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Review

The Multifaceted Role of STK35/STK35L1 in Human Diseases: A Time for Critical Appraisal

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Abstract: Dysregulation of protein kinases is associated with developmental defects and various human diseases. The human kinome comprises 518 kinases, including several orphan kinases whose functions remain to be fully characterized. The NKF4 family, which includes STK35L1 and PDIK1L, is one such uncharacterized kinase family. STK35L1, also known as Clik1, was initially identified as a nuclear kinase associated with actin fibers. Subsequent studies have demonstrated that STK35L1 plays critical roles in cellular processes such as cell cycle regulation, migration, angiogenesis, the DNA damage response, and related processes such as spermatogenesis. STK35L1 has also been implicated in various developmental processes and its knockout mice exhibited defects in the testis, ovary, and eye. STK35L1 acts as a central regulator of the fundamental cellular functions, and its dysregulation leads to various diseases. Research has established that STK35L1 regulates tumor growth and proliferation in cancers such as osteosarcoma, colorectal cancer, and acute myeloid leukemia. Notably, it also affects chemosensitivity in colorectal cancer and metabolism in acute myeloid leukemia. Additionally, STK35L1 is crucial for the infection of hepatocytes by Plasmodium sporozoites during the liver stage of Malaria. This review discusses the current understanding of STK35L1, highlighting its role in various diseases.

Keywords: STK35; STK35L1; PDIK1L; cell migration; DNA repair; angiogenesis; cell cycle; malaria; colorectal cancer; AML; endothelial cells

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1. Introduction

Protein kinases phosphorylate proteins on serine (Ser), threonine (Thr), or tyrosine (Tyr) residues and are the largest superfamily of enzymes, comprising ~1.7% of all human genes [1]. Dysregulation of protein kinases is linked to developmental defects and several human diseases, including cancers, neurodegenerative diseases, and autoimmune disorders [2]. Protein kinases represent highly promising therapeutic targets with numerous kinase inhibitors currently in clinical trials. To date, the U.S. Food and Drug Administration has approved multiple kinase inhibitors for clinical use, particularly the treatment of different types of cancer [3,4].

Since the release of the first draft of the human genome in 2001, various strategies have been employed to catalog human kinases. Depending on the methods and criteria used, different studies have reported a total of 448 [5], 510 [6], or up to 518 [1,7,8] kinase-encoding

genes. Protein kinases are classified into eukaryotic (typical protein kinases) and atypical protein kinases. Typical kinases were further classified into 10 groups (AGC, CAMK, CK1, CMGC, STE, NEK, RGC, TYR, TKL, and Other) [8]. Atypical kinases were classified into eight groups (PDHK, Alpha, RIO, A6, Other, ABC1, BRD, and PIKK) [1]. The group "Other" of typical kinases comprises 37 families with 83 kinases in humans [7]. The NKF3, NKF4, and NKF5 families of group "Other" are found only in humans, and the functions of their members are largely unknown [1].

STK35L1 and PDIK1L are members of the NKF4 family of Ser/Thr Kinases [1]. The first member of this family, STK35, also known as Clik1, was initially identified as a nuclear kinase associated with actin fibers via interacting with an α-actinin-1 binding protein, CLP36, in the osteosarcoma cell line, U2OS [9]. The following year, PDIK1L (PDLIM1 Interacting Kinase 1 Like) was identified by high-throughput sequencing of a human fetal brain cDNA library [10]. In 2009, Goyal et al. performed a comprehensive genomic analysis of the STK35 family of kinases and discovered an ambiguity in the *STK35* gene coding sequence. This led to the identification of a novel longer form of STK35 named STK35L1 (STK35 Long isoform 1) that contains an additional exon at the 5′ of the *STK35* gene (Figure 1A) [11]. Thereafter, Goyal et al. also demonstrated that STK35L1 interacts with nuclear actin, regulates the expression of various cell cycle genes, and is essential for endothelial cell migration and angiogenesis [12]. Subsequently, STK35L1 has been established as a critical regulator in diverse cellular processes such as apoptosis regulation and DNA damage response. STK35L1 is also implicated in diseases such as osteosarcoma, colorectal cancer (CRC), acute myeloid leukemia (AML), and malaria. Notably, STK35L1 has modulated drug resistance in CRC and metabolic pathways in AML [13–17]. This review summarizes current knowledge on STK35L1 and its functional roles in human disease pathogenesis, with particular emphasis on oncogenic processes and malaria infection.

