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TLX: A Master Regulator for Neural Stem Cell Maintenance and Neurogenesis

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Abstract

The orphan nuclear receptor TLX, also known as NR2E1, is an essential regulator of neural stem cell (NSC) self-renewal, maintenance, and neurogenesis. In vertebrates, TLX is specifically localized to the neurogenic regions of the forebrain and retina throughout development and adulthood. TLX regulates the expression of genes involved in multiple pathways, such as the cell cycle, DNA replication, and cell adhesion. These roles are primarily performed through the transcriptional repression or activation of downstream target genes. Emerging evidence suggests the misregulation of TLX might play a role in the onset and progression of human neurological disorders making this factor an ideal therapeutic target. Here, we review the current understanding of TLX function, expression, regulation, and activity significant to NSC maintenance, adult neurogenesis, and brain plasticity.

Keywords

TLX; Neurogenesis; Neural Stem Cell; NR2E1; Nuclear Receptor

INTRODUCTION

The orphan nuclear receptor subfamily 2 group E member 1 (NR2E1), commonly known as TLX, is an evolutionarily conserved member of the nuclear receptor superfamily of transcription factors found in both vertebrates and invertebrates [1]. An alignment of frog, mouse, chick, zebrafish and human TLX proteins reveals remarkable interspecies conservation with at least 89%–97% homology between the five species [2–6]. The vertebrate *Tlx* gene was first cloned nearly 20 years ago from a chick cDNA library screen using an *RXRβ* probe [3]. The following year, the mouse *Tlx* gene was cloned using the Drosophila *tailless* (*tll*) as the probe [4]. With a mouse model in hand, TLX was extensively characterized and implicated in the regulation of neurogenesis and the maintenance of neural stem cell (NSC) populations. TLX expression is specific to the neurogenic regions of the

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forebrain and retina during mouse development and adulthood [4]. The regulation of progenitor cell proliferation and timing of neurogenesis by TLX is necessary for the correct establishment of the pallio-subpallial boundary, ventral pallial identity, and superficial cortical layers during mouse forebrain development. Further, TLX regulates retinal stem cell proliferation and cell cycle re-entry during retinogenesis by directly controlling the expression of the tumor suppressor *Pten*.

Spatiotemporal expression of *Tlx*

Expression of *Tlx* is specific to the developing forebrain and retina in multiple species, including the frog [2], zebrafish [6], and mouse [4]. In the developing embryo and adult mouse, *Tlx* is specifically localized to the neurogenic regions of the telencephalon, diencephalon, nasal placode, and retina (Figure 1A, B, C, D) [3, 4]. This *Tlx* expression becomes detectable at embryonic day 8 (E8), peaks at E13.5, and declines from E13.5 until birth. *Tlx* expression then gradually increases with high levels detectable in the adult brain [4]. Immunohistochemical staining with a TLX-specific antibody reveals a sparse distribution of TLX throughout the cortex, strong yet dispersed expression in the subgranular zone (SGZ) of the dentate gyrus (DG), and clustered expression in the subventricular zone (SVZ) of lateral ventricle (LV; Figure 1C, D) [7]. The NSCs found in the SVZ are a rare population of relatively quiescent cells [8]. Recently, TLX expression has been shown in the rapidly dividing neural progenitor cells of the adult SVZ, although most TLX-positive cells in the SVZ are quiescent [9].

Biological roles for TLX

Brain formation and behavior—The brains of *Tlx*-null mice exhibit no obvious defects during early development; however, mature mice suffer retinopathies, limbic defects, reduced copulation, and progressively violent behavior [10, 11]. Adult *Tlx*-mutant brains also show severe deficits in active neurogenic regions such as reduced hippocampal DG size, significantly expanded lateral ventricles, and smaller olfactory bulbs [12, 13]. The mutation of mouse *Tlx* results in hyperactivity and extremely aggressive behavior suggesting a potential role for TLX in human neurological disorders [14]. In support of this hypothesis, mutations in the regulatory regions of the human *Tlx* gene have been positively correlated with bipolar disorder. Similarly, several mutations in the transcriptional regulatory elements of *Tlx* are strongly associated with microcephaly.

