members, and strictly relies on the Erbin PDZ domain. *In vivo* evidence of the contribution of Erbin in ERBB2-mediated tumorigenesis was obtained in *Erbin*-deficient mice crossed with transgenic mice overexpressing ERBB2 in the mammary gland (MMTV-Neu mice) which are less prone to mammary tumor growth compared to wild type mice overexpressing ERBB2 (Tao et al 2014). This effect is ERBB2-specific as deficiency of Erbin has no effect in the context of tumor development triggered by polyomavirus middle T antigen (PyVT). Tao et al. showed that Erbin stabilizes ERBB2 by promoting the formation of a tripartite complex formed by Erbin, ERBB2 and the HSP90 chaperon. Erbin loss destabilizes this complex leading to ERBB2 proteasomal degradation (Tao et al 2014). A similar study showed that upregulation of Erbin inhibits EGFR ubiquitination and stabilizes it by interacting with c-CBL in colorectal cancer (Yao et al 2015). Overexpression of Erbin and ERBB2 in breast cancer patients with poor prognosis strengthened the hypothesis that Erbin facilitates tumor development, as is the case in MMTV-Neu mice (Tao et al 2014). Others studies related to breast cancer showed that, *in vitro*, depletion of Erbin in cancer cells leads to trastuzumab resistance and to invasion and metastasis *via* trastuzumab-induced AKT activation (Liu et al 2013) and enhanced TRAIL sensitivity, which triggers tumorigenicity *via* the ERBB2/AKT/NF- $\kappa$ B pathway (Liu et al 2008). In the normal skin, subcellular localization of Erbin and ERBB2 varies during cell differentiation. In basal cell carcinoma (BCC), the most common form of skin cancer, Erbin and ERBB2 are redistributed from the plasma membrane to cytosolic aggregates, whereas in keratoacanthoma and squamous cell carcinoma, they remain normally distributed, suggesting a possible impact of this defective subcellular localization on BCC malignancy (Lebeau et al 2005).

In cervical cancer cells, depletion of Erbin induces cell proliferation and migration, and STAT3-dependent resistance to anoikis (Hu et al 2013) or induction of AKT-SKP2-p27

signaling (Huang et al 2015). Through its PDZ domain, Erbin can also modulate the Wnt/ $\beta$ -catenin (Ress and Moelling 2008) and NF- $\kappa$ B (Hrdlickova et al 1995) pathways. Erbin was also shown to inhibit cell proliferation and promote cell death of acute myeloid leukemia (AML) cells. However, increased miR-183-5p levels in certain AML patients negatively regulate Erbin expression and thus enhance RAF-MEK-ERK and PI3K/AKT/FoxO3 signaling (Zheng et al 2019).

Two studies have described the implication of Erbin in the two branches of TGF $\beta$  signaling (SMAD and PAK-dependent) which plays a crucial role in embryonic development, adult life and diseases including cancer (Sflomos et al 2011, Wilkes et al 2009). Wilkes et al. found that, in epithelial cells, the serine/threonine kinase PAK2 activity induced by TGF $\beta$  is repressed by Erbin leading to lower phosphorylation and more potent tumor suppressive function of Merlin. In contrast, in fibroblasts where Erbin expression is much lower, Merlin phosphorylation by active PAK2 is high and induces increased cell proliferation (Wilkes et al 2009). Erbin also contributes to the negative regulation of TGF $\beta$ /ActivinA signaling in SMAD2/3-dependent transcription. Indeed, Erbin interacts with and sequesters phosphorylated SMAD2/3 in the cytoplasm, inhibits its association with SMAD4, and thus abolishes SMAD2/3 dependent transcription upon TGF $\beta$  activation. SARA competes with SMAD2/3 for the interaction with Erbin *via* its SSID (SARA and SMAD interacting domain), allows SMAD2/3 phosphorylation upon TGF $\beta$ /ActivinA stimulation, facilitates its nuclear transfer, and hence modulates the inhibitory effect of Erbin on transcription (Dai et al 2007, Sflomos et al 2011, Warner et al 2003). In a totally different context, Erbin was found to modulate TGF $\beta$  signaling. Indeed, it has been shown that, in T lymphocytes, STAT3 negatively regulates TGF $\beta$  signal *via* Erbin by formation of a STAT3-Erbin-SMAD2/3 complex in the cytoplasm. Deregulation of this pathway in *Erbin* or *STAT3* mutated patients leads to increased T helper type 2 cytokine expression and IgE production (Lyons et al 2017).

A somatic mutation of *Erbin* was also found in a patient with metastatic cholangiocarcinoma, leading to a CD4<sup>+</sup> T cell-directed immune response and remarkable cancer regression by adoptive transfer (Tran et al 2014). Here, Erbin behaves as a *bona fide* tumor-associated antigen with therapeutic potential.

As previously mentioned for Scribble (Godde et al 2014, Pearson et al 2011), Erbin is also a potent regulator of the RAF-MEK-ERK pathway essential in tyrosine kinase signaling. As a known partner of Erbin and Scribble LRR domains, the scaffold LRR protein SHOC2/SUR8 clusters RAS and RAF, and functions as a regulatory protein for the PP1 phosphatase (Dai et al 2006, Young et al 2013). In the complex, Scribble and Erbin function as switches to down-regulate ERK activation and downstream events. Indeed, the SHOC2-PP1 holoenzyme interacts with M-RAS and therefore stimulates RAF activity through dephosphorylation of its inhibitory serine 259 and induction of ERK activation. The presence of Scribble in the protein complex prevents RAF activation by competing with SHOC2 and M-RAS for binding to PP1 (Young et al 2013).