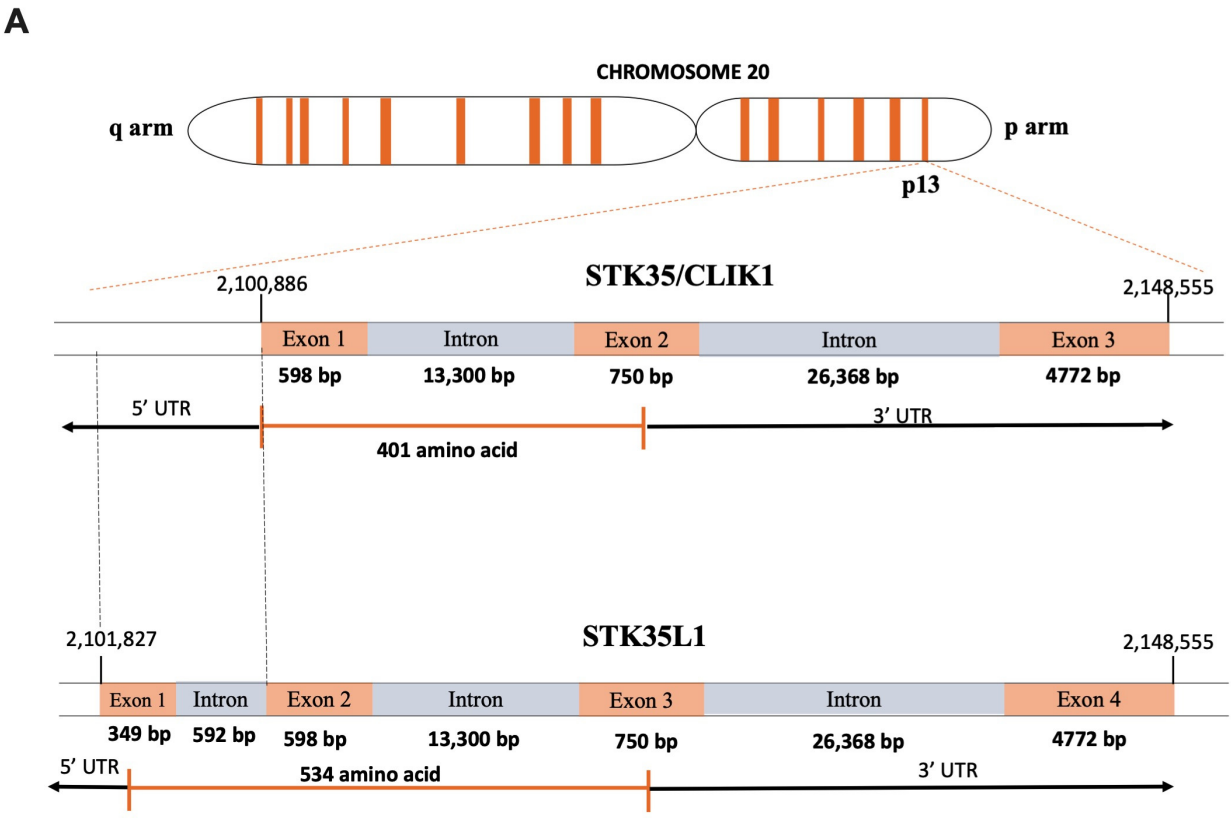


Figure 1. *Cont.*

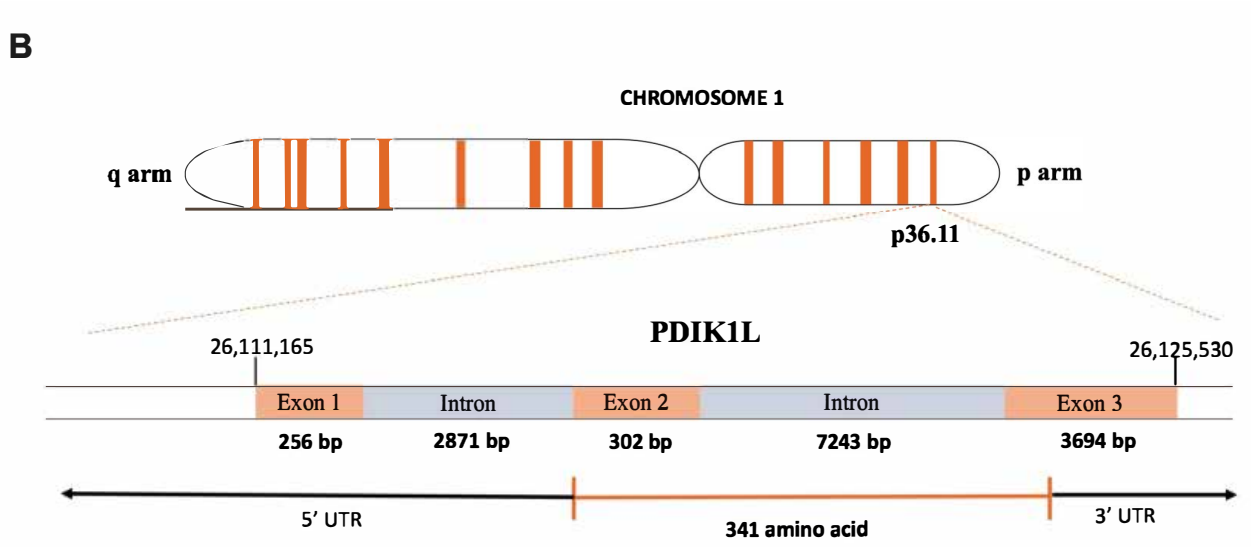


Figure 1. Pictorial depiction showing the chromosomal gene locus of STK35 and PDIK1L. (**A**) STK35 (Clik1) and STK35L1 are located on chromosome 20p13. STK35 (Clik1) gene comprises three exons and two introns and codes for a protein of 401 amino acids. STK35L1 comprises four exons and three introns: exons 1–3 code for a protein of 534 amino acids. (**B**) PDIK1L is located on chromosome 1p36.11, comprises three exons and two introns, and codes for a protein of 341 amino acids.

2. Characterization of the STK35 Locus

The human *STK35* gene is located on chromosome 20 subregion p13. The *STK35* gene, first characterized by Vallenius et al., comprises three exons and two introns encoding a 401aa protein with a predicted molecular weight of 44.58 kDa (Figure 1A). We detected a 58 kDa band in endothelial and HEK cells using STK35-specific antibodies [11]. We analyzed the STK35 genomic locus to investigate this discrepancy and identified a new 5′-extended transcript containing four exons and three introns. This transcript encodes a 534 aa protein with a predicted molecular weight of 58 kDa, which we designated STK35L1 (Figure 1A) [11]. Interestingly, multiple bands of different sizes of STK35L1 were observed in HeLa cells, suggesting the *STK35* gene locus is contributing more than one transcript that might be involved in a cell-specific or condition-specific manner [11].

In the mouse genome, the *stk35* gene is located on chromosome 2 and consists of four exons. The mouse *stk35* gene locus contributes two splice variants (NM_183262 and NM_001038365) named STK35L1, STK35L1b, and a long noncoding RNA (stk35os1). In the STK35L1b transcript, the third exon was spliced out and coded for a STK35L1 protein with the truncated kinase domain. The stk35os1 is transcribed from the second exon antisense strand of the mouse *stk35* gene locus [18]. The *stk35* gene locus in the mouse contributes more than one transcript that might be involved in distinct functions that need further study.