Eye development—*Tlx* can be detected in the optic processes of the developing mouse eye as early as E9 [4]. By E11.5, expression is restricted to the innermost retinal surface corresponding to the end feet of retinal progenitor cells found in the neuroblast layer of the developing embryo [15]. Peak *Tlx* expression in this layer is observed at E15.5 supporting its role in early retinogenesis [15, 16]. *Tlx*-null mice exhibit retinal and optic nerve dystrophy resulting in blindness [11, 16, 17]. A developing *Tlx*-null mouse exhibits deregulated retinal progenitor cell proliferation and increased apoptosis in the ganglion cell layer. This results in a marked reduction of thickness for each distinct layer of the adult retina [15, 17]. Additionally, *Tlx*-null animals suffer from retinal vasculature defects illustrating the critical role for this gene in the assembly of fibronectin matrices secreted by proangiogenic astrocytes [18].

NSC self-renewal—The primary function of TLX in the developing and adult brain is to prevent the precocious differentiation of NSCs [7, 12, 19]. This key transcriptional regulator controls the expression of a broad network of genes to maintain NSC pools in an undifferentiated, self-renewing state [12, 20, 21]. These undifferentiated precursor cells, with the capacity to give rise to both neuronal and glial lineages, are the driving force behind the formation of a complete and functional central nervous system (CNS) [22–25].

Tlx-null neural cells isolated from adult *Tlx*-mutant mice are non-proliferative and fail to self-renew. Importantly, the ectopic expression of *Tlx* in these cells rescues their ability to proliferate and self-renew [12]. Inducible lineage tracing and genetic markers for adult NSCs have demonstrated that *Tlx*-expressing cells can generate both quiescent and activated postnatal NSCs [20]. TLX plays an essential role in NSC activation and governs the localization of NSCs to the neurogenic niche [20]. Furthermore, whole-genome RNA-sequencing revealed that TLX coordinates multiple signaling pathways to regulate NSC behavior [20]. Specifically, TLX modulates signaling in the p53 pathway to control NSC activation.

Adult Neurogenesis—NSCs are found in at least two discrete regions of the adult CNS, the SGZ and SVZ. It is here that multipotent neural stem/progenitor cells generate new neurons, a fundamental process known as neurogenesis. This process occurs throughout the developing embryonic brain and localizes to these distinct regions during adulthood. In most mammals, new neurons are continually generated throughout life. As a central regulator of adult hippocampal neurogenesis, TLX balances the maintenance of NSC populations with terminal neuronal differentiation [12, 26].

Recent studies show that activated NSCs and transit-amplifying progenitors (TAPs) in the neonatal subependymal zone of the LV express TLX [27]. TLX-positive cells in the adult SVZ are relatively quiescent stem cells and the inactivation of TLX in these cells leads to a complete loss of neurogenesis in the SVZ [9, 28, 29]. TLX positively and negatively modulates gene expression in both cell types. The absence of *Tlx* in activated NSCs, but not TAPs, leads to the upregulation of negative regulators of the cell cycle and proliferation arrest. Moreover, the homeobox transcription factor DLX2, which promotes neurogenesis, is downregulated in both cell types in the absence of *Tlx*. This is paralleled by increased OLIG2 expression in activated NSCs and heightened GFAP expression in TAPs, indicating that TLX decreases gliogenesis in both populations [27].