Erbin also negatively modulates the RAF1-MEK-ERK pathway (Huang et al 2003) by preventing SHOC2 interaction with RAS and RAF in a different manner than Scribble (Dai et al 2006). The interaction between Erbin and DSG1 also suppresses EGFR/ERK signaling in head and neck squamous cell carcinoma (Valenzuela-Iglesias et al 2019). In colorectal cancer, Erbin suppresses RAS/RAF signaling by interacting with KSR1 (Kinase suppressor of Ras1) and negatively regulates EMT and tumorigenesis (Stevens et al 2018).

### *Lano*

Less data is available regarding the contribution of Lano to cancer development. The first report of a role of Lano in cancer described its upregulation in hepatocellular carcinoma (HCC) patient samples. By multiple approaches, the authors provided evidence that its

overexpression promotes tumorigenesis. In addition, the gene is located on chromosome 6p12.1, a region frequently amplified in HCC (Li et al 2013).

In an attempt to define the molecular mechanisms that drive HCC, *LANO* was later found to be one of twelve genes shown to be overexpressed and hypomethylated in patient samples. Its expression is negatively associated with overall survival of HCC patients (Hua et al 2020). Moreover, overexpression of *LANO* is associated with its mislocalization from the plasma membrane to the cytoplasm, as already described for *Scribble*. In the case of *Scribble*, this mislocalization correlates with activation of AKT/ATF2 pathway and loss of membranous E-cadherin (Wan et al 2018). Like *Scribble*, *Lano* was considered by the authors as a potential prognostic marker in HCC.

Recently, our lab discovered that low *Lano* expression is associated with a stem cell signature in the human mammary epithelial hierarchy and with cancer stem cell signatures in breast cancer samples. *In vitro* and *in vivo* studies suggest that *Lano* regulates breast cancer stem cell fate through the WNT/ $\beta$ -catenin signaling, likely by modulation of ligand secretion. Here, in contrast to HCC, *Lano* thus behaves as a potential tumor suppressor (Lopez Almeida et al 2018).

Overall, these studies highlight the role of LAP proteins in many signaling pathways with some overlapping contributions, especially in the Wnt and ERK pathways (**Figure 4**). The *LAP* genes belong to a class of genes that exhibit both oncogenic and tumor suppressive functions (**Table 2**) and thus behave similarly to cancer genes such as *WT1*, *PTP1B*, *NOTCH*, *FAS*, *TP53*, *SYK* or cell polarity genes (*PAR6*, *CDHI*, *FAT1*) which are in general not disease-specific. Such is the case for *LAP* genes. However, in the case of *NOTCH*, the cellular context is important as it acts as an oncogene in T-lineage acute lymphoblastic leukemia and as a tumor suppressor in solid tumors (Aster et al 2017). Proto-oncogenes with tumor suppressor

function (POTSF) tend to be hub genes in protein-protein interaction networks with more than 100 interacting partners on average, whereas oncogenes and tumor suppressors have much less binding partners (Shen et al 2018). With more than 100 interactors each as mentioned above, *LAP* genes can be classified as hub genes. We can infer that their over- or downregulation, or delocalization in tumors may similarly destabilize the composition, localization and regulation of LAP-associated signaling and architectural networks important in physiology, promoting cancer development.

### **Redundancy between the LAP family members**

Despite their conserved modular organization, their overlapping expression/localization pattern in cells and tissues and some intra-family biochemical interactions, genetic studies in the mouse have demonstrated no obvious functional commonalities between LAP family members (see above). Moreover, only a few common interactors have been described so far, including those for the PDZ domains. In *Drosophila*, loss of scribble alone leads to mislocalization of apical proteins and adherens junctions to the basolateral membrane (Bilder and Perrimon 2000). The situation is more complicated in mammalian cells as Scribble, Erbin and Lano are co-expressed and colocalized at the basolateral membrane. Deletion of either LAP has no profound effect on the epithelial organization. Recently, Choi et al. simultaneously silenced Scribble, Erbin and Lano in polarized epithelial cells and showed that this combinatorial deletion disorganizes cell junctions and the cytoskeleton, and leads to mislocalization of apical and basolateral determinants. Interestingly, these defects can be rescued by reexpressing the LAP N-terminal region which is required for basolateral targeting (Choi et al 2019) (Dow et al 2007, Legouis et al 2003, Navarro et al 2005, Zeitler et al 2004). Using a series of rescuing transgenes, Zeitler et al. also found that the N-terminal region of *Drosophila* Scribble is mandatory for cell polarity, cell proliferation control, and other

Scribble functions (Zeitler et al 2004). We can infer from accumulated results that this conserved region encompassing the LRRs and LAPSDs contains important information for LAP functions. Mutations in *Drosophila scribble* causes loss of cell polarity and hyperproliferation of larval wing imaginal discs and brain lobes, resulting in the formation of neoplastic tumors and metastasis in cooperation with activated the Ras and Notch oncogenes (Bonello and Peifer 2019, Stephens et al 2018). This tumor suppressing effect is not as strong in *scribble*-deficient mice, probably due to redundancy between the LAP family members, especially through their N-terminal region which exerts anti-proliferative activities at the plasma membrane. We suspect that overexpression of Scribble (or Erbin and Lano) in tumors may cause a dramatic effect because of competitive displacement of other members of the family away from their physiological location leading to aberrant regulation of polarity and proliferation (**Figure 5**).