3. Evolution of STK35 Family Members

Gene synteny analysis is a powerful method often used in comparative genomics to identify the orthologs of a gene in different species [19]. Using syntenic searches, gene pattern data analysis, and homology searches, three members of the STK35 family, namely, STK35L1, PDIK1L (also known as STK35L2), and STK35L3, were identified and were conserved throughout vertebrate genomes [11]. The homologs of STK35L1 were identified as orthologous, as STK35L1 and PDIK1L were found to have independent origins (Figure 2) [11].

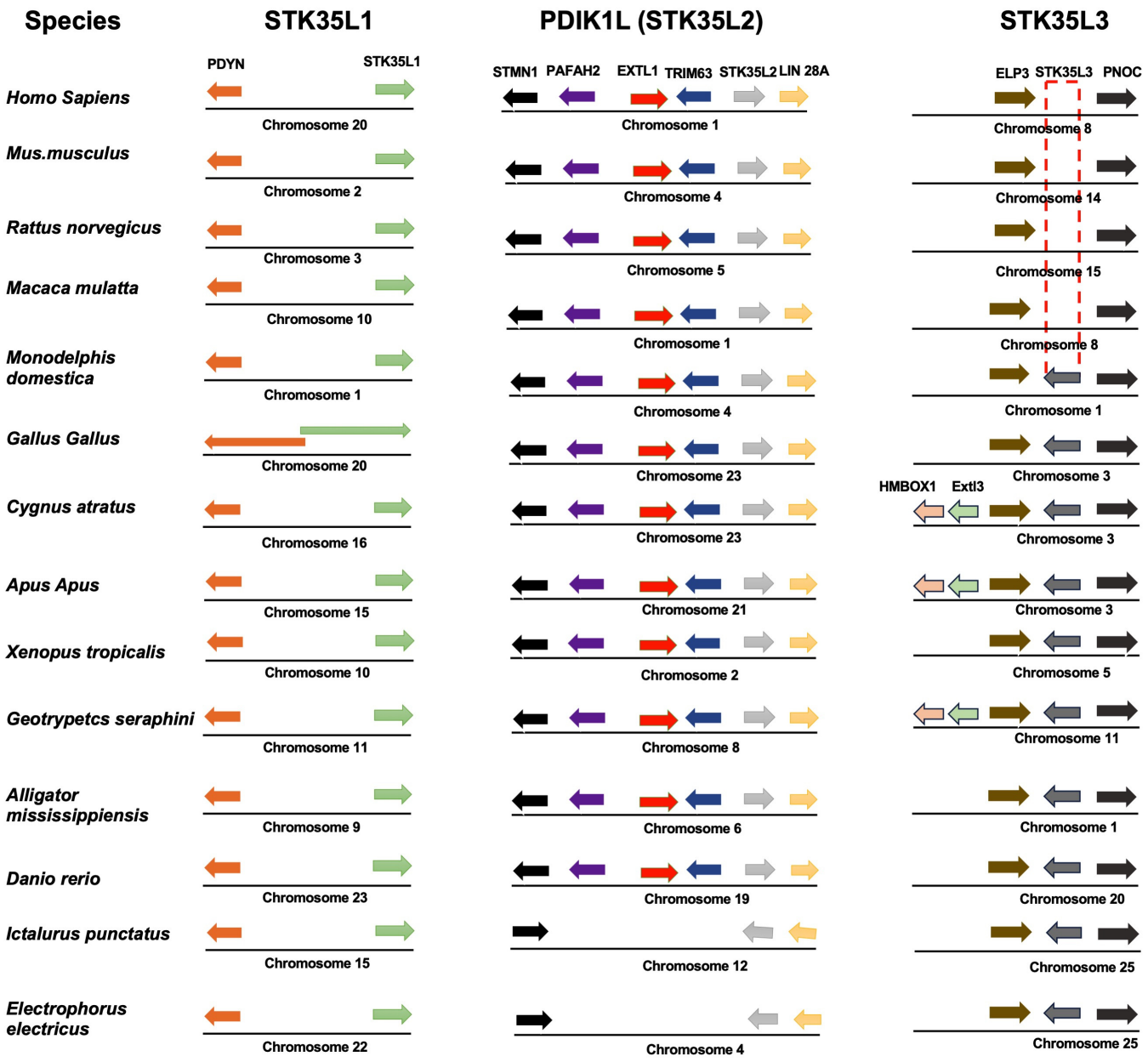


Figure 2. Microsynteny analysis of STK35L1 family members. Genomic localizations with flanking genes of STK35L1, PDIK1L (STK35L2), and STK35L3 across vertebrates are shown. STK35L3 was lost during the evolution of placental mammals and is shown here by a gray box with broken lines.

The first homolog of the STK35L1, namely PDIK1L, was identified by Guo et al. in 2003 and showed 69% homology with STK35L1 in the kinase domain [10]. This gene is located on chromosome 1p36.11 and has five exons (Figure 1B). In contrast to STK35L1, PDIK1L mainly consists of the kinase domain. STK35L1 and PDIK1L are highly conserved across different vertebrate species during evolution (Figure 2).

Another homolog of STK35L1, STK35L3, was found to be conserved from fishes to marsupial mammals. Fishes exhibit four exons/three introns gene structural organization; however, during evolution, an intron was lost in higher vertebrates such as frogs and opossums [11]. Interestingly, STK35L3 was lost in placental mammals during the time of divergence of marsupials and placental mammals, some 173–190 million years ago, implicating its role in egg laying or egg development [11].

