Emerging roles of POLR2L of RNA polymerase II dynamics and disease mechanisms (Review)

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Received September 9, 2025; Accepted February 24, 2026

DOI: 10.3892/mmr.2026.13869

Abstract. RNA polymerase II (Pol II) is an essential eukaryotic enzyme that transcribes protein-coding genes and various non-coding RNAs. RNA polymerase II, I and III subunit L (POLR2L) is a highly conserved component shared by RNA polymerase subunits I, II, and III, which contributes to transcriptional regulation, enzymatic structural integrity, key cellular processes such as proliferation, differentiation, and stress responses. Recent research has shown that POLR2L is not merely a Pol II structural subunit but also plays key roles in disease progression, particularly cancer, where POLR2L dysregulation contributes to tumor growth, metastasis, and resistance to chemotherapy. Additionally, POLR2L is closely linked to major signaling pathways including the PI3K-Akt, Wnt/β-catenin, and TGF-β pathways, highlighting the diverse roles played by POLR2L in cellular signaling. This review summarizes current knowledge on the structural and functional properties of POLR2L, its involvement in various diseases, and its potential as a therapeutic target. By outlining the diagnostic and therapeutic relevance of POLR2L, this review aims to provide a framework for understanding how POLR2L related research may inform transcriptional regulation and its impact on human health and disease.

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Key words: RNA polymerase II, I and III subunit L, RNA polymerase II, transcription regulation, cancer, cell growth

Contents

1. Introduction

RNA polymerase II (Pol II) is a key enzyme of eukaryotic cells. Pol II transcribes messenger RNAs (mRNAs) and various non-coding RNAs (ncRNAs) that play key roles in cellular growth, differentiation, and stress responses (1). Pol II is a large multi-subunit complex of 12 distinct proteins, each contributing to the overall structural integrity and functional specificity of the enzyme (2). Among these proteins, RNA polymerase II, I and III subunit L (POLR2L), a highly conserved 7.6-kDa subunit featuring an atypical zinc finger domain, plays vital roles in terms of maintaining the stability and efficiency of the Pol II complex (3). Despite its small size, POLR2L is essential for both Pol II assembly and enzymic interactions with DNA and RNA throughout transcription (4). Although extensive structural and functional studies of the RNA polymerase II complex have been conducted, most previous research has primarily focused on the overall architecture of the enzyme and its major subunits (5-7). As a result, small Pol II subunits such as POLR2L, POLR2H, and POLR2K have often been treated as structural components rather than as subjects of systematic comparative analysis (8,9). This gap highlights the need for a more integrative perspective that places POLR2L in a direct structural and evolutionary context with other small Pol II subunits (10,11). AlphaFold, an artificial intelligence

system, predicts the three-dimensional structures of proteins based on their amino acid sequences. This advanced machine learning approach uses multiple sequence alignments to yield physical and biological insights into how deep learning algorithms operate, significantly enhancing the accuracy of protein structure prediction (12). This approach has yielded predictions of the POLR2L, POLR2H, and POLR2K protein structures. The structural role of POLR2L aside, the subunit is of broader biological significance (13). Emerging evidence indicates that POLR2L regulates transcriptional programs that influence both cellular homeostasis and pathological conditions (14). POLR2L serves as a key regulator of various cellular processes, actively participating in cell proliferation, differentiation, and energy metabolism (15). POLR2L dysregulation has been linked to various diseases, particularly cancer. POLR2L overexpression has been associated with tumor growth, metastasis, and resistance to chemotherapy (16). These findings suggest that POLR2L is not merely a structural component of the transcriptional machinery but also an active regulator of critical cellular pathways (17). Recent research has revealed the involvement of POLR2L in several major signaling pathways, including the PI3K-Akt, Wnt/β-catenin, and TGF-β (18). pathways that regulate cellular survival, proliferation, the immune responses, and tissue remodeling (19). Within these signaling networks, POLR2L plays a crucial role in terms of coordinating intricate molecular cascades, further emphasizing its biological importance (20). POLR2L critically regulates the immune responses and DNA damage repair pathways, further highlighting the diverse functionality and significance of the subunit in disease (21). The clinical relevance of POLR2L is becoming increasingly apparent (16). Its overexpression has been linked to poor prognosis, increased metastatic potential, and resistance to chemotherapy of various cancers, including hepatocellular carcinoma (HCC), gastric cancer, and prostate cancer (17). Some studies found that POLR2L inhibition suppressed tumor growth and improved drug sensitivity in preclinical models, emphasizing its potential as a therapeutic target (18). The role of POLR2L in cancer aside, the protein affects the progression of viral infections and immune-mediated diseases, further underscoring its broad significance in terms of human health. This review comprehensively analyzes the structural and functional attributes of POLR2L and the roles played by the subunit in disease progression and the development of new therapeutic strategies. The advanced methodologies used include RNA sequencing, CRISPR-Cas9 gene editing, and protein-protein interaction analysis. The review highlights the potential of POLR2L as both a diagnostic biomarker and a therapeutic target, emphasizing its relevance in both future research and precision medicine. By synthesizing the findings of POLR2L-related studies, the review establishes a foundation for future advances in personalized medicine.