### **Concluding remarks**

The LAP family can be considered as an archetypal cell polarity protein family whose members have specific subcellular localizations, and scaffolding/signaling functions in many different polarized cell types. Functional redundancy between the four LAP members remains an issue that needs to be addressed in the future using available *lap*-deficient mouse models. In this review, we have focused on their role in cancer and have eluded some other important LAP functions, in particular their role in immunity, atherosclerosis, pregnancy and neuronal functions (Bonello and Peifer 2019, Ludford-Menting et al 2005, Schurmann et al 2019, Yuan et al 2019).

The role of Scribble, Erbin and, more recently Lano, in cancer is now well established in many contexts, from solid to hematological tumors. However, their precise contribution to the different steps of tumorigenesis (cancer cell stemness, EMT,...) remains to be further

investigated, especially considering the complexity of their associated protein networks and their numerous post-translational modifications of unknown significance (**Figure 3**). Regarding stemness, Scribble and Lano have been involved in the biology of stem cells in muscles (Ono et al 2015) and in solid and hematological malignancies (Althoff et al 2020, Cordenonsi et al 2011, Lopez Almeida et al 2018).

The initial assumption that these proteins would behave as tumor suppressors as is the case for *Drosophila* Scribble activity is now taken with caution. There is now growing evidence that overexpression of cell polarity proteins also occurs in cancer and that this correlates with poor prognosis and therapeutic resistance. The cell polarity PAR6 protein is for instance overexpressed in precancerous breast lesions and advanced primary human breast cancers (Nolan et al 2008), and planar cell polarity proteins are upregulated in many cancers (Daulat and Borg 2017). In the case of Scribble, and to some extent of Lano, overexpression is often associated with mislocalization of the protein and, most probably, of its partners, thus affecting the regulation of downstream pathways. Another possibility could be that downregulation of ZDHHC7, a protein involved in S-palmitoylation of LAP proteins, may lead to their mislocalization and to disruption of their function (Chen et al 2016). Chemical compounds able to restore palmitoylation may have some potential therapeutic value, by relocating the proteins at cell-cell junctions. Interestingly, acyl protein thioesterase (APT1, APT2) inhibitors are able to repress Scribble depalmitoylation, favoring Scribble membrane localization and decreased cell growth (Hernandez et al 2017). This is apparently a mammalian specific feature which would be worthwhile exploiting in the future (Izawa et al 2008, Khoury and Bilder 2020). Drugs affecting palmitoylation-depalmitoylation could thus constitute new cancer treatments by restoring the balance between tumor suppressor and oncogene properties of molecules such as the mammalian LAP proteins. Lastly, considering the binding partners of Erbin, especially of its PDZ domain, it is possible that inhibiting Erbin

interactions could contribute to counteracting cancer progression, in particular in the case of the ERBB2 interaction (Tao et al 2014). However, given the promiscuity of PDZ domains, achieving specific inhibition remains a major challenge.

### **Acknowledgements**

We thank Philippe Roche and the Phyre2 web portal for the generation of images, and Valérie Depraetere for careful reading of the manuscript. J.-P.B's lab is funded by La Ligue Nationale Contre le Cancer (Label Ligue Equipe labellisée 2019), Fondation de France (fellowship to RK), the European PDZnet consortium (EU Horizon 2020 RIA under the Marie Skłodowska-Curie grant agreement No. 675341), and by Excellence Initiative of Aix-Marseille University-A\*Midex, "Investissement d'avenir" (CapoStromEx). J.-P.B. is a scholar of Institut Universitaire de France.

### **Competing interests**

The authors declare no competing interests.



## Legends

**Figure 1:** The LAP family is conserved in evolution. The modules which composed the LAP are: **Leucine Rich Repeat (LRR)**, **LAP Specific Domains (LAPSD)** and **PSD-95/Dlg/ZO-1 (PDZ)**, and **PDZ Binding Motives (PDZ-BMs)**. Conserved cysteine residues are represented by two red triangles and dual S-Palmitoyl groups as green zigzags. The grey scale bar corresponds to 100 amino-acid residues.

**Figure 2:** Structure of LAP domains. **A.** The Erbin LRR domains were modeled with the Phyre2 software using the PDB4u08 LRR protein (35% identity with Erbin LRRs) as a template. The  $\alpha$ -helices and the  $\beta$ -sheets are shown in orange and blue, respectively. **B.** The Scribble PDZ1 domain bound to a  $\beta$ -PIX C-term peptide (turquoise blue) (PDB Scrib: 5VWK) (Lim et al 2017) and the Erbin PDZ domain (**C**) bound to ERBB2 C-terminal peptide (PDB: 1MFG) (Birrane et al 2003) are represented using the Phyre2 software (Kelley et al 2015).

**Figure 3:** Post-translational modifications in LAP family proteins. Analysis based on HTP (High Throughput Papers) and LTP (Low Throughput Papers) data available in the Phosphositeplus database. A cut-off of 5 references was set to select the phosphorylation sites.

