

THE TCL1 FAMILY OF ONCOPROTEINS: CO-ACTIVATORS OF TRANSFORMATION

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Abstract | The T-cell leukaemia/lymphoma 1 (TCL1)-family oncoproteins augment AKT signal transduction and enhance cell proliferation and survival. Chromosome rearrangements, faulty developmental silencing and Epstein–Barr virus infection appear to dysregulate the expression of TCL1-family genes, provoking several important types of lymphocyte cancer. A key role for TCL1 proteins in cell transformation has been established in studies of transgenic mouse models, which develop a unique spectrum of T- and B-cell malignancies. How TCL1 proteins are regulated and dysregulated, how they promote transformation and the potential for therapies modelled on TCL1 interactions have important implications for understanding and treating lymphocyte cancers.

AKT

In 1991, *v-Akt* was cloned as the transforming oncogene of the AKT8 murine leukaemia retrovirus. Three mammalian AKT homologues control cell growth, survival, glucose metabolism, transcription and cell migration.

The TCL1 family of genes is expressed mainly in developing embryos, fetal tissues, germ cells and lymphocytes^{1–3}. They encode a related group of small, intracellular, non-enzymatic proteins that bind AKT proteins, which are essential serine/threonine kinases that relay pro-growth and survival signals from the environment, and which are thought to participate in tumour progression^{4,5}. TCL1 proteins do not activate or deactivate AKT proteins; instead, they augment AKT activation, probably by forming stable heteromeric complexes with AKT at the cytoplasmic membrane^{6,7}. In this way, TCL1 proteins behave like signalling rheostats to regulate AKT signal transduction in a concentration-dependent manner.

The control of TCL1-family expression is crucial for the health of organisms. Too little TCL1 could have deleterious effects on reproduction and development, whereas too much might predispose to cancer. This is highlighted by the fact that the deletion of *Tcl1* impairs mouse reproduction and moderately perturbs early T- and B-cell lineage development^{8,9}. Conversely, abnormal expression of TCL1-family members — resulting from chromosome rearrangements, possibly by Epstein–Barr virus (EBV) infection or from faulty

developmental silencing — promotes the transformation of mature human T and B cells^{1,10,11}. Mice with dysregulated human TCL1-family gene expression develop lymphocyte cancers that resemble cognate human malignancies that have not been seen with other genetic, viral and environmental manipulations^{12–15}.

However, a model for TCL1 oncogenesis that solely depends on inappropriate AKT signalling at the membrane seems to be too limited. Therefore, beginning with a short historical perspective, in this brief review I highlight the regulation, function and transforming features of TCL1 oncoproteins — including areas in which our knowledge is limited or the data are inconclusive — and I close with some likely future directions for this exciting, and enigmatic, protein family.

Discovery of TCL1 and its family members

The TCL1 family of genes was discovered because of its involvement in characteristic chromosome rearrangements in mature T-cell tumours (reviewed in REFS 16–20). T-cell malignancies from children with ATAXIA TELANGIECTASIA and adults with sporadic T-cell leukaemia showed recurrent chromosome translocations and inversions that juxtaposed coding regions at 14q32 or Xq28 with T-cell receptor (TCR) loci at

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Summary

- The T-cell leukaemia/lymphoma 1 (TCL1) gene family consists of three genes in humans and seven genes in mice and these encode for small, intracellular, β -barrel-shaped proteins. Members of the human TCL1 family are known to bind and augment AKT kinase activity, thereby regulating signal transduction from the environment.
- Normal expression of TCL1 family members seems to be limited mainly to early embryogenesis, germ cells, specific fetal and adult tissues, and precursor/immature T and B lymphocytes.
- Dysregulated TCL1-family gene expression in T cells, by chromosome rearrangements, or in B cells, possibly by Epstein–Barr virus infection or aberrant silencing, enhances cell proliferation and survival and leads to cell transformation following a prolonged latency.
- Transgenic mice that aberrantly express TCL1 genes provide unique models of mature human lymphoid malignancies (including T-cell prolymphocytic leukaemia, Burkitt lymphoma, diffuse large B-cell lymphoma, rare follicular lymphoma, and B-cell chronic lymphocytic leukaemia) that have not been seen after other genetic, viral or environmental manipulations.
- The precise mechanism for TCL1-mediated transformation is not resolved. There are potentially relevant AKT target proteins in the cytosol and possibly the nucleus. To determine how TCL1 proteins cause cancer, it is crucially important that we determine the mechanisms of TCL1-family gene regulation and dysregulation, understand potential AKT-independent effects, discover complementing alterations required for malignancy, and determine transforming activity beyond lymphocytes.

ATAXIA TELANGIECTASIA

An autosomal recessive neurodegenerative disorder with onset in early childhood, that results from mutations in the ataxia telangiectasia mutated (ATM) gene. Patients are predisposed to develop cancer, especially leukaemia and lymphoma.

BLASTOCYST

Post-fertilization early embryonic structure composed of an inner cell mass surrounded by a fluid-filled cavity formed of extra-embryonic tissue. The inner cell mass will become the definitive offspring.

PRO-B CELL

Early-stage B-cell precursor within the bone marrow, in which developing B-cells first begin to genetically rearrange their immunoglobulin genes in preparation for making functional antibodies.