4. Structural Features of STK35L1

STK35L1 showed significant similarity to other Ser/Thr kinases, presenting all the major characteristics attributed to the S-TKc family kinase domains. However, it did not belong to any major kinase group of the human kinome cataloged by Manning et al. [1,8]. The STK35L1 kinase domain is 333 aa long, located at the C-terminal of the protein (from position 201 to 534) [9]. The kinase domain of eukaryotic kinases comprises 12 catalytically conserved subdomains (I to V, VIA, VIB, and VII to XI). STK35L1 possesses two unique inserts between catalytic subdomains IV and V (Insert 1) and VII and VIII (Insert 2) (Figure 3). The significance of these sequences is not yet known. Members of other Kinase families are found to have such unique inserts within them, like Interferon-induced protein kinase (PKR), which possesses an insert between subdomain IV and V that is essential for its kinase activity [20]. Calcium-calmodulin-dependent kinase is yet another example that possesses an insert between its subdomains II and III that is responsible for the recruitment and orientation of the substrate within the catalytic cleft and recognition of downstream kinases for phosphorylation [21,22]. PTEN-induced kinase 1 (PINK1) also contains three inserts in its sequence with unique functional significances; mutations within insert 1 have been identified in patients with Parkinson's disease [23], whereas insert 3 is a key motif that is crucial for the protein's substrate recognition and interaction function, particularly ubiquitin interaction and phosphorylation [24]. Several other protein kinases like Tie2 kinase, platelet-derived growth factor receptor kinase, and mitogen-activated protein kinase-interacting kinase also exhibit unique insert regions at distinct locations in the kinase domain [25–27]. These inserts regulate the binding of protein substrates, ATP, or other regulatory proteins. These examples indicate that the unique inserts in STK35L1 may be functionally significant.

The crystal structure of STK35L1 has not yet been resolved. However, the 3D structure of STK35L1 was generated in our laboratory using AlphaFold 3 (Figure 3B). It shows that the N-terminal region of STK35L1 is intrinsically disordered and predominantly displays loop conformation. It is observed that the intrinsic disordered region is a hub for the various post translational modifications such as phosphorylation, which induces a disorder-to-order transition in various protein such as myosin [28], the cystic fibrosis transmembrane conductance regulator (CFTR) [29], and the kinase-inducible domain (KID) [30]. We speculate that the N-terminal region of STK35L1 might be a target site for various PTMs that could induce its disorder-to-order transition and regulate its functions.

STK35L1 is a nuclear and nucleolar protein kinase [9,12]. Localization of a protein in the nucleus requires a nuclear localization signal (NLS), a basic amino acid-rich stretch responsible for the nuclear import of protein [31,32]. STK35L1 possesses a highly conserved and functional bipartite NLS in the N-terminal region (142–153 aa) (Figure 3) [12]. STK35, which lacks the 133 aa of the N-terminus, was mainly localized in the nucleus [9], suggesting that the extended N-terminal sheltered the Nucleolar localization signal (NoLS); however, no specific nucleolar localization sequences have yet been identified [12]. This could be due to the presence of novel uncharacterized nucleolar recognition motifs within the extended N-terminus of the STK35L1 protein. Earlier studies using the gene trap method identified the DEAD-box motif as the canonical motif found in most nucleolar proteins [33]. However, proteomic analysis of human nucleoli showed several proteins that lacked the canonical nucleolar localization signals (NoLS), implicating the existence of alternative nucleolar targeting mechanisms [34,35]. The MDM2 protein found in the nucleoplasm is sequestered into the nucleolus by binding with ARF protein, an example of protein-protein interaction-mediated nucleolar localization [36].