**Figure 4:** Signaling pathways associated to LAP proteins in normal and cancer cells. The upper panel represents normal polarized epithelial cells, the middle panel migratory epithelial/fibroblastic cells and the lower panel cancer cells. Localization of LAP proteins is pinpointed in each situation. In cancer cells, LAP protein expression can be lost or increased, usually with associated mislocalization.

**Figure 5:** Multiple partners and functions are associated with Scribble. Direct Scribble interactors are in orange (PDZ interactors) and green (ERK interacts with the Scribble C-terminal region) bullets. Indirect and/or functional Scribble interactors are in white bullets. The Scribble-associated functions are in grey boxes.

**Table 1:** Role of PDZ interactions of LAP proteins in cancer. **ITC:** Isothermal Calorimetry; **MS:** Mass Spectrometry; **(co)IP:** (co)Immunoprecipitation; **Y2H:** Yeast Two Hybrid; **MST:** Mesoscale thermophoresis; **BLI:** Bio-Layer Interferometry; **SPR:** Surface Plasmon Resonance; **ELISA:** Enzyme-Linked ImmunoSorbent Assay.

**Table 2:** Expression of LAP proteins in cancer. **Low exp.:** low expression; **High exp.:** High expression; **Misloc.:** mislocalization.

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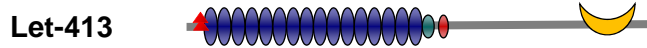
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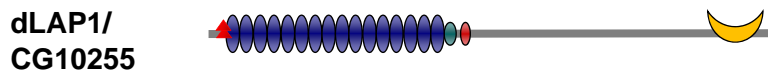
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*Caenorhabditis elegans*



*Drosophila melanogaster*



*Homo sapiens*

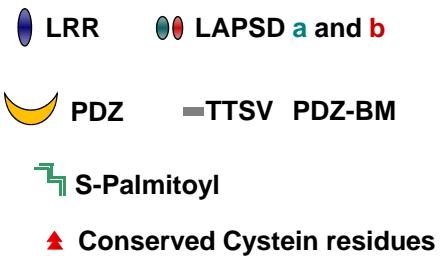
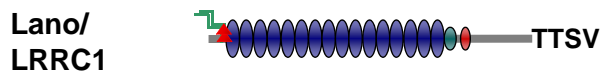
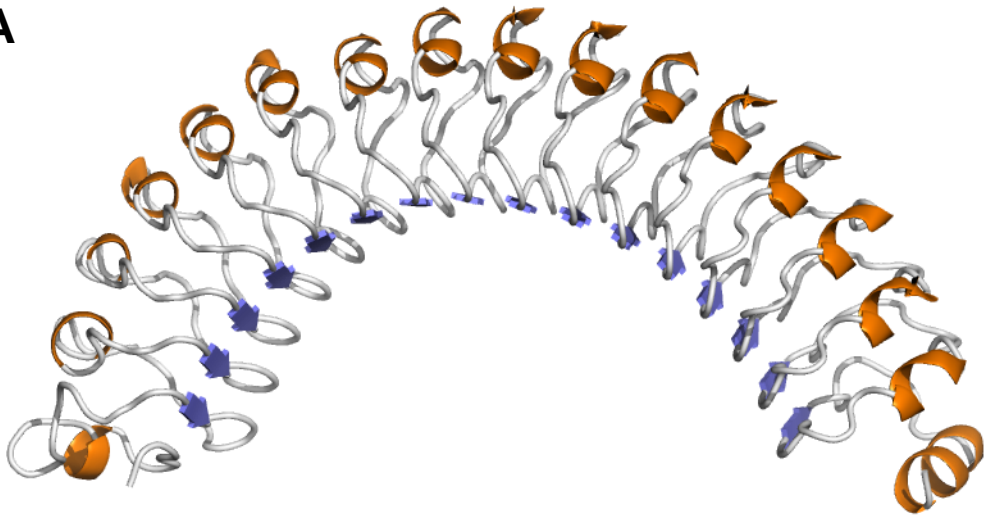
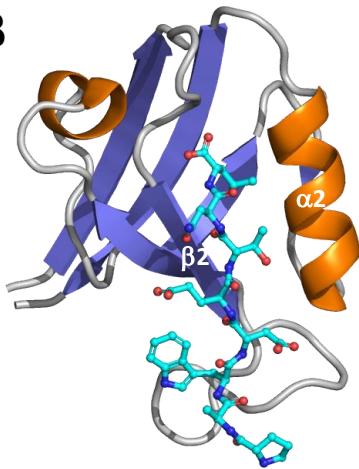