2. Structure and biochemical properties of POLR2L

To contextualize the structural and functional role of POLR2L within the RNA polymerase II complex, we performed a comparative structural, sequence-based analysis of POLR2L alongside two other small Pol II subunits, POLR2H and POLR2K (8,9,22). Pol II plays a central role in the gene expression of eukaryotic cells, facilitating the transcription of both protein-coding mRNAs and various ncRNAs (2,6). Of the 12 subunits that constitute the Pol II complex, POLR2L is a small (7.6 kDa), highly conserved subunit, reflecting its profound evolutionary significance (6,23). As shown in Fig. 1A, AlphaFold-based structural models have suggested that POLR2L adopts a compact globular fold with a surface-exposed zinc-binding pocket (12,24), whereas POLR2H and POLR2K display more extended conformations with distinct surface charge distributions (2,25). Although this in silico prediction should be interpreted as hypothesis-generating and requires experimental validation, such differences support the notion that POLR2L may provide a flexible interaction module that can bridge specific subunits within the Pol II core, in contrast to the mainly architectural roles proposed for POLR2H and POLR2K (26,27).

Clustal Omega was used to perform multiple sequence alignment (MSA) of POLR2L, POLR2H, and POLR2K (28). Although POLR2L, POLR2H, and POLR2K contain 67, 175, and 58 amino acid residues, respectively, several conserved residues were identified (Fig. 1B). Sequence alignment analysis (Fig. 1B) revealed that POLR2L, POLR2H, and POLR2K share conserved residues despite differences in overall sequence length, supporting their functional relatedness as small RNA polymerase II subunits (29,30). Notably, POLR2L has strongly conserved cysteine residues that are predicted to coordinate zinc ions, indicating additional evolutionary constraints that may underlie specialized structural contributions within the Pol II complex (25,31). These include regions potentially involved in both metal ion coordination and subunit interaction, highlighting functionally relevant similarities across these Pol II components (32). The alignment supported the hypothesis that the three small subunits share conserved biochemical features critical for Pol II complex assembly and stability (33). POLR2L contains an atypical zinc finger domain that is essential for the maintenance of Pol II structural stability and functionality (34). This domain appears to support efficient complex assembly and transcriptional activity, although direct experimental dissection of its contribution to these processes remains limited (1,35).

The atypical zinc finger motif of POLR2L, which is characterized by a conserved Cys-X_2-Cys-X_{12}-Cys-X_2-Cys configuration, resembles zinc-coordinating motifs in other multi-subunit RNA polymerases that reinforce subunit-subunit interactions (36,37). By analogy, POLR2L may contribute to Pol II assembly and transcriptional stability through metal-mediated structural reinforcement, although this mechanistic role remains to be directly validated (3,38) (Fig. 1C). POLR2L is proposed to contribute to Pol II stability and transcriptional precision, primarily based on structural predictions and sequence conservation analyses, rather than direct mutational or structural experiments focused on POLR2L itself (25,39). These predictions provide a useful framework for hypothesis generation; however, dedicated biochemical and biophysical studies will be required to establish definitively how POLR2L influences Pol II assembly and function (8,35).