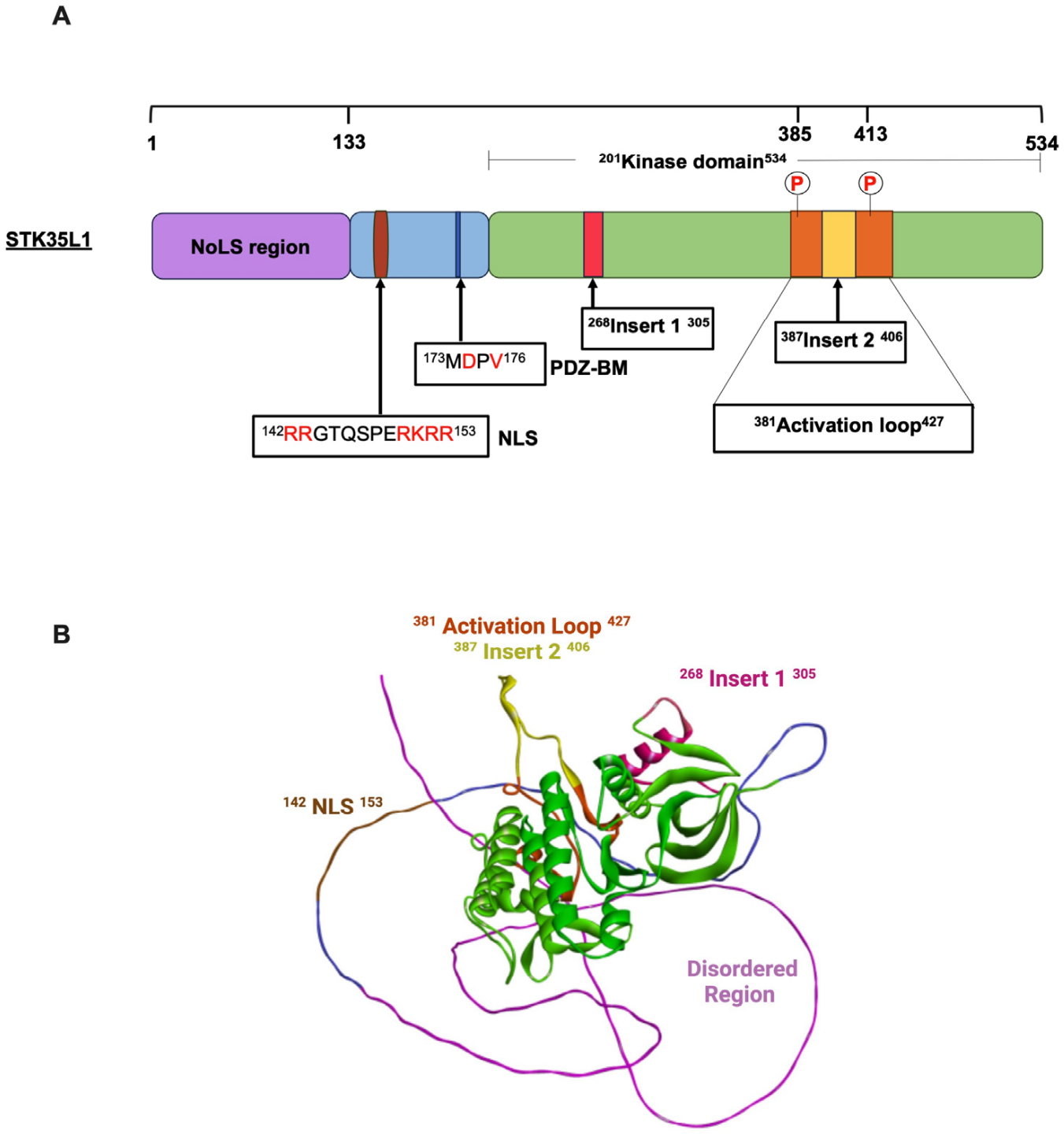


Figure 3. Structural features of STK35L1. (**A**) The cartoon shows the STK35L1 structural features. The kinase domain is shown in green. Two unique inserts, Insert-1 (red) and Insert-2 (yellow), are present in the kinase domain of STK35L1. NLS and NoLS are shown in brown and purple, respectively. PDZ-BM and the activation loop are shown in blue and orange, respectively. (**B**) The 3D structure of STK35L1 was generated from the AlphaFold 3 server (https://deepmind.google/science/alphafold/alphafold-server/, accessed on 3 April 2025).

STK35 is primarily a nuclear protein. In the U2OS osteosarcoma cells, STK35 interacts with CLP36, an α-actinin binding protein, and localizes to actin stress fibers in the cytoplasm [9,37,38], suggesting its potential role in regulating actin dynamics and other cellular activities like cell movement, cell adhesion, protein/ RNA transport etc. [39]. However, in endothelial cells, co-transfection of CLP36 along with STK35 did not show localization of STK35 in the cytoplasm. It remained predominantly localized in the nucleolus [11]. STK35 was found to interact with nuclear actin through its class III PDZ domain at the N-terminal region (173–176 aa) (Figure 3) [12]. The role of nuclear actin is well-established in gene expression, DNA damage repair, and DNA replication [40]. Differential subcellular distribution of the STK35L1 suggests that they might have distinct functions in different cellular contexts or regulate condition-specific functions.

5. Cellular Functions of STK35L1

5.1. Cell Cycle

Nuclear localization of STK35L1 suggests its involvement in various nuclear processes such as transcription, DNA replication, and cell cycle regulation. Silencing of STK35L1 in endothelial cells by siRNA accelerated the progression of the cell cycle from G1 to S phase, establishing STK35L1 as a key cell cycle regulator kinase [12]. Various cell cycle-related genes, including CDKN2A and GADD45A, were also downregulated in STK35L1-silenced endothelial cells [12]. Similar results were also observed in SKT35L1-knockdown HepG2 cells [13]. CDKN2A is a tumor-suppressor gene that plays a crucial role during the G1 to S phase transition. The CDKN2A gene locus is frequently found to be mutated or deleted in various tumors [41,42], indicating its central role in cell cycle regulation. Two partially overlapping transcripts are expressed from the CDKN2A locus, and the alternatively spliced mRNA transcripts named α-transcript and β-transcript encode two distinct proteins, p16INK4a and p14ARF, respectively [43]. The $p16^{INK4a}$ is a tumor suppressor that induces G1 cell cycle arrest by inhibiting the cyclin-dependent kinase CDK4, and the p14ARF induces an arrest in both G1 and G2/M phases via activation of the p53 pathway [44]. The regulation of α-transcript of CDKN2A ($p16^{INK4a}$) expression by STK35L1 may represent a novel signaling mechanism that regulates the progression of the cell cycle from G1 to S phase.

Interestingly, a report showed that STK35 was a potential target of GSK3β in Xenopus [45]. GSK3β regulates the expression of β-catenin by phosphorylating it, followed by its proteasomal degradation [46]. Nuclear β-catenin regulates the expression of $p16^{INK4a}$ in various cancer cell lines [47,48]. These data suggest a novel GSK3β-dependent signaling pathway that might regulate STK35-dependent expression of CDKN2A.

Besides CDKN2A, the downregulation of GADD45A, a protein involved in DNA repair and G1 cell cycle arrest, led to increased G1 to S phase transition [49–52]. Knockdown of STK35L1 in RPE1 cells showed a significant increase in the proportion of cells in the S phase of the cell cycle [17]. Various cell cycle genes, e.g., CCNB2, CDC2, CDC20, CDK6, CDKN3, GTSE1, MKI67, and CDK5R1, which are involved in the M-phase and G2-M-phase transition of the cell cycle, were downregulated after silencing of STK35L1 in HepG2 and endothelial cells [12,13]. These findings support the hypothesis that STK35L1 is a key regulator of the cell cycle and is not only crucial for G1 to S phase transition but might also be involved in various other cell cycle-related processes. The precise role and mechanism of regulation of STK35L1 remain largely to be deciphered.