Figure 1: Santoni *et al.*

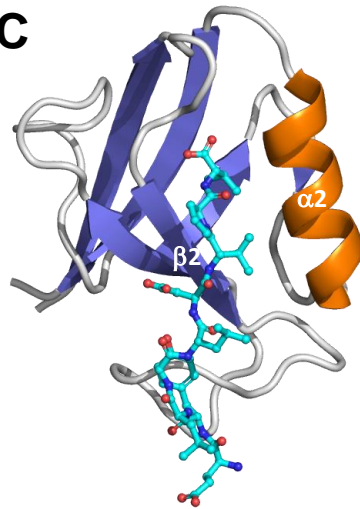
**A**



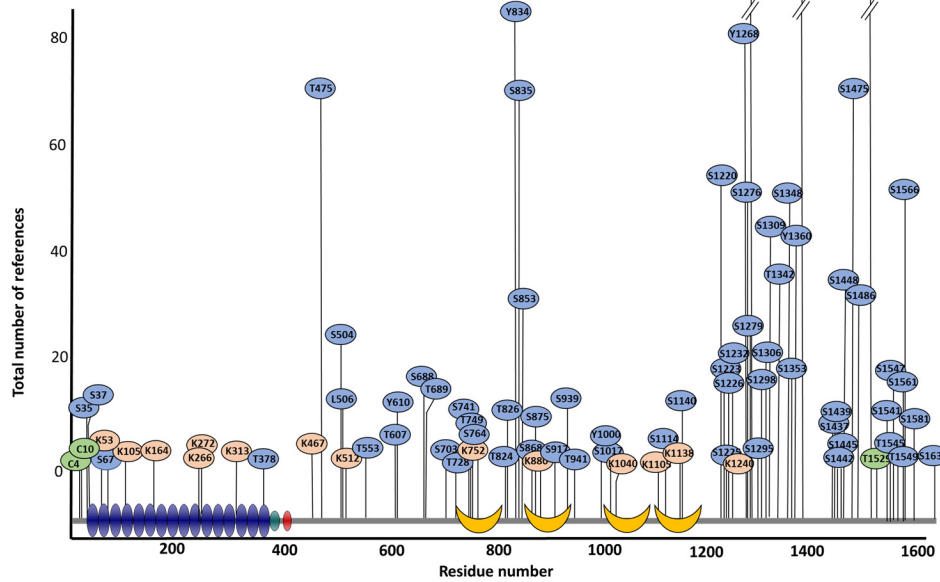
**B**



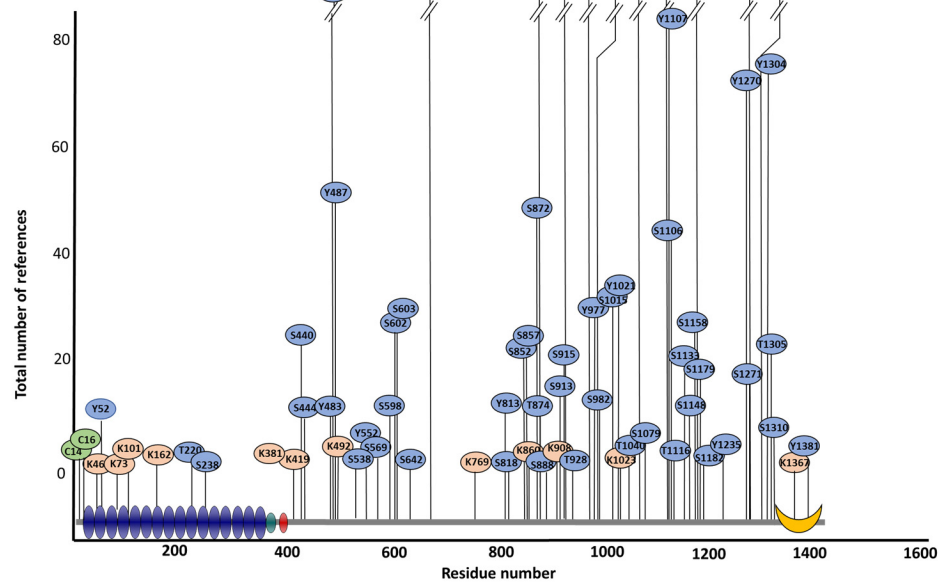
**C**



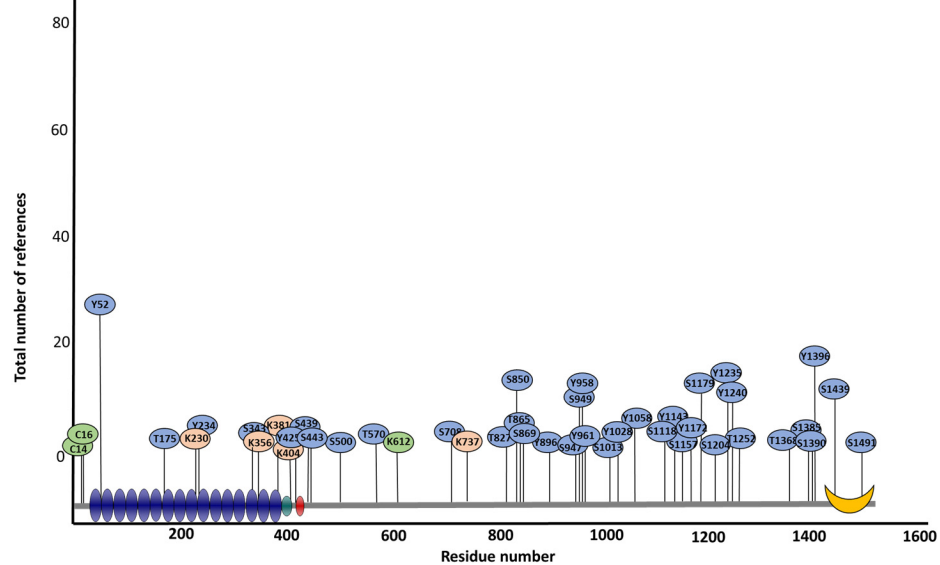