Unlike the TLX-positive NSCs of the SVZ, NSCs in the DG produce neurons with unique roles in hippocampal-dependent learning and memory [30]. The conditional disruption of *Tlx* in the mouse has been shown to reduce cognitive aptitude and incite abnormal behavior [30]. This might suggest that the status of adult neural progenitors in the SGZ and aberrations in neurogenesis are forerunners to neuropsychiatric diseases such as dementia, mood disorders, and cognitive deficits [31]. TLX-positive NSCs of the adult SGZ (type 1 NSCs) have long radial glia-like processes spanning the entire granule cell layer. These cells express nestin, GFAP, SOX2, and brain lipid-binding protein (BLBP). Although the majority of type 1 NSCs remain in an inactive state, a subset divides slowly to yield transiently amplifying type 2 cells. These type 2 cells are tangentially oriented with short

processes and rapidly proliferate to generate type 3 cells. These cells resemble immature DCX^+ neuroblasts and ultimately mature into granule neurons that functionally integrate into the existing neural networks. Deletion of *Tlx* in the DG results in complete loss of transiently amplifying cells and neuroblasts.

Mechanism of action

Like most members of the nuclear receptor superfamily, TLX has at least two structural domains. The first is a highly conserved DNA-binding domain (DBD) required for targeting a consensus DNA motif - AAGTCA. The second is a moderately conserved ligand-binding domain (LBD) critical to cofactor interactions (Figure 2A) [3, 32]. Despite its conservation, no ligand has yet been identified for TLX, hence this receptor is classified as an orphan nuclear receptor.

TLX has been shown to function primarily through the transcriptional repression of downstream target genes by complexing with transcriptional corepressors like the epigenetic modifier lysine-specific histone demethylase 1 (LSD1) [33–36]. TLX also recruits histone deacetylases (HDACs) to target genes, which repress transcription and, in turn, regulate NSC proliferation [33]. TLX was shown to recruit both HDAC3 and HDAC5 to target gene promoters in cultured NSCs (Figure 2B) [33].

Recently, yeast two-hybrid screens of cDNA libraries prepared from adult human brain tissues were used to identify and characterize novel proteins that interact with TLX [37]. The physical interaction of TLX and atrophin-1 (ATN1), a member of a newly identified class of nuclear receptor corepressors, earlier reported by Zhang et al. and Wang et al. was confirmed in this study (Figure 2B) [16, 38–42]. The direct association of TLX and ATN1 has been shown to prevent retinal dystrophy, a condition of visual impairment typically observed in developing *Tlx*-null mice [16]. In addition to ATN1, the screen by Estruch et al. identified B-cell lymphoma/leukemia 11A/CTIP1 (BCL11A), an oncoprotein and transcription factor, as a novel TLX regulator [37]. This selective interaction with TLX relies on two copies of the BCL11A signature motif F/YSXXLXXL/Y [43].

With respect to intercellular signaling, bone morphogenetic protein 7 (BMP7) and Sonic Hedgehog (SHH) have been shown to relieve TLX-mediated PAX2 repression [44]. SMAD1 of the BMP7 pathway and GLI2 of the SHH pathway are suspected of binding TLX to modulate PAX2 expression.

TLX downstream targets

TLX has diverse roles in gene regulation that affect a broad range of cellular processes from the cell cycle and DNA replication to mitogen-activated protein kinase signaling and even cell adhesion [20, 29, 30, 33]. TLX binds a highly conserved 5′-AAGTCA-3′ motif to promote or repress target gene expression [16]. The TLX targets *Ascl1*, *Pou5f1*, *Pax2*, *Mir9*, *Mir137*, *Pten*, *Cdkn1a*, *Sirt1*, and *Wnt7a* were each identified through DNA binding assays or conserved motif analyses [11, 12, 16, 26, 27, 33, 35, 45–49].

Transcription factors: ASCL1, POU5F1, and PAX2—Proneural basic helix-loop-helix (bHLH) transcription factors are integral to the initiation of neurogenesis and terminal

neuronal specification. ASCL1 (MASH1), an early proneural bHLH transcription factor broadly expressed in brain and spinal cord progenitors, drives the specification of neurons and oligodendrocytes in multiple neurogenic brain regions like the hippocampus [50–52]. Recently, TLX was shown to target and activate *Ascl1* thereby promoting neuronal induction in adult hippocampal neuroprogenitors [26].