GERMINAL CENTRE B CELLS

B cells in peripheral lymphoid organs, such as lymph node and spleen, which undergo T-cell-dependent antigenic stimulation in a germinal center. A germinal center is a secondary lymphoid structure in which T-cell-dependent antigens drive B-cell antibody affinity maturation in a genetically error-prone process

14q11 or 7q35. The first family member, mature T-cell proliferation 1 (*MTCPI*), was identified by northern-blot-analysis probes that spanned the breakpoint region on Xq28, and this was quickly followed by exon-trap cloning of the family namesake *TCL1* (also called *TCLIA*) at 14q32 (REFS 1,21). Indeed, aberrant rearrangements during TCR–VDJ recombination in pre-T cells result in dysregulated TCL1-family gene expression¹⁶. Murine *Mtcp1* and *Tcl1* were subsequently identified by homology^{2,3}, and human *TCLIB* (also called *TML1*) was isolated from mature T-cell tumours rearranged at 14q32, 15 kb downstream of *TCLIA* (REFS 22,23). Expanding the family further, five additional mouse genes (*Tcl1b1*, *Tcl1b2*, *Tcl1b3*, *Tcl1b4* and *Tcl1b5*) were cloned using their homology with human *TCLIB*²⁴. All told, there are three members of the human and seven members of the mouse TCL1 gene family, and there are uncharacterized homologous genes in additional vertebrates. The absence of TCL1-family members in lower and non-mammalian eukaryotes indicates that, evolutionarily, the TCL1 family has recently acquired a role in mammalian physiology, probably related to reproduction and immune-cell development and function.

TCL1 expression patterns

Normal expression patterns. Broadly speaking, the expression of TCL1-family genes in mice is most prominent in early embryogenesis, select fetal and adult tissues and precursor lymphocyte differentiation. In mice, *Tcl1* and the genes *Tcl1b1* to *Tcl1b5* are expressed in oocytes and early-cleavage embryos, and there is progressive *Tcl1* silencing through the BLASTOCYST

stage^{8,24,25}. *Tcl1*, *Tcl1b2* and *Mtcp1* expression are also detected in early to mid-gestation^{3,8}. *Tcl1* and *Mtcp1* are expressed in fetal liver and the yolk sac, whereas *Tcl1* is also expressed in fetal thymus and fetal bone marrow³, which might reflect embryonic lymphopoiesis. In adult tissues, *Tcl1b2* is broadly expressed, whereas *Tcl1* and *Tcl1b4* are seen in the testes²⁴. *Tcl1* is also expressed during B-cell development from the PRO-B CELL through GERMINAL CENTRE (GC) B-CELL stages and in T-cell development — mainly in immature CD4⁺CD8⁺ and CD4⁺CD8⁺ THYMOCYTES^{3,9}. *Mtcp1* is expressed following the activation of lymph-node T cells using staphylococcal enterotoxin B superantigen, which is a powerful pan-T-cell mitogen²⁶.

Expression of TCL1-family genes has not been evaluated in early human embryogenesis. Nevertheless, *TCLIA* and *TCLIB* expression has been detected in fetal liver, fetal kidney, fetal thymus, testis, spleen, tonsil, bone marrow and peripheral blood lymphocytes^{8,22,24}. *TCLIA* is also expressed by plasmacytoid dendritic cells²⁷ and *TCLIB* is also expressed in fetal spleen, placenta and kidney. *MTCPI* is expressed in two main forms, resulting in type A1 and type B1 transcripts. Type B1 transcripts encode a TCL1-related protein that has low expression in most tissues, whereas type A1 transcripts encode an 8-kDa mitochondria protein that is structurally unrelated to TCL1-family proteins and is abundantly expressed in most tissues except placenta and kidney²¹. Although encoded by a TCL1-family gene, a role for the 8-kDa form of human MTCPI in physiology or cancer pathogenesis is yet to be determined. During lymphocyte differentiation, *TCLIA* expression begins in pre-B cells, is downregulated in GC B cells, and is silenced in memory B and PLASMA CELLS^{1,28–30} (FIG. 1). *TCLIA* is only expressed in early T-cell development, before the appearance of surface TCRs, and possibly with the robust activation of PERIPHERAL T CELLS^{1,31,32} (FIG. 1). Expression by human lymphocytes of *TCLIB* and *MTCPI* has not yet been defined.

TCL1-family genes span 4 to 8 exons, transcribe mRNAs that are between 1.2 and 2.0 kb long, and are located at 14q32 and Xq28 in humans and on chromosomes 12 and X in mice^{1,3,21–24,33}. The *trans*-factors, *cis*-elements and epigenetic mechanisms that regulate TCL1-family transcription in mice and humans are mostly unknown. The *TCLIA* core promoter contains a TATA box and a classic C₂G-RICH ISLAND, and other TCL1-family promoters show either similar or strikingly divergent features^{11,34}, indicating independent gene regulation of these family members, although evaluation of the *TCLIB* and *MTCPI* promoters has not yet been carried out. For *TCLIA*, the ubiquitous DNA-binding transcription factor Sp1 is required at three consensus sites for robust expression, whereas dense DNA methylation might occur in transcriptionally silent non-lymphoid cells and in mature B and T lymphocytes after gene silencing^{11,34}. Crucially, no mechanisms have been described for the control of tissue- or development-specific expression of the TCL1 genes. Also, nothing is known about the mRNA