Scribble



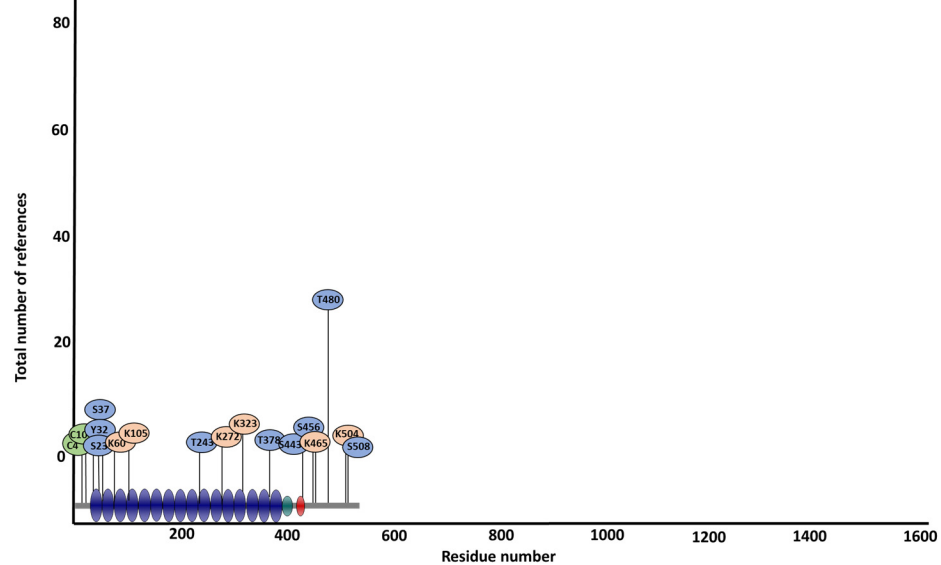
Erbin



Densin -180  
LRRC7



Lano  
LRRC1



- Phosphorylation
- Ubiquitylation
- Acetylation
- ◻ LRR
- ◻ ◻ LAPS a and b
- ◻ PDZ