Interestingly, TLX balances dichotomous roles under hypoxic conditions, the regulation of NSC commitment to the neuronal lineage by *Ascl1* and the maintenance of proliferating neural progenitor pools through the fine-tuning of *Pou5f1* (*Oct3/4*) expression [26, 27, 45]. In this second role, TLX serves as a critical mediator of hypoxia-induced NSC proliferation and neural progenitor pluripotency. Early hypoxia-induced *Tlx* expression potentiates neural progenitor proliferation and imparts a stem cell-like phenotype exhibiting NSC markers under differentiation conditions [45]. TLX is recruited to the *Pou5f1* proximal promoter under hypoxic conditions to augment transcription and, in turn, promote proliferation and progenitor pluripotency. *Pou5f1* knockdown significantly reduces TLX-mediated NSC proliferation. This highlights the TLX-POU5F1 interdependent relationship required for maintenance of the progenitor cell reservoir [45].

Another downstream target of TLX, *Pax2*, was shown to transiently overlap with *Tlx* expression in the developing chick optic vesicle. TLX represses *Pax2* transcription by binding a conserved 5′-AAGTCA-3′ motif approximately 80 nucleotides upstream of the TATA box [11, 15].

microRNAs: miR-137 and miR-9—Recent studies have uncovered multiple brain-specific microRNAs (miRNAs) with roles in neuronal differentiation and maturation [53, 54]. The brain-specific miR-137 has been shown to promote the neuronal differentiation of adult subventricular NSCs and to inhibit the maturation of adult hippocampal neurons [55, 56]. *Mir137* is a bonafide TLX target and a novel upstream regulator of LSD1. TLX represses *Mir137* in NSCs by recruiting LSD1 to the genomic regions of *Mir137* [34]. *Mir9*, another direct TLX target, forms a negative-feedback loop regulating TLX expression in NSCs to affect the status of progenitor proliferation and differentiation [57].

PTEN—The tumor suppressor gene *Pten* was identified as a TLX target during a global gene expression-profiling study [16]. The tight regulation of stem cell proliferation by TLX was demonstrated in mice with the individual deletion of *Cdkn1a* (*P21*, *Cip1*), *Tp53* (*P53*), and *Pten* [58]. PTEN has a fundamental role in brain development and mutations can result in multiple forms of human cancer [59–62]. Through negative regulation of the G0 to G1 cell cycle transition, TLX precisely balances progenitor cell proliferation and differentiation via the PTEN-cyclin D1 pathway [16, 63]. As a negative regulator of NSC proliferation, *Pten* is repressed by TLX in both the developing retina and the adult brain [16, 28, 33, 60, 63]. TLX is thought to regulate NSC proliferation by governing expression of the Cip/Kip family cyclin-dependent kinase inhibitors such as *Cdkn1a* (*P21*), *Cdkn1c* (*P57*, *Kip2*) and several genes downstream of *Tp53* (*P53*) [12, 16, 20, 28–30]. The observation that p21 and p57 are expressed in differentiating neural precursor cells (NPCs) supports this molecular paradigm [64].

SIRT1—SIRT1, a NAD-dependent protein deacetylase, has been shown to co-localize with TLX in neural precursor cells [49]. In HEK293 cells, TLX increases *Sirt1* expression by binding to the TLX-activating element in the *Sirt1* promoter. Moreover, *Tlx* knockdown with small interfering RNAs diminishes SIRT1 protein expression in NPCs [49].

WNT7A—Wnt/β-catenin signaling influences the self-renewal of multiple stem cell types, including hematopoietic stem cells, epidermal progenitors, and adult brain NSCs [65–69]. TLX activates this pathway in the adult mouse to stimulate NSC proliferation [48]. A gene profiling analysis of RNAs isolated from the brains of adult wild-type and *Tlx* mutant mice identified *Wnt7a* as a direct target of TLX [48]. The promoter region of *Wnt7a* contains multiple consensus TLX binding sites and cell-based reporter assays indicate that TLX interacts with this regulatory region [48].