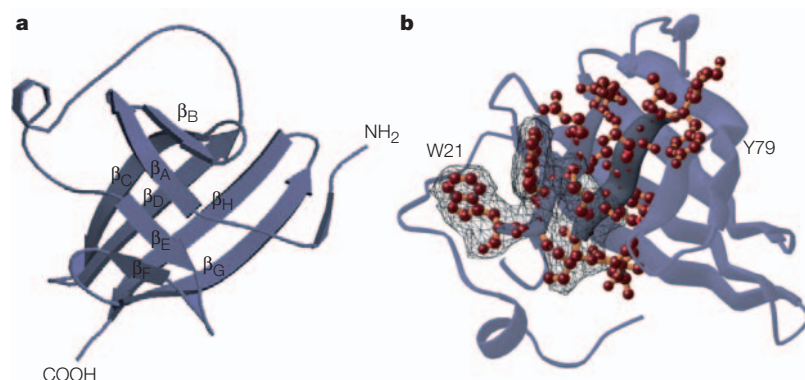


Figure 2 | TCL1 family protein structure and binding surfaces. a | Shown is a top view of the novel T-cell leukaemia/lymphoma 1 (TCL1) family β -barrel structure, which is bounded by two four-stranded β -chains surrounding a hydrophobic and tightly packed core. Amino (NH_2) and carboxy (COOH) termini are shown. The β -strands β_A , β_B , β_E and β_F form one face of the barrel that interacts with the β_1 and β_5 strands of the AKT pleckstrin homology (PH) domain (not shown), whereas the β -strands β_C , β_D , β_G and β_H form a second face behind the plane of the first face. The long flexible loop that contains a short α -helix and connects the β -barrel faces participates in binding AKT, although it has divergent sequences between TCL1 family members⁷. The TCL1A β_C strand contains a homodimerization domain that is lacking in MTCP1 (REFS 41,58). Part **a** modified with permission from REF. 42 © (1998) National Academy of Sciences. **b** | van der Waals surface contour of the exposed hydrophobic, tryptophan-rich face (shown as red spheres) of TCL1A that binds to AKT. The purple ribbon in this figure is the peptide backbone of TCL1A. The TCL1A homodimerization domain on its β_C strand is on the opposing face of the molecule. Tryptophan-21 (W21) and tyrosine-79 (Y79) are indicated to mark the boundaries of this hydrophobic interaction domain. Part **b** modified with permission from REF. 6 © (2002) American Chemical Society.

T-CELL PROLYMPHOCYTIC LEUKAEMIA
An aggressive leukaemia of peripheral T cells that frequently contains chromosome rearrangements that activate *TCL1A* or *MTCP1*.

SEMINOMA
Tumour of primitive germ cells in male testes. This tumour is identical to dysgerminoma in female ovaries.

DYSGERMINOMA
Tumour of primitive germ cells in female ovaries. This tumour is identical to seminoma in male testes.

CD4/CD56 HAEMATODERMIC NEOPLASM
Also termed CD4/CD56 blastic tumour of skin, this entity is a rare and aggressive malignancy probably derived from the transformation of a plasmacytoid dendritic cell.

MANTLE ZONE
Region surrounding a GC central follicle in which pre-GC B-cells are prevented from entering the GC reaction for B-cell antibody affinity maturation by having an incorrect immunoglobulin for the inciting T-dependent antigen.

or protein stability of TCL1 family members, or about potential post-translational modifications, which could also be involved in the regulation of the expression and biological function of TCL1 proteins.

Dysregulated expression patterns. In cancer, dysregulation of *TCL1A*, *MTCP1* and probably *TCL1B* occurs in T-CELL PROLYMPHOCYTIC LEUKAEMIA (T-PLL, formerly called T-cell chronic lymphocytic leukaemia), and *TCL1A* dysregulation has been further described in B-cell lymphomas and in germ-cell tumours, including SEMINOMA and DYSGERMINOMA^{1,8,21,22,28,35}. *TCL1A* expression in tumours that comprise pre-GC B cells^{29,36} and in a recently described cancer derived from plasmacytoid dendritic cells, called CD4/CD56 HAEMATODERMIC NEOPLASM^{27,37}, probably reflects normal developmental rather than aberrant expression, as *TCL1A* is expressed at moderate to high levels in the normal precursors of these tumours.

In T-PLL, rearrangements between a TCL1-family gene and TCR- α/δ or β loci places it under the control of elements that regulate TCR expression, resulting in dysregulated TCL1-family gene expression beginning in early thymocytes (FIG. 1). However, the situation in mature B-cell tumours is more complicated. Increased *TCL1A* expression is seen in follicular lymphoma, Burkitt lymphoma, diffuse large B-cell lymphoma (DLBCL), and B-cell chronic lymphocytic leukaemia (B-CLL), all of which derive from GC or post-GC B-cells that have reduced or absent *TCL1A* levels^{28,29,36,38}. Importantly, no chromosome

rearrangements have been linked to this dysregulation^{11,34}. Instead, it has been inferred — mainly from studies of EBV-infected Burkitt lymphoma cells — that EBV infection dysregulates *TCL1* by an undefined mechanism, although sporadic, EBV-negative Burkitt lymphoma cells show similarly dysregulated *TCL1A* expression^{10,29,39}. For EBV-negative cases in particular, faulty GC silencing, by impaired transcriptional and/or epigenetic mechanisms^{11,34} seem to be implicated, because non-malignant pre-GC MANTLE ZONE B cells show the high-level expression that is maintained by these tumours. The mechanism(s) that increase *TCL1A* expression in seminoma and dysgerminoma still need further investigation⁸.