From a functional perspective, the evolutionary conservation of POLR2L and its zinc-binding motif strongly suggests a role in stabilizing Pol II assembly and facilitating subunit interactions (25,35). Previous biochemical and structural

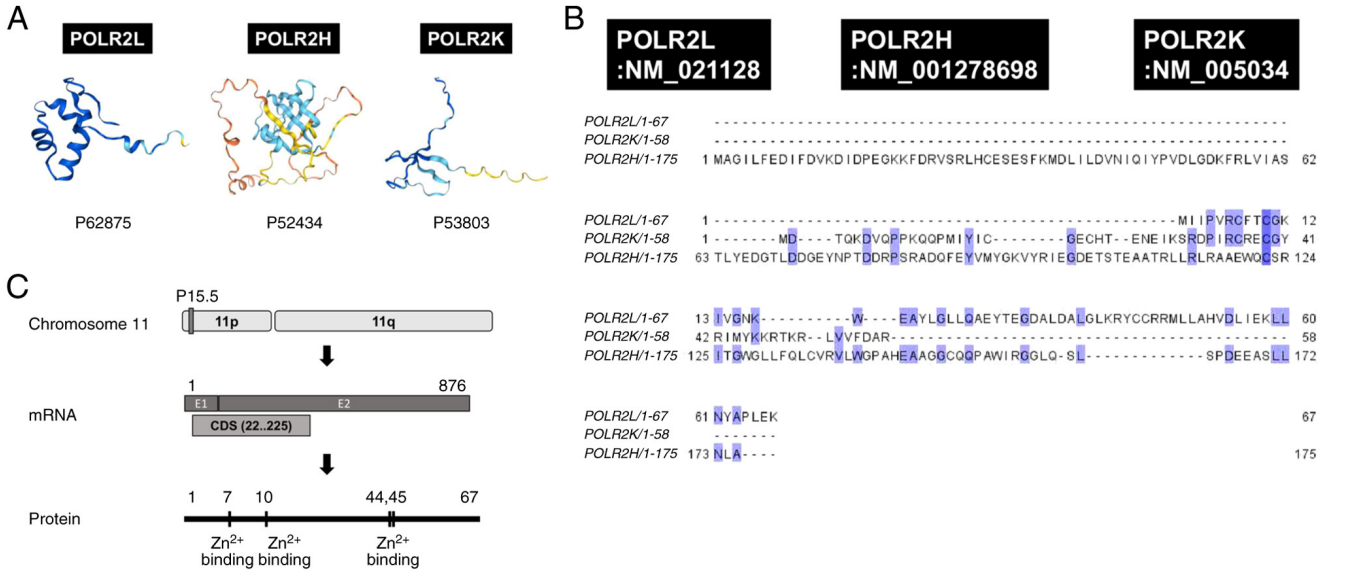

Figure 1. Structural characteristics of POLR2L, POLR2H and POLR2K proteins and genomics organization of POLR2L. (A) The predicted three-dimensional structures of POLR2L, POLR2H and POLR2K proteins are illustrated. (B) Multiple sequence alignment of POLR2L, POLR2H and POLR2K highlights conserved residues, including cysteines within the POLR2L zinc finger motif that are predicted to coordinate zinc ion (Zn^{2+}) and are more stringently conserved than in POLR2H or POLR2K. These conserved positions likely demarcate functionally important interfaces for subunit-subunit interactions in the RNA polymerase II complex. (C) The POLR2L gene is located on chromosome 11 (11p15.5), comprises two exons, and encodes a 67 amino acid protein with four predicted Zn^{2+} binding sites arranged in an atypical Cys-X_2-Cys-X_{12}-Cys-X_2-Cys configuration, consistent with a specialized metal binding scaffold. POLR2, RNA polymerase II, I and III subunit.

studies of RNA polymerase complexes have demonstrated that small zinc-binding subunits frequently act as structural scaffolds that reinforce interactions among core subunits. In yeast and archaeal RNA polymerases, the disruption of homologous zinc-binding subunits impairs the assembly of POLR2C-POLR2J (RPB3-RPB11) subcomplexes and diminishes transcriptional initiation efficiency, providing a functional precedent for the putative scaffolding role of POLR2L in the human Pol II complex (40-42). In this context, conserved cysteine residues within the POLR2L zinc finger motif are likely to contribute to the stabilization of the POLR2C-POLR2J subcomplex and maintenance of Pol II structural integrity (3,34,43).