BMP-SMAD signaling pathway—Bone morphogenetic proteins (BMPs) are members of the transforming growth factor beta (TGFβ) superfamily that signals through the phosphorylation of SMAD family transcription factors. BMPs play a vital role in NSC neurogenesis and astrogliogenesis [70]. It was recently shown that TLX controls the timing of postnatal astrogenesis by modulating the BMP-SMAD signaling pathway [71]. TLX directly binds to the enhancer region of *Bmp4* to suppress its expression in the NSCs and *Bmp4* is markedly upregulated in nestin-positive cells from $Tlx^{-/-}$ mice [71].

TLX regulation

While the fundamental roles of TLX in NSC self-renewal and neurogenesis are well established, relatively little is known about the molecular mechanisms that regulate the spatiotemporal expression and activity of TLX (Figure 2B). Mounting evidence points to both transcriptional and post-transcriptional mechanisms of regulation. miRNAs post-transcriptionally regulate a diverse number of neurogenic genes, generally negatively, by binding the 3′ untranslated region of target mRNAs [72–76]. The overexpression of miR-9, a highly expressed miRNA in the vertebrate CNS, such as zebrafish embryo, mouse embryonic cortex, and chick spinal cord, reduces the proliferation of neural progenitors [57, 77, 78]. Interestingly, this reduction can be rescued by TLX overexpression suggesting that TLX and miR-9 might participate in a negative feedback loop [57]. Additional molecular evidence for this claim is found in the *Mir9* locus where consensus TLX binding sites have been identified. Moreover, cells derived from adult *Tlx*-null mice exhibit increased expression of pre-miR-9 transcripts [57].

In an attempt to shed light on the dynamic multidimensional regulation of TLX expression and activity, Zhao et al. recently demonstrated that the miRNA let-7d modulates TLX expression through a conserved binding site in the 3′ untranslated region of *Tlx* mRNA transcripts [79]. The overexpression of let-7d inhibits NSC proliferation, promotes neuronal differentiation, and induces neuronal migration in embryonic mouse brains, a phenotype similar to TLX knockdown models. This phenotype can be rescued by the *in vivo* co-electroporation of a truncated *Tlx* transcript lacking a 3′ untranslated region [79]. Prior to this work on let-7d, let-7b and miR-137 were also highlighted as potential regulators of NSC proliferation [34, 80]. Remarkably, miR-137 targets the TLX transcriptional corepressor

LSD1, which itself is recruited by TLX to the regulatory regions of *Mir137* to downregulate its expression.

Interleukin-1 beta (IL-1β), a negative regulator of embryonic and adult hippocampal neurogenesis, represses TLX expression in NPCs. IL-1β also acts to repress TLX in differentiating new-born neurons, mature neurons, and astrocytes [81–83]. Recently, it has been demonstrated that this repression of TLX and hippocampal NPC proliferation is mediated through the interleukin-1 receptor type I [84].

Sex determining region Y-box 2 (SOX2), another transcription factor with prominent roles in the regulation of adult NSC proliferation, was recently shown to bind the upstream regulatory region of *Tlx* and activate its promoter activity in adult mouse NSCs [85–88]. SOX2 knockdown in cultured adult mouse NSCs moderately reduces TLX expression indicating multiple independent factors are involved in TLX regulation [88].

TLX as a therapeutic target

Bipolar disorder is a highly heritable multifactorial psychiatric disorder linked to abnormalities in the 6q21–22 chromosomal locus [89–95]. Interestingly, *Tlx* is located within this region and has been genetically linked to bipolar I disorder. Several strains of *Tlx*-null mice exhibit neuroanatomical abnormalities similar to those observed in human bipolar patients. These include diminished neurogenesis, dysfunction of GABAergic interneuron, olfactory dysfunction, enlarged lateral ventricles, and reductions in the size of the hippocampus, cerebral cortex, corpus callosum, amygdala, and cortical layers II/III [10, 12, 17, 19, 30, 96–103].