TCL1 in cell transformation

The prevailing view of the role of TCL1 proteins in cancer is related to their involvement in the AKT signal-transduction pathway, although this notion is controversial and still evolving, as described below. The AKT protein kinase family is a central regulator of many essential cellular processes, including mammalian cell proliferation and survival. Once it has been activated by signals relayed from the environment, AKT phosphorylates serine and threonine residues of target proteins that control these processes. However, unchecked or excessively strong AKT signalling also enables tumour progression by overstimulating crucial signalling pathways that regulate, for example, cell survival, protein translation and cell-cycle progression. Several recent structural, biochemical and functional studies have improved our understanding of how TCL1 proteins interact with AKT in relaying these signals, providing clues for a potential TCL1 transforming mechanism.

Structure of TCL1 proteins. TCL1-family proteins range in size from 13 to 15 kDa, and there is moderate sequence conservation between members^{1,3,21–24,36,40}. TCL1 proteins are non-enzymatic and their structures, expression patterns and physical locations dictate their physiological and tumorigenic properties. Human *TCL1A* and *MTCP1*, and mouse *TCL1*, show a tightly packed internal hydrophobic core and share a novel β -barrel structure that includes two four-stranded β -chain sheets connected by a long looping strand^{41–43} (FIG. 2). A molecular model for human *TCL1B* and mouse *TCL1B* based on the solved structure and 35% amino acid sequence conservation to *TCL1A* has also been proposed²⁴. Although human *TCL1A* purification has provided evidence of protein dimerization⁴¹, structural analyses have failed to provide informative clues about the family's functions, as there are no homologous β -barrel motifs or regions similar to TCL1-family proteins in other protein families for comparison. An exception to the novel β -barrel structure of TCL1 proteins arises from the alternative splicing of *MTCP1* and *Mtcp1* transcripts (resulting in the type A1 and type B1 transcripts mentioned earlier), which, in human tissues, results either in low expression of the 13-kDa TCL1-family

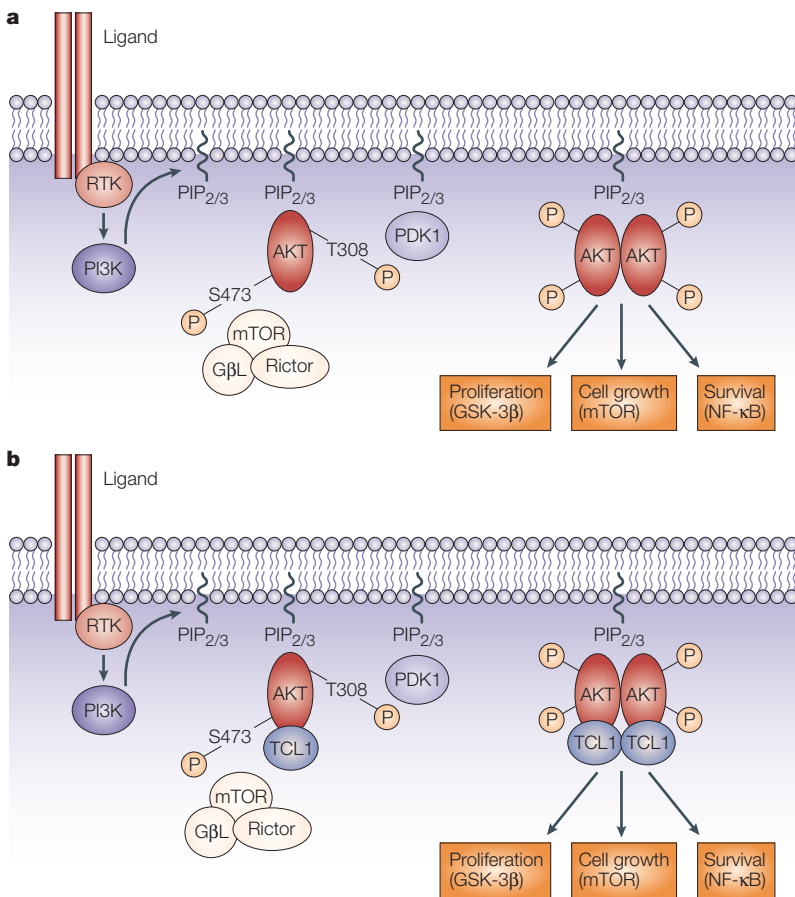


Figure 3 | TCL1 co-activation of AKT. **a** | The AKT signalling pathway. Ligand-induced activation of a receptor tyrosine kinase (RTK) phosphorylates and activates phosphatidylinositol 3-kinase (PI3K) to produce phosphatidylinositol-3,4-bisphosphate (PIP₂) and phosphatidylinositol-3,4,5-triphosphate (PIP₃). AKT is then activated by recruitment to the plasma membrane and phosphorylation. The tumor suppressor phosphatase and tensin homologue (PTEN; not shown) opposes AKT activation by dephosphorylating the PIP_{2/3} membrane docking sites for AKT, blocking membrane recruitment. At the membrane, AKT is phosphorylated on Thr-308 (T308) by the pleckstrin homology (PH)-domain-recruited kinase 3-phosphatidylinositol-dependent kinase 1 (PDK1, also known as PDK1). Phosphorylation of AKT Ser-473 (S473) is by another kinase(s), such as the complex between Rictor, mammalian target of rapamycin (mTOR) and G-protein β-subunit-like protein (GβL)⁵⁰, or because AKT can multimerize, possibly by AKT itself through transphosphorylation^{45–47,51–56,58}. Activated AKT promotes cell proliferation, growth and survival. The phosphorylation status of the T308 and S473 sites is not yet linked to distinct functional outcomes, but is linked to maximal AKT activation. AKT inactivation (not shown) is caused by protein phosphatase 2A (PP2A), which dephosphorylates AKT on T308, and by the PH domain leucine-rich repeat protein phosphatase (PHLPP), which dephosphorylates S473 (REFS 70,71). The effect of T-cell leukaemia/lymphoma 1 (TCL1) proteins on AKT dephosphorylation is unknown. **b** | The binding of TCL1 proteins to AKT increases AKT effector functions. In some studies, this TCL1–AKT interaction increases the phosphorylation state of AKT^{5,54,57}, while other studies have not found increased phosphorylation on T308 or S473 (REFS 8,9,27). Both sets of studies agree, however, that the interactions of TCL1 with AKT enhance the phosphorylation of downstream AKT target substrates *in vitro*, such as glycogen synthase kinase-3β (GSK3β).