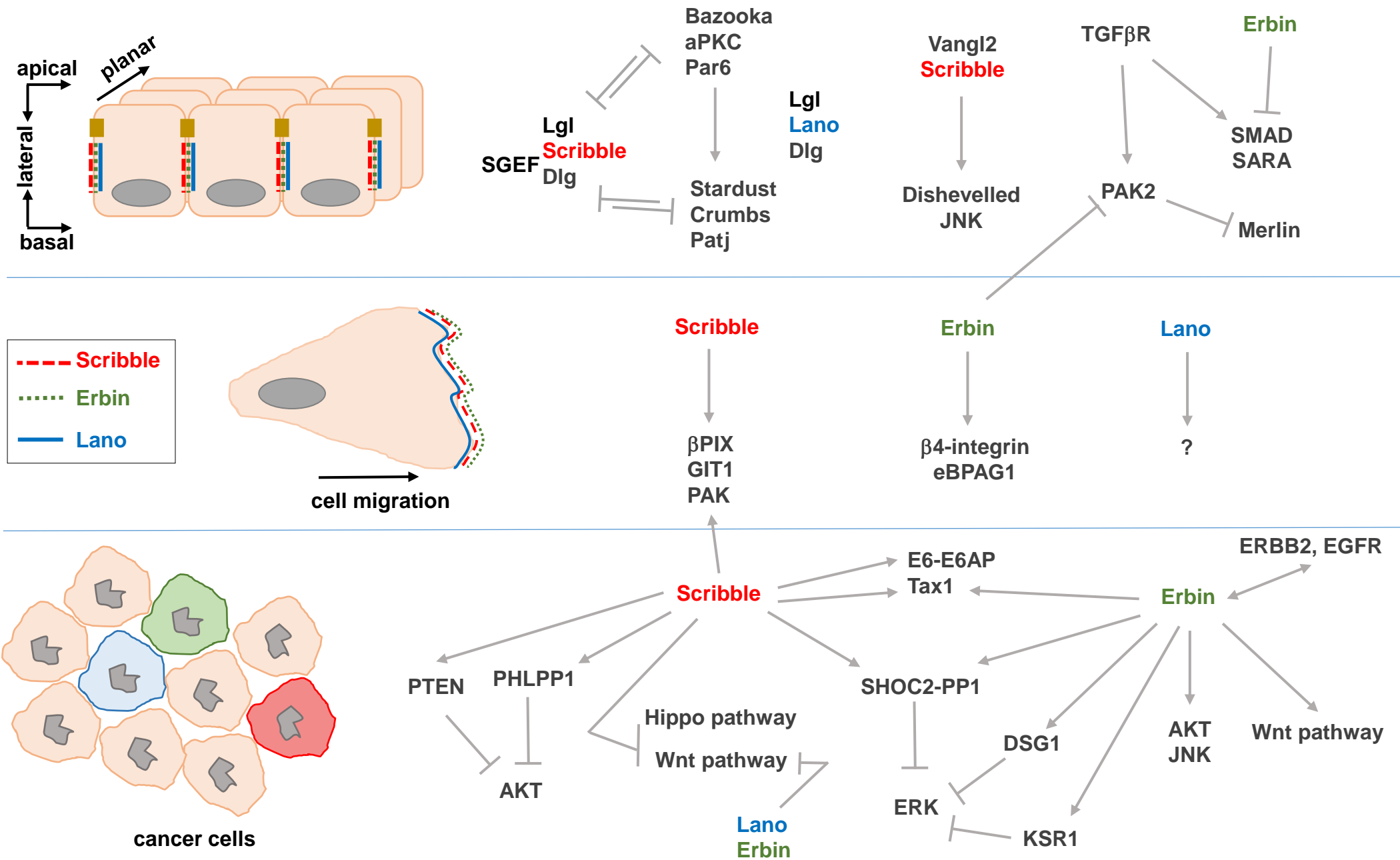


Figure 4: Santoni *et al.*

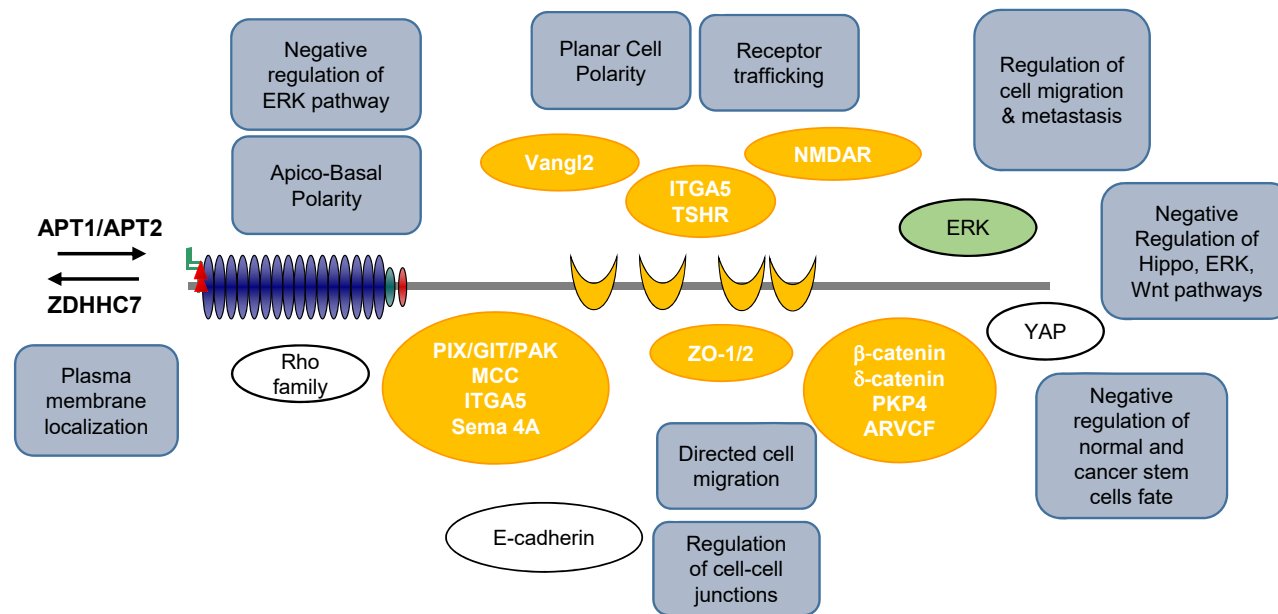


Figure 5: Santoni et al.