5.2. Angiogenesis

Angiogenesis is a complex process involved in the development of several diseases, including cancer. Expression of STK35L1 is upregulated during the late regulation of angiogenesis in human microvascular endothelial cells [53]. An upregulation of STK35L1 was also reported in endothelial cells during early angiogenesis, and its silencing inhibited in vitro sprouting, which is a crucial step for angiogenesis [12]. STK35L1 is localized in the nucleolus of endothelial cells [12]. The nucleolus is a functional nuclear sub-compartment critical for regulating various processes, such as synthesizing precursor rRNA and assembly of ribosomal subunits, cell-cycle regulation, senescence, and stress responses [54–57]. These data suggest that STK35L1 could play a crucial role in regulating angiogenesis. STK35L1 also regulates the expression of GADD45A, which is known to be a suppressor of angiogenesis [12,58]. STK35L1 is associated with angiogenesis in endothelial cells, and GADD45A might mediate its regulation. This opens new questions and research avenues to understand the complex pathways and explore new therapeutic targets related to angiogenesis.

5.3. Cell Migration

Cell migration is involved in various physiological processes such as development, tissue repair, wound healing, cancer metastasis, and angiogenesis [59,60]. The process of cell migration involves coordinated biophysical processes, i.e., adhesion, cytoskeleton, and nuclear dynamics, as well as matrix remodeling [61]. Studies by Goyal et al. showed that the knockdown of STK35L1 in endothelial cells resulted in reduced cell migration and a lack of stable lamellipodia formation in the direction of migration [12]. The role of actin dynamics in cell migration is well established [62]. Besides this, nuclear actin plays a role in chromatin remodeling and gene transcription of various genes involved in different cellular functions, such as cell migration [40]. Interaction of STK35L1 with both nuclear and cytoplasmic actin suggests its key role in cell migration by regulating actin dynamics and altering other gene expressions.

5.4. Cell Death

Cell turnover and tissue homeostasis depend on robustly functioning programmed cell death (PCD) mechanisms, including apoptosis and controlled necrosis. PCD dysregulation is a major concern and is strongly linked to aging and aging-related diseases [63]. Nuclear accumulation of importin α2 in HeLa cells resulted in a slight but significant increase in the expression of STK35L1 while studying the non-transport functions of importin α2 in response to oxidative stress [64]. Importin α2 interacts with the promoter of *STK35* and drives its mRNA expression. The elevated levels of STK35L1 in HeLa cells triggered an increased non-apoptotic cell death, i.e., caspase-independent cell death [64]. Interestingly, in osteosarcoma cell line U2OS, the knockdown of STK35L1 led to enhanced apoptosis via the caspase-dependent pathway [16]. In colorectal cancer, elevated STK35L1 expression promotes cell survival and tumor growth, and knockdown of STK35L1 in SW620 and HCT116 led to reduced tumor growth via apoptotic cell death (Caspase-dependent pathway) [14], implicating it as a potential therapeutic target in CRC. STK35L1 shows a paradoxical role, promoting cell death under stress and contributing to cell proliferation in cancerous states. This calls forth further studies to unravel the precise regulation of cell death and proliferation under different physiological and pathophysiological conditions.

5.5. DNA Damage and Repair

Silencing STK35L1 has been shown to alter several DNA repair genes (GADD45A, DDX11, and RAD51) [12,13]. GADD45A is known to interact with several DNA repair-related proteins and is considered a prime regulator of nucleotide/base excision repair [51,52]. DDX11, a 5′ to 3′ DNA helicase, is implicated in double-stranded break (DSB) repair. Knockout of DDX11 in various cells leads to the accumulation of DNA damage, jeopardizing the genomic stability [65,66]. RAD51 is a critical player in homologous recombination-based DNA repair and is required for homologous DNA pairing and strand exchange [67]. Depletion of STK35L1 leads to decreased levels of ɤH2AX and Ataxia telangiectasia mutated (ATM) phosphorylation, which is the hallmark of DNA damage [17]. The knockdown of STK35L1 in RPE1 cells led to G2/M phase cell cycle arrest upon cisplatin-induced DNA damage [17]. Furthermore, these knockdown RPE1 cells were sensitive to cisplatin, suggesting a major role of STK35L1 in DNA damage response (DDR) [17]. This collaborative data suggests that STK35L1 plays a pivotal role in DNA repair mechanisms and has a complex role in its regulation, accentuating the need for extensive investigation to find the underlying molecular mechanisms.

6. Pathophysiological Role of STK35L1 in Diseases

Research has shown the involvement of STK35L1 in diseases like cancer, Parkinson's, and malaria, but the precise role of STK35L1 in disease development is yet to be deciphered [13–16,68,69].

6.1. STK35L1 in Malaria

In the recent past, a significant focus in the field of infection biology has been to study the relationship between parasite and host kinases to understand how the parasite manipulates the host kinases to infect and survive in the host [70]. Various host kinases, which might be crucial in the liver stage of malarial infection, were identified via kinome-wide high-throughput screening [69,71]. STK35L1 was identified to be a crucial protein during hepatocyte infection by *P. berghei* sporozoites [69]. However, further studies are required to elucidate its precise function in malaria. Recently, Goyal et al. reported that STK35L1 expression was upregulated in HepG2 cells and mouse liver during *P. berghei* sporozoites. Furthermore, the knockdown of STK35L1 in the HepG2 cells remarkably suppressed the sporozoite infection [13]. The transcription factor STAT3 is upregulated and phosphorylated during *P. berghei* sporozoites infected HepG2 cells. STAT3 is required to upregulate STK35L1 and STAT3 [13].

Along with the upregulation of STK35L1, specific cell cycle genes were also upregulated during the sporozoite infection, and the knockdown of STK35L1 inhibited the basal expression of STK35L1-linked cell cycle genes except CDKN3 and GTSE1 [13]. Studies also showed that various cell cycle-associated genes were differentially and temporally regulated during infection of the mouse hepatoma cell line, Hepa1-6, and the HepG2-A16 cell line, implicating their role in parasite growth, development, and survival within the host [72,73]. Of note, higher expression of CDKN2A is observed during an acute malarial stage, and STK35L1 is involved in regulating CDKN2A expression in endothelial and HepG2 cells [12,13,74]. Other STK35L1-associated genes RAD51 and DDX11 were upregulated during *P. berghei* sporozoites infection, which are known to be involved in DNA replication and repair [66,67]. The role of STK35L1 in hepatocyte infection and intra-hepatocytic parasite development at the molecular level has not yet been deciphered. Identifying STK35L1-mediated signaling pathways that are active during the liver stage of malaria will provide a newer understanding to develop STK35L1 as a potential novel therapeutic drug target that could be used to treat drug-resistant malaria.