LIPID RAFT
A putative detergent-resistant microdomain of the plasma membrane that might concentrate specific molecules and complexes to facilitate key membrane processes, including signal transduction.

protein or moderate to high expression of the uniquely shaped 8-kDa cysteine-rich mitochondrial protein of unknown function^{21,44}.

Interaction between TCL1 and AKT — structural and biological studies. A potential breakthrough in understanding the function of TCL1 proteins occurred when TCL1A was identified in a yeast-two-hybrid search for

proteins that interact with AKT⁵. In a separate study, researchers reasoned that because each protein shares an ability to transform T cells, they might participate in a common tumorigenic pathway, and a TCL1A–AKT interaction was discovered using co-immunoprecipitation^{4,5}. Importantly, neither of these approaches excludes the possibility that there are additional interacting molecules for TCL1-family proteins that have not yet been identified.

Like TCL1, AKT comprises a multiprotein family that includes **AKT1**, **AKT2** and **AKT3** (also called PKBα, PKBβ and PKBγ, respectively), which have idiosyncratic but largely overlapping functions^{45–48}. AKT activation is initiated by the binding of an appropriate growth- or survival-stimulating ligand to a cell-surface receptor (FIG. 3), such as epidermal growth factor (EGF) binding to the EGF receptor, or, in the case of T and B cells, by the stimulation of the TCR or surface immunoglobulin M (IgM) with peptide-loaded major histocompatibility complex molecules or soluble antigens, respectively. The bound cell-surface receptor recruits a receptor tyrosine kinase that then triggers phosphatidylinositol 3-kinase activation at the membrane. This results in the production of the AKT-docking phospholipids phosphatidylinositol-3,4-bisphosphate (PIP₂) and phosphatidylinositol-3,4,5-triphosphate (PIP₃) (collectively called phosphatidylinositol phosphates (PtdIns-P)) by lipid phosphorylation and recruitment of AKT to the inner leaflet of the cytoplasmic membrane lipid bilayer, perhaps within a functional microdomain such as a cholesterol-rich **LIPID RAFT**⁴⁹ that facilitates the assembly of the signalling complex. For membrane relocalization, AKT needs its pleckstrin homology (PH) domain for direct binding to the docking phospholipids. At the membrane, AKT is activated by phosphorylation by 3-phosphatidylinositol-dependent kinase 1 (PDK1, also known as PDK1) and by another kinase (or kinases), such as the newly described Rictor–mTOR–GβL complex⁵⁰, or possibly by AKT itself through transphosphorylation^{45–47,51–56}.

It is during membrane recruitment and activation of AKT that TCL1 proteins might become involved in augmenting AKT kinase activity (FIG. 3). If TCL1 gene expression is aberrant, excessive AKT kinase activity could act to promote cell transformation. Although not fully resolved, TCL1A, TCL1B and MTCP1 seem to bind AKT1 and AKT2, whereas AKT3 binds only TCL1A, indicating preferences among family members that might be functionally important and dependent on which TCL1- and AKT-family members are expressed in specific cell types^{4,5,57}. The AKT-binding domain on TCL1 consists of a tryptophan-rich exposed hydrophobic patch on one face of the TCL1 β-barrel^{6,7,41,57} (FIG. 2). Structural studies have shown that there is a functional TCL1 homodimerization domain on the opposite side of the TCL1A molecule, although MTCP1 lacks a similar dimerization domain^{5,41,58}. The absence of a dimerization domain on MTCP1 indicates that TCL1A and MTCP1 might activate AKT through distinct mechanisms, although when they are aberrantly expressed, both proteins are