**Table 1. Role of PDZ interactions of LAP family proteins in cancer**

LAP proteins	PDZ domains	Interacting partners	Methods	References	Role in cancer	References
<b>Scribble</b>	PDZ 1, -2, -3	β-PIX	ITC, pulldown, MS	Audebert et al., 2004, Lim et al., 2017	Scribble and β-PIX are associated with PAK. The complex controls cell polarity and directed migration in cancer cells. Scribble is shown to inhibit apoptosis in an β-PIX-Rac-JNK pathway-dependent manner, and promotes proliferation in a Ras/MAPK-dependent manner in mammary and prostate epithelia.	Nola et al., 2008, Dow et al., 2007, Zhan et al., 2008, Pearson et al., 2011
	PDZ 1, -2, -3	APC	Pulldown, IP, ITC	Takizawa et al., 2006, How et al., 2019	Scribble co-localizes with APC at the membrane protrusions. Scribble siRNA disrupts localisation of APC in Caco-2 cells	Takizawa et al., 2006.
	PDZ 2, -3, -4	Vangl2	Y2H, IP, pulldown	Montcouquiol et al 2006, Kallay et al., 2006		
	PDZ 1, -3	MCC	Pulldown, IP, ITC	Arnaud et al., 2009, Sundell et al., 2018	MCC and Scribble colocalize at the plasma membrane of breast cancer cells. Reduced expression of MCC results in impaired cell migration	Arnaud et al., 2009
	PDZ 1, -3	HPV16 E6	Phage library screening, MS	Nakagawa et al., 2000, Kranjec et al., 2016	Proteasome mediated degradation of Scribble after HPV infection, Scribble is required for HPV E6 expression in cervical tumour-derived cells	Nakagawa et al., 2004, Kranjec et al., 2016
	PDZ 2, -3	Tax 1	Pulldown, IP, fluorescence polarization assays	Okajima et al., 2008; Ivarsson et al., 2014	Scribble interacts with Tax 1 and is essential for T-cell immortalization	Okajima et al., 2008, Pearès et al., 2018
	PDZ 3, -4	Fat1	Co-IP	Skouloudaki et al., 2009	Scribble and Fat1 directly interact and play a role in Hippo signaling	Skouloudaki et al., 2009
	PDZ 3, -4	ZO-2	Pulldown, MS, Co-IP	Metais et al., 2005		
	PDZ 1	RPS6KA1, A2	ProP-PD, MST and ITC	Sundell et al., 2018		
	PDZ 1	TANC1, TAZ, YAP1	ProP-PD, MST and ITC	Sundell et al., 2018		
	PTEN	IP	Feigin et al., 2014	In breast cancer, delocalization of Scribble promotes increased PTEN levels and activates AKT/mTOR/S6K pathway	Feigin et al., 2014	
PDZ 4	p22phox	BLI, pulldown, IP	Zheng et al., 2016	Scribble modulates the NOX pathway by inducing ROS generation with implications for chronic inflammatory diseases, sepsis and cancer	Zheng et al., 2016	
<b>Erbin</b>	PDZ	ERBB2	Y2H, IP, ELISA, SPR	Borg et al., 2000, Laura et al., 2002, Jaulin-Bastard et al., 2001	Erbin regulates ERBB2 stability in breast cancer	Tao et al., 2014
	PDZ	β-catenin	SPOT assay, ELISA, CoIP	Boisguerin et al., 2004, Ress et al 2006 & 2008	Erbin modulates beta-catenin-dependent transcription and acts as a negative regulator	Ress et al., 2006 & 2008
	PDZ	APC	Y2H, IP	Ress et al., 2006	Erbin/Apc double knockout mice have increased tumor initiation potential and activation of Wnt signaling is observed	Stevens et al., 2018
	PDZ	p0071/Plakophilin-4	Y2H, Co-IP, SPR	Jaulin-Bastard et al., 2001, Izawa et al., 2002		
	PDZ	Tax1	SPOT assay, Y2H, ProP-PD	Ress et al., 2006, Song et al., 2009, Ivarsson et al., 2014		
	PDZ	BCR	SPOT assay, IP	Boisguerin et al., 2004		
	PDZ	c-Rel	Y2H, IP	Ress et al., 2006		
	PDZ	Delta catenin, ARVCF	ELISA, pulldown, IP	Laura et al., 2002		

**Table 2. LAP family proteins and Cancer**

Protein	Alteration	Tumor type	Proposed mechanisms	References
<b>Erbin</b>	Low exp.	Breast cancer	Erbin regulates sensitivity to TRAIL via ErbB2/AKT/NF-kB Absence of Erbin destabilizes ErbB2 at the membrane	Liu N. et al., 2008 Tao Y. et al., 2014
	Low exp.	Cervical cancer	Erbin induces a STAT3-dependent resistance to anoikis	Hu Y. et al. 2013
	Low exp.	Colorectal cancer	Erbin inhibits EGFR ubiquitination and stabilizes it by interacting with c-Cbl Erbin interacts with KSR1 and displaces it from the RAF/MEK/ERK complex	Yao S. et al., 2015 Stevens P.D. et al. 2018
	High exp.	Pancreatic ductal adenocarcinoma	Causal role of Erbin accumulation in Gemcitabine chemo-sensitization	Li H. et al., 2017
	High exp.	Hepatocellular carcinoma	Erbin destabilizes ER $\alpha$	Wu H. et al., 2017
	Low exp.	Head and neck squamous cell carcinomas (HNSCC)	Dsg1 requires Erbin to decrease EGFR/ERK signaling	Valenzuela-Iglesias A. et al., 2019
	Low exp.	Acute Myeloid Leukemia (AML)	miR-183-5p negatively regulates Erbin and inhibits AML progression	Zheng Z. et al., 2019
<b>Scribble</b>	High exp.	Breast cancer	Scribble shRNA reduces the growth of breast cancer cells in xenografts Scribble mutant promotes an increase of PTEN level and activates AKT/mTOR/S6K pathway	Anastas J.N. et al., 2012 Feigin M.E. et al., 2014
	Low exp.	Breast cancer	Mislocalization MAPK/Fra1 activation	Navarro C. et al., 2005 Zhan L. et al., 2008 Godde N.J. et al., 2014
	Low exp. misloc.	Invasive cervical cancer	Proteasome mediated degradation of Scribble after HPV infection	Nakagawa S. et al., 2004
	High exp. misloc.	Prostate cancer	Scribble negatively regulates the MAPK pathway	Pearson H.B. et al., 2011
	High exp.	Hepatocellular carcinoma	Scribble mislocalization contributes to activate AKT/ATF2	Wan S. et al., 2018
	Low exp. misloc.	Lung carcinoma	Loss of Scribble and KRas hyperactivation cooperates in vivo	Elsun I.A. et al., 2014
	Low exp.	Skin carcinogenesis	Loss of Scribble enhances skin carcinogenesis	Pearson H.B. et al., 2015
	Low exp.	Lymphoma	c-Myc deregulation	Hawkins E.D. et al. 2016
<b>Lano</b>	Low exp.	Breast cancer	Inhibition of Wnt secretion	Lopez-Almeida L. et al., 2018
	High exp. misloc.	Hepatocellular carcinoma	Hypomethylation of the gene	Li Y. et al., 2013 Hua S. et al., 2020