As a potent regulator of stem cell proliferation, TLX has been implicated in gliomagenesis. Gene expression profiling has shown that various types of human brain tumors, such as astrocytoma and ependymomas, exhibit elevated *Tlx* expression [104–109]. Similarly, a fraction of primary glioblastoma patients exhibit increased *Tlx* copy number [29]. The ectopic expression of *Tlx*, in combination with *p53* or *Ink4a/arf* inactivation, is sufficient to induce gliomagenesis in the mouse [29, 110]. Genetic analyses further revealed that *Tlx* deletion significantly impedes this glioma formation within the adult neurogenic niches, while the potential for gliomagenesis in other brain regions remains unaffected [58]. Interestingly, the direct TLX target and tumor suppressor *Pten* is often mutated in cases of malignant glioma [16, 28]. These findings suggest that the misregulation of TLX expression or activity can promote the initiation of gliomagenesis in the SVZ.

Conclusion

TLX is a master regulator of adult NSC behavior. A detailed, mechanistic understanding of TLX activity and regulation will provide significant insights into NSC maintenance, adult neurogenesis, and brain plasticity. Its essential role in postnatal neurogenesis makes TLX an attractive candidate for further studies into the relationship of adult neurogenesis and tumorigenesis. With fundamental roles in NSC maintenance and neurogenesis timing, TLX holds promise as an ideal therapeutic target for glioblastoma, neurological injury, and neurodegenerative diseases.

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Highlights for Review

1. A thorough review of current literatures on TLX in the central nervous system.
2. TLX is an orphan nuclear receptor controlling gene expression.
3. TLX plays a critical role in neural stem cells and neurogenesis.
4. TLX is regulated at both the transcriptional and posttranscriptional level.
5. Dysregulation of TLX might lead to neurological diseases.

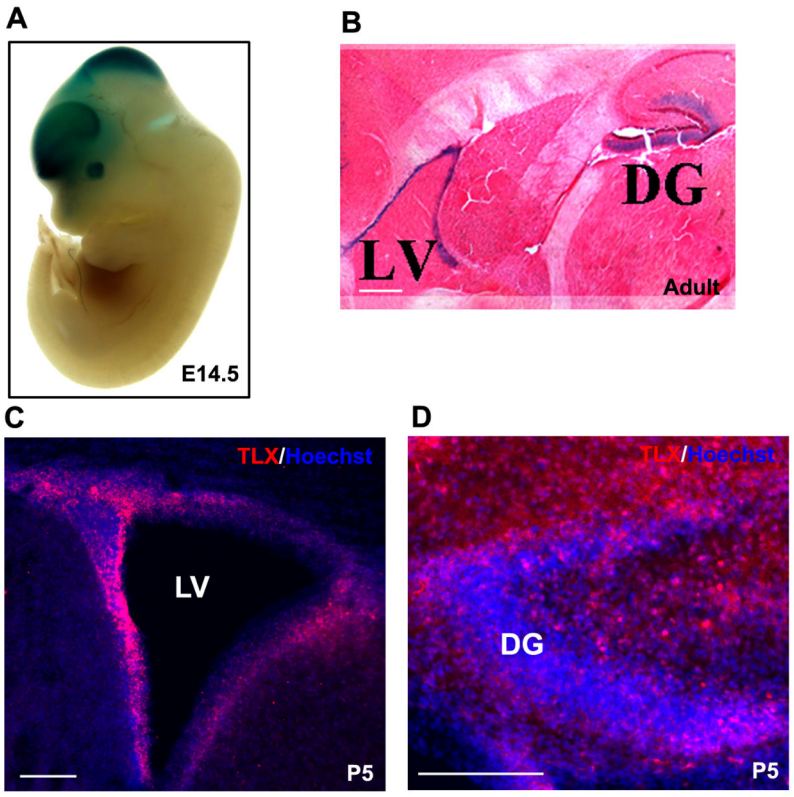

Figure 1. Spatiotemporal TLX expression

A, B. Expression of the *lacZ* marker targeted to the endogenous locus of *Tlx* in the embryonic (A) and adult (B) mouse. **C, D.** TLX-specific immunostaining of postnatal day 5 (P5) mouse brain sections reveals TLX expression in the subventricular zone (SVZ) of the lateral ventricle (LV) and the subgranular zone (SGZ) of the dentate gyrus (DG). Scale bars: 20 μm (B,C,) and 10 μm (D).