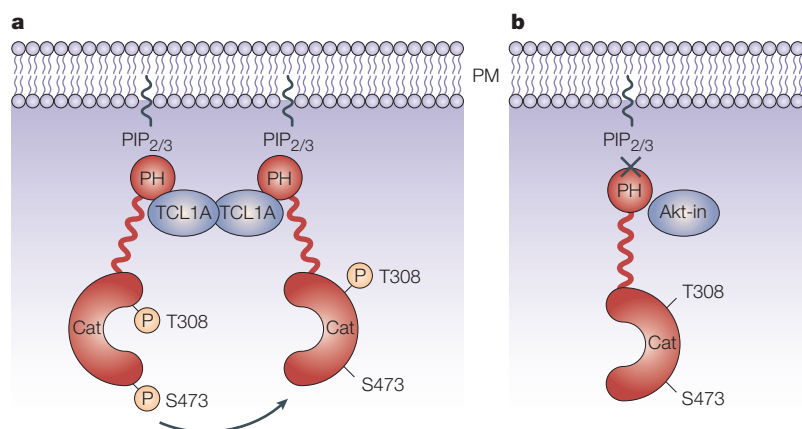


Figure 4 | Modelled interaction between TCL1A and AKT at the membrane and the blocking of AKT activation by a TCL1A-derived peptide. **a** | T-cell leukaemia/lymphoma 1A (TCL1A)-mediated AKT transphosphorylation is potentially an activity-enhancing mechanism. The AKT monomer is shown as two discontinuous red-shaded domains (the pleckstrin homology (PH) and catalytic (Cat) domains) connected by a 30-amino-acid linker strand. AKT binds phosphatidylinositol-3,4-bisphosphate (PIP₂) and phosphatidylinositol-3,4,5-trisphosphate (PIP₃) at the plasma membrane through the VL1 and VL2 loops of its PH domain^{7,72,73}. TCL1A might stabilize this interaction through concurrent binding of its β_A , β_B , β_E , and β_F β -barrel strands to the AKT β_A and β_B strands on the opposite side of the PH domain, without disturbing the AKT VL1–VL2 loop interaction domain that binds PIP_{2/3} (REFS 6,7,58). This binding is coupled with TCL1A homodimerization through the β_C strand on the TCL1A surface opposite the PH-binding face^{41,58}, forming a dimer of TCL1A–AKT heterodimers. The linker connecting the AKT PH and Cat domains provides flexibility so that the two AKT Cat domains could physically contact each other and increase AKT activation by transphosphorylation (arrow). **b** | The AKT inhibitor Akt-in is generated from a TCL1A β_A strand peptide and blocks AKT activation⁶⁰. Akt-in binds the β_E and β_F strands of the AKT PH domain, causing an allosteric deviation of VL1 on the opposite face of the PH domain. This prevents PIP_{2/3} binding and AKT phosphorylation by inhibiting the recruitment of AKT to the plasma membrane⁷.

still able to transform lymphocytes^{12–15}. This distinction hints at additional AKT-linked processes and/or AKT-independent mechanisms for the transforming potential of the TCL1 family.

Several models for TCL1–AKT interactions have been proposed^{6,7,58,59}. In theory, TCL1A could interact with AKT before, during and/or after membrane recruitment from the cytoplasm. TCL1A and MTCP1 interact with the AKT PH domain on the face opposite the PtdIns-P-binding pocket, although the interaction between MTCP1 and AKT is ~100-fold weaker than the TCL1A–AKT interaction^{4,5,7,41,58}. Because augmented AKT activity appears to rely on its binding to members of the TCL1 family, the relatively weak MTCP1–AKT interaction and lack of a MTCP1 dimerization domain again indicates that MTCP1 has a distinct mechanism of AKT co-activation, and possibly a transforming mechanism that is separate from the augmentation of AKT activation. TCL1–AKT interactions in solution do not disturb the conformation of the AKT PH domain and therefore would not compete with PtdIns-P for binding during AKT activation, leaving open the possibility that TCL1-family proteins interact with AKT before, during or after membrane translocation⁷.

Functional and structural studies also support a model in which TCL1 binds and stabilizes AKT at the membrane, and in which TCL1 and PtdIns-P

interact simultaneously on opposite faces of the AKT PH domain and concomitant to TCL1 homodimerization^{6,7} (FIG. 4). This model is consistent with structural data regarding AKT once it has arrived at the membrane. However, AKT-inhibition studies indicate that the β_A strand of TCL1 allosterically binds the AKT PH domain and blocks membrane recruitment by altering the PtdIns-P binding pocket⁶⁰.

From the current data, a working model is that TCL1 proteins bind AKT in the cytoplasm before membrane recruitment (FIG. 3). This model is consistent with solution-based interactions regardless of AKT activation state⁴, the maintenance of the proper conformation of the PtdIns-P binding pocket on the AKT PH domain, and a stabilized TCL1A–AKT complex at the membrane^{6,7}. These features are also compatible with a role for TCL1 in AKT membrane recruitment and augmentation of AKT activity through increased phosphorylation and/or other mechanisms (see below). The ability of the β_A strand of TCL1A to block AKT membrane recruitment also indicates that the entire TCL1 binding surface is required to maintain the conformation of the AKT PH domain PtdIns-P binding pocket⁶⁰. Therefore, inhibitors with properties that are similar to the β_A strand of TCL1A could provide novel reagents for blocking additional PH-domain kinases that depend on membrane recruitment for activation. It is from these detailed structural and biochemical studies of TCL1–AKT interactions that new strategies for targeted cancer therapies could emerge.

Interaction between TCL1 and AKT — mechanisms and biological outcome. The mechanism by which TCL1 proteins augment AKT function is not completely resolved, and it has not been proven that aberrant enhancement of AKT activity is wholly responsible for lymphocyte transformation. Biochemical studies using wild-type cell lines and cell lines that overexpress TCL1A show that TCL1A causes the hetero-oligomerization of AKT1 and AKT3, which increases AKT phosphorylation, potentially by AKT transphosphorylation (which would not require additional participating kinases)^{5,54,57}. Also, AKT isolated from TCL1A-transgenic thymocytes is better than wild-type AKT at phosphorylating the AKT target substrate glycogen synthase kinase-3 β *in vitro*⁴. However, the enhanced phosphorylation of AKT has been more difficult to detect *in vivo*. Mouse spleen B cells that have targeted deletion of *Tcl1* did not show distinct levels of AKT phosphorylation following stimulation with the pan-B-cell stimulator lipopolysaccharide⁹. Also, premalignant spleen B cells from TCL1A-transgenic mice showed only a minimal increase in AKT phosphorylation following stimulation of surface IgM¹⁵. In this case, the kinetics of AKT inactivation were unaltered in the transgenic cells compared with wild-type cells, indicating that TCL1A does not sustain AKT activity, unlike deficiency of PTEN or the myristoylation of AKT. A potential explanation for these results is that there are lower levels of TCL1