6.2. Colorectal Cancer

Misregulation of *STK35* is observed in colorectal cancer (CRC) [75]. STK35L1 was one of the significantly upregulated kinases in CRC when a panel of 125 kinases was screened [75]. Later, Yang et al. explored the role of STK35L1 in CRC prognosis and progression at the molecular level and observed similar upregulation [14]. Both in vivo and in vitro studies showed that STK35L1 promotes tumor growth and regulates CRC-related cellular activities [14]. Additionally, NEDD4L, an E3 ubiquitin ligase, has been reported to inhibit CRC and promote degradation of STK35L1 through ubiquitination [14,76]. Of note, the expression of NEDD4L was significantly lower in CRC [76], whereas STK35L1 expression was significantly higher, leading to tumor progression [14]. STK35L1 also promotes drug resistance in colorectal cancer cell lines SW620 and SW480 to 5-Fluorouracil. Regulation of glycolysis and apoptosis in CRC has been linked with STK35L1 through AKT signaling that promotes glycolysis while negatively regulating apoptosis and promoting CRC tumor growth [14]. STK35 is a potential downstream target of GSK3β [45]. The role of GSK3β has been implicated in various cancers, including colorectal cancer [77]. In CRC, the nuclear accumulation of GSK3β is associated with overall poor clinical outcome, increased tumor proliferation, and acts as a tumor promoter aiding CRC development [77,78]. Also, AKT kinase regulates the function of GSK through phosphorylation-mediated degradation [78]. Therefore, GSK3β, STK35L1, and AKT may be part of a new signaling network in colorectal cancer that promotes tumor progression and glycolysis.

6.3. Osteosarcoma Cancer

STK35L1 expression was significantly higher in osteosarcoma patients. In vitro and in vivo studies showed that STK35L1 influenced cell proliferation and apoptosis in the osteosarcoma cell line U2OS. The transcription factor STAT3 was identified as a positive regulator of STK35L1 expression. STAT3 binds to the *STK35L1* promoter between the nucleotide positions −230 and −132 and regulates its expression. Knockdown of STK35L1 in osteosarcoma cell lines MG63 and HOC hampered cell proliferation by inducing cell apoptosis, indicating that STK35L1 is negatively associated with apoptotic pathways in a cancerous state [16].

6.4. Acute Myeloid Leukemia

The expression of STK35L1 has been recently linked to AML; it supports cell proliferation, amino acid biosynthesis, and transport in AML [15]. The double knockdown of STK35L1 and PDIK1L in the AML cell line MOLM-13 reduced the proliferation of malignant cells [15]. Interestingly, it was found that SCP4, a nuclear phosphatase, regulates the expression of STK35L1 and PDIK1L in the MOLM-13 cell line. Further investigation revealed that SCP4 binds with STK35L1 and PDIK1L, dephosphorylates phospho-S385 and phospho-S194 in the catalytic domain of STK35L1 and PDIK1L, respectively, and enhances the activity of these kinases [15]. This nuclear SCP4-STK35L1/PDIK1L signaling complex might play a critical role in the pathogenesis of AML.

7. Reproduction

Comparative expression profile analysis of 27 different human tissues revealed that expression of *STK35L1* is significantly higher in the human testis compared to other tissues. Similar expression patterns were observed in mice (unpublished data). Additionally, a higher expression of STK35L1 was also observed in the mouse ovary and eyes [18]. STK35L1, STK35L1 b, and stk35os1 were sequentially and overlappingly expressed at different stages of spermatogenesis. STK35L1 is expressed in the initial stages of spermatogenesis, i.e., spermatogonia and early spermatid; stk35os1 is expressed during the middle

stages, i.e., pachytene stage-round spermatid, and STK35L1b is expressed in the latter stages, i.e., round spermatid-early elongated spermatid [18]. STK35L1 and STK35L1 b are present in somatic cells of the WT follicles in the mouse ovary, whereas higher expression of STK35L1 b mRNA is found in larger follicles [18]. The evidence strongly suggests that *STK35* gene products play an important role during gametogenesis. Further investigations are needed to comprehend the role of the *STK35* allele in oogenesis.

STK35(−/−) knockout mouse showed testicular defects and abnormal ovarian development (reduced size and fewer follicles), suggesting its role in gonad development [18]. Additionally, several phenotypic defects like extensive germinal epithelium vacuolization, Sertoli cell sloughing into the tubule lumen, and areas lacking germ cells were observed. All these observations suggest that the absence of *stk35l1* gene products results in male germ cell loss, Sertoli cell dysfunction, and ultimately reduced male fertility [18]. Characterizing the precise regulation of different gene products of the *stk35* locus will enhance our understanding of the role of STK35L1 and its variants in reproduction.