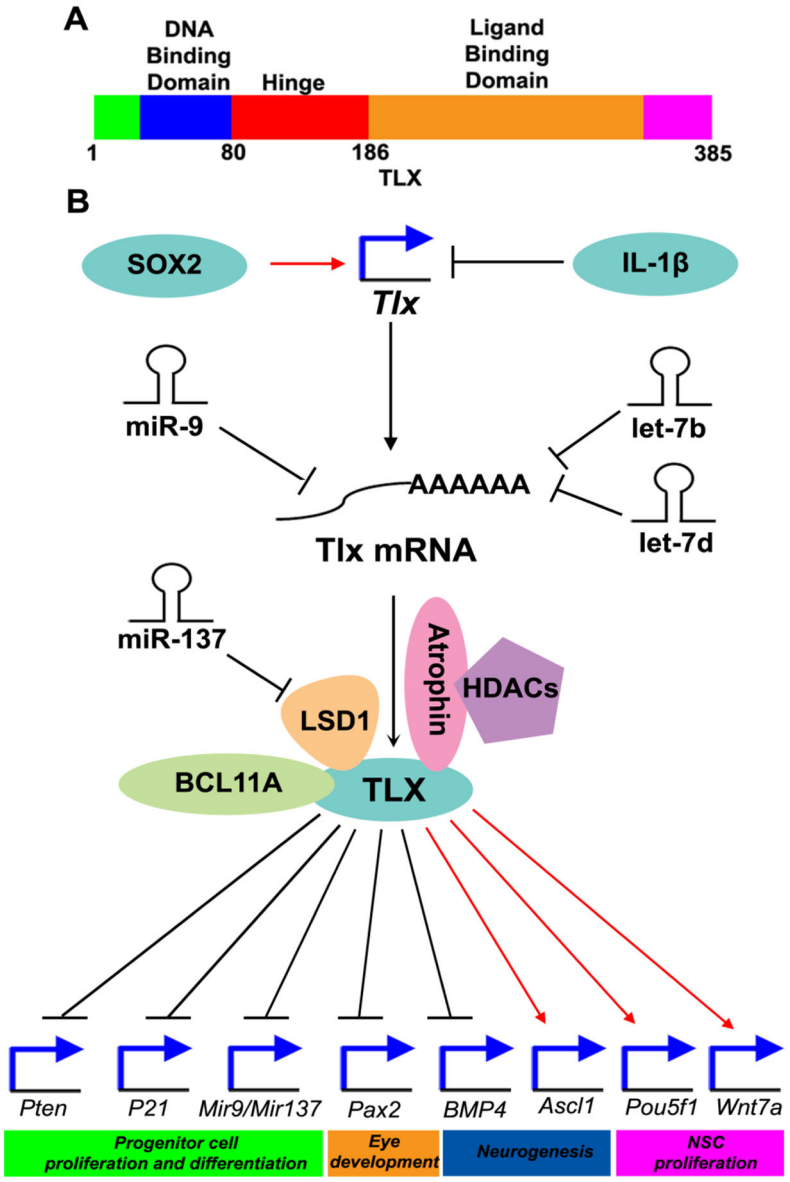

Figure 2. The TLX-associated regulatory pathway

A. A schematic diagram depicting the basic structure of TLX. DBD, DNA-binding domain; LBD, ligand-binding domain. **B.** A TLX-centric overview of gene expression, protein interaction, target regulation, and biological functions.