in transgenic lymphocytes than in transiently transfected cell lines, or that there are low endogenous levels of mouse TCL1. Low levels of TCL1 might preclude the detection of minimally increased but biologically significant differences in phosphorylation states that might regulate the transformation potential of TCL1A. Furthermore, phosphorylated AKT has not been detected by immunostaining of most patient-derived TCL1A-expressing CD4/CD56 haematodermic neoplasms, or of most TCL1A-expressing T-PLLs, whereas AKT is phosphorylated in more than half of T-cell lymphomas that do not express TCL1A (REF. 27). Phosphorylated AKT has also been undetectable by immunostaining in human seminomas that overexpress TCL1A (REF. 8). Together, these studies of primary human neoplasms indicate that TCL1A could augment AKT kinase activity independently of increased Thr-308 and Ser-473 AKT phosphorylation.

Together, these studies indicate that TCL1-enhanced AKT activity causes increased cell proliferation and survival, probably through the augmented phosphorylation of AKT downstream-target proteins^{4,5,15,58}. However, the relevant targets of AKT in this context have not been resolved, and the shuttling of TCL1 and AKT proteins between the cytoplasm and nucleus might further expand the number and type of potential target proteins beyond the cytosol^{4,6,40}. In fact, it has recently been suggested that TCL1 proteins could help AKT block the exodus of TR3 orphan receptor (also called NR4A1) from the nucleus (REF. 61 and Pedersen, I. M. *et al.*, unpublished observations). It has been shown that TR3 binds cytosolic BCL2, thereby changing the conformation of BCL2 and turning it from a cell protector into a pro-apoptotic protein⁶². By blocking the nuclear efflux of TR3, TCL1A might enhance cell survival independently of cytoplasmic-membrane activities on AKT, providing an alternative mechanism for TCL1 promotion of malignant transformation. Over and above the effects on cell growth or cell survival in embryonic development and cancer, the regulation by TCL1-family members of lymphocyte function seems to be modest. Mice that lack TCL1 have small deficiencies in pre-B-cell and T-cell genesis, a mild increase in T-cell susceptibility to apoptosis, fewer peripheral B cells, and slightly reduced IgG1 and IgG2b antibody production resulting from T-cell-dependent antigenic challenge, possibly from reductions in CD4⁺ T-cell help⁹.

These modest findings could reflect the low level of TCL1 expression in mouse lymphocytes, possible compensation by other members of the mouse TCL1 family, and/or an alternative role for TCL1 in mice, as endogenous TCL1–AKT interactions in mice have not yet been shown.

Unique models of B-cell and T-cell cancer

The dysregulation of TCL1-family genes in mature T- and B-cell tumours prompted the generation of several transgenic models using human TCL1-family cDNAs^{12–15} (TABLE 1). In general, these mice form unique

models of mature human lymphoid malignancies that have not been seen after other genetic, viral or environmental manipulations. Impressively, mice with dysregulated *TCL1* and *MTCPI* in T cells develop mature, peripheral T-cell cancers that resemble the pathogenesis of T-PLL in humans. Unlike plasma membrane-anchored myristoyl-modified AKT, which causes rapid thymic lymphomas in transgenic mice⁶³, TCL1 acts more like constitutively active but freely mobile AKT, which causes peripheral T-cell transformation⁶³. Potential explanations for the difference between the effects of plasma membrane-anchored AKT and TCL1 include that TCL1 augments the growth and survival of mature but not immature mouse T cells³² and that the transforming potential of TCL1 might arise from non-membrane-linked functions, such as within the nucleus. TCL1-expressing T-cell expansions precede leukaemic transformation, indicating that additional molecular changes are required for the emergence of overt leukaemia, but these changes have not yet been described.

In B-cell transgenic models, *TCL1A* dysregulation again causes mature peripheral malignancies despite expression beginning at precursor stages in the bone marrow¹⁵. In one model, *TCL1A* expression in both B-cell and T-cell lineages causes mainly GC B-cell transformation, with Burkitt lymphoma, DLBCL and, more rarely, follicular lymphoma pathologies^{15,64}. A key role for TCL1A in GC transformation might be the help that TCL1A provides T cells to support premalignant GCs. Although speculative, this idea is bolstered by transgenic mice in which aberrant *BCL2* expression only permits follicular lymphoma if concurrent *BCL2* dysregulation in T-cells supports premalignant GC B-cell expansions⁶⁵. In both the *TCL1A* and *BCL2* models, augmented T-cell help might be required to generate enough apoptosis-resistant B cells for secondary transforming events and emergent transformation. It will be crucial to determine what these complementing genetic/epigenetic alterations are and what the mechanisms are of their occurrence. Separately, a transgenic model that restricts *TCL1A* expression to B cells provides a model for human B-CLL¹⁴. In this model, premalignant CD5⁺ B cells are arrested in the G0/G1 phase of the cell cycle, pointing to the importance for increased survival before malignant degeneration. It is important to note that a non-exclusive possibility for the different tumour types that develop in these two B-cell transgenic models is the use of different transgene promoters. Nevertheless, TCL1-family transgenic models provide new insights on lymphocyte cancer, by providing unique systems for determining the mechanisms that regulate transformation in major types of human leukaemia/lymphoma.