8. Eye Development

Compared to adult mice, higher *stk35l1* mRNA levels were detected in the ganglion cell layer (GCL) and inner nuclear layer (INL) of the mouse eye during the initial postpartum period, suggesting its role in eye development [18]. Consistent with this, STK35L1 knockout mice also showed abnormal eye phenotypes in adult mice, reiterating STK35L1's role in eye development. Phenotypic eye defects of KO mice ranged from gross deformity to mild goniodysgenesis. The gross deformities were aniridia, corneal opacity, retinal dysplasia, lens malformation, iridocorneal adhesions, failure of anterior chamber formation, and proliferative vitreoretinopathy [18]. PAX6 is the transcription factor that plays a vital role in eye development, and mutation of *PAX6* gene leads to an array of eye abnormalities, including aniridia and corneal opacity [79,80]. During the early stages of eye development, TGFβ and Wnt/β-catenin signal transduction pathways are the two crucial signaling networks involved in eye development and are associated with PAX6 regulatory network [80,81]. TGFβ2 is the most important isoform in eye development, as loss of TGFβ2 leads to multiple defects in ocular structures [82]. A report showed STK35L1 is associated with SMAD, which is disrupted upon receiving the TGFβ signal [83]. Literature suggests links between STK35L1 and Wnt/TGFβ pathways, which indicates that STK35L1 might be one of the downstream kinases regulating the activation and activity of the Wnt/TGFβ/PAX6 signaling pathway in eye development during embryogenesis.

9. Conclusions

STK35L1 is emerging as a critical kinase regulating several human diseases, including malaria and various types of cancer (Figure 4). STK35L1 plays a diverse role in numerous cellular processes, such as cell cycle, DNA damage repair, angiogenesis, cell migration, and cell death. STK35L1 has a paradoxical role in apoptosis, which should be further studied. The substrate of STK35L1 and the molecular mechanism regulating its functions have not been discovered yet. This is a major obstacle to establishing its precise function in various human diseases. The oncogenic role of STK35L1 is identified in a few tumors, and it is essential to investigate this kinase in other types of cancers to establish it as a prooncogenic protein kinase. A few studies demonstrated that STK35L1 causes drug resistance, which should be further investigated at the molecular level. STK35L1 is crucial for the sporozoite infection during the liver stage of malaria. Identifying its signaling during the liver stage will provide an opportunity to develop STK35L1 as a novel therapeutic drug target to treat drug-resistant malaria. The future research must focus on identifying the molecular

mechanism governing its actions, which will expand our understanding of this kinase and its importance in various diseases.

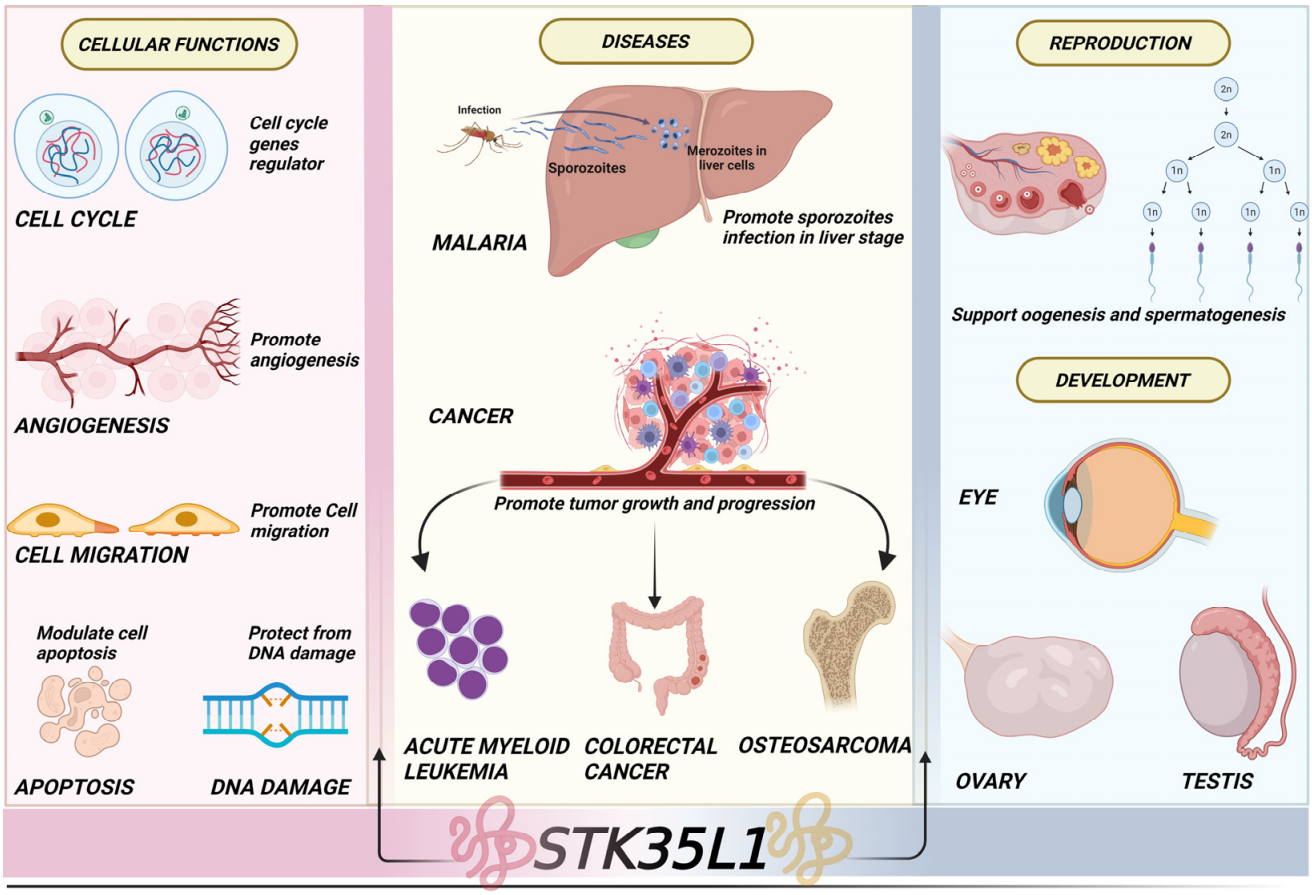


Figure 4. Overview of STK35L1 cellular functions, disease progression, reproduction, and development. Created in BioRender. Goyal, P. (2025) https://BioRender.com/p79a189, accessed on 3 April 2025.

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