New directions and unresolved questions

Clinical implications — for therapy, prognosis and use of biomarkers — are emerging from the new understanding of TCL1-family proteins. A peptide comprising the TCL1-interaction domain has been developed, called Akt-in (for AKT inhibitor), which blocks AKT

Table 1 | Mouse models with altered expression of TCL1-family oncoproteins

Expression pattern	Construct	Phenotype	MMHCC classification	References
T-lineage-specific <i>TCL1</i>	<i>lck-TCL1</i> tg	CD8 ⁺ T-PLL/T-CLL	STL	12
T-lineage-specific <i>MTCP1</i>	<i>CD2-MTCP1</i> tg	CD8 ⁺ T-PLL/T-CLL	STL	13
B- and T- lineage <i>TCL1</i>	<i>Eμ-B29-TCL1</i> tg	Mature B-cell lymphomas	FBL, BLL, DLBCL	15
B-lineage-specific <i>TCL1</i>	<i>Eμ-V_H-TCL1</i> tg	B-CLL	SBL	14
<i>Tcl1</i> knockout	Exons 2-4 deleted	Impaired early embryonic, B-cell and T-cell development	NA	8,9

BLL, Burkitt-like lymphoma; B-CLL, B-cell chronic lymphocytic leukaemia; DLBCL, diffuse large B-cell lymphoma; FBL, follicular B-cell lymphoma; MMHCC, mouse models of human cancer consortium; NA, not applicable; SBL, small B-cell lymphoma; STL, small T-cell lymphoma; T-CLL, T-cell chronic lymphocytic leukaemia; tg, transgene; T-PLL, T-cell prolymphocytic leukemia.

kinase activation (FIG. 4), possibly providing the first specific target to block AKT signalling⁶⁰, although an *in vivo* evaluation of this approach has not yet been carried out⁶⁰. Unfortunately, the interaction between Akt-in and the AKT PH domain is approximately four times weaker than the TCL1A–AKT interaction, indicating that this inhibitor might have limited efficacy in *TCL1A*-expressing tumours.

Although this will require independent confirmation, *TCL1A* overexpression might be correlated with relapse in DLBCL, and expression of the *TCL1A* protein might be associated with an adverse clinical outcome and reduced 5-year overall survival⁶⁶, which could help tailor the aggressiveness of therapy. In pilot studies, *TCL1A* has also been found to be useful in helping determine the histogenesis of, and establishing the clinical diagnosis of, rare CD4/CD56 haematodermic neoplasms^{27,37}. The potential for the *TCL1* family as a diagnostic and prognostic biomarker in the clinical setting requires further evaluation.

A key unresolved mechanistic issue in cancer is the connection between *TCL1*-enhanced AKT activity and the transformation of lymphoid and non-lymphoid cells. Although complicated, the association of kinase-dead or -deleted or membrane-anchored AKT isoforms with the dysregulated expression of *TCL1*-family members could provide insight into the dependence of heightened AKT kinase activity on the *TCL1* transforming mechanism. In some contexts, it seems that constitutive AKT activation is not enough to cause transformation, again indicating that a *TCL1*-mediated AKT effect might not be sufficient for tumour formation. For example, homozygous deletion of the AKT inhibitor *Pten* in mouse B cells results in constitutive, robust activation of AKT without B-cell transformation⁶⁷. It is possible that *TCL1* redirects AKT to new targets that AKT alone would not phosphorylate, whereas the inactivation of PTEN (which is upstream of AKT) does not redirect AKT to new target proteins. Conversely, pleiotropic biochemical and/or cell population changes resulting from PTEN deficiency might oppose the transformation of B cells⁶⁸.

The activity of *TCL1* proteins in the nucleus (as opposed to their interaction with AKT at the cytoplasmic membrane and so-far uncharacterized AKT-independent functions of *TCL1* proteins) might hold the key for transforming lymphoid and non-lymphoid cells and will require further investigation. Also, mechanisms that override *TCL1* to inactivate AKT or destabilize a stable *TCL1*–AKT complex need clarification, because the kinetics of *TCL1*-mediated AKT hyperactivation in *TCL1A*-transgenic B cells appear to be unaltered compared with wild-type B cells. It is possible that a protein similar to the carboxy-terminal modulator protein (*CTMP*), which inhibits AKT by blocking Thr-308 and Ser-473 phosphorylation, or protein phosphatase 2A and PH domain and leucine-rich repeat protein phosphatase (*PHLPP*), which dephosphorylates Thr-308 and Ser-473, will block or inactivate *TCL1*-protein-augmented AKT hyperactivation^{69–71}. Equally important, the factors that regulate the normal and non-T-cell dysregulated expression of *TCL1*-family members require identification, as the tumorigenic effect of *TCL1* proteins derives from aberrant expression and not from alterations in coding regions or alternative splicing. These factors could operate to regulate transcription, translation, and the stability or subcellular localization of encoded gene products.

Cooperating mutations that convert premalignant lymphocyte expansions into malignant neoplasms are unknown but will be essential for revealing tumorigenic pathways and new therapeutic targets. It will be interesting to see if these complementary lesions are similar or distinct in *TCL1A*-dysregulated germ-cell tumours as well, because this might tell us whether common transforming features occur between distinct cell types. The roles of additional members of the *TCL1* family and molecular functions for this family in early development, non-human vertebrate physiology, and cancer are currently lacking and will be required to see if these additional proteins share common features with known tumour-causing isoforms. In summary, much remains to be discovered about how *TCL1*-family proteins are regulated and how they, in turn, regulate physiology and provoke cell transformation.

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Competing interests statement

The authors declare no competing financial interests.

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