Although direct experimental evidence specifically dissecting individual POLR2L residues remains limited, studies in yeast and mammalian systems have shown that the perturbation of small Pol II subunits disrupts polymerase assembly, reduces transcriptional efficiency, and destabilizes elongating RNA-DNA hybrids (44-47). Given the strong conservation of cysteine residues within the POLR2L zinc finger motif, and the sensitivity of small Pol II subunits to perturbation in other systems, these residues likely constitute key anchoring points for subunit-subunit interfaces that support Pol II assembly and elongation competence (25,37). Therefore, the high degree of sequence conservation observed in POLR2L likely reflects evolutionary pressure to preserve these structural and functional interactions within the Pol II complex (48). Future mutational and structural analyses will be required to validate the mechanistic contributions of conserved residues and the zinc finger domain to Pol II function (37). Although the atypical zinc finger domain of POLR2L likely plays an important role in maintaining structural integrity within the RNA polymerase II complex, its precise functional contributions remain incompletely defined (8). In addition to stabilizing subunit interactions, this zinc-binding motif may play complementary roles, such as facilitating conformational flexibility during transcriptional initiation or elongation, acting as a scaffold for transient protein-protein interactions, or contributing to the dynamic regulation of Pol II under stress or signaling conditions (49). The functional relevance of the zinc finger domain may also be context-dependent, varying across cell types or transcriptional states (50). Importantly, most current insights into the POLR2L zinc finger are derived from structural predictions, evolutionary conservation, and indirect functional studies, underscoring the need for future biochemical and mutational analyses (25).

A comparative analysis of POLR2L with other small RNA polymerase II subunits, particularly POLR2H and POLR2K, provides additional insight into the organizational principles of the Pol II complex (1,2,6,24). Although all three subunits are relatively small and evolutionarily conserved, they display distinct structural and biochemical features that suggest functional specialization (13,34,40). POLR2H and POLR2K primarily function as architectural components that stabilize core Pol II subcomplexes, whereas POLR2L is distinguished by its atypical zinc-binding motif and compact fold, which may confer greater flexibility in mediating subunit interactions (3,14,23,34). Sequence alignment analyses have revealed that POLR2L exhibits a higher degree of conservation within its zinc-coordinating residues, compared to POLR2H and POLR2K, indicating stronger evolutionary constraints on metal binding functionality (23,28,34). This distinction suggests that POLR2L may play a more dynamic role in reinforcing Pol II assembly or maintaining transcriptional stability under variable cellular conditions (4,41). By placing POLR2L in a direct structural and evolutionary context with POLR2H

and POLR2K, this comparative framework advances our current understanding of small Pol II subunit organization, while highlighting features that may underlie functional specialization within the transcriptional machinery (6).

3. Interaction network of POLR2L

POLR2L has been proposed to regulate transcription with other subunits of the Pol II complex, principally POLR2C and POLR2J. These physical connections are thought to contribute to the assembly and stability of the Pol II complex. POLR2L also interacts with other proteins involved in transcription and signaling (Fig. 2), such as POLR2C, POLR1A, POLR3B, and POLR2E, further underscoring its importance within the general transcription machinery (3). POLR2L has been implicated in stabilizing RNA-DNA hybrids and may influence the elongation phase of transcription (51). POLR2L mutations have been reported to disrupt Pol II complex assembly and impair transcriptional activity associated with transcriptional repression and metabolic dysfunction (16). Such mutations have been identified in various cancers, where they significantly reduce cell survival and proliferation (16). Notably, structural defects in POLR2L have been linked to chemotherapy resistance in cancer cells, which suggests that POLR2L may affect cancer progression and treatment responses (16).

4. Evolutionary conservation and biological significance of POLR2L

POLR2L amino acid sequence and structural features are highly conserved across eukaryotes and archaea, highlighting its critical roles in Pol II function (40). Despite its structural simplicity, POLR2L engages in transcriptional activation, enhancing the adaptability of the overall enzyme complex (3). Its evolutionary conservation suggests that POLR2L acts as a key regulatory component of the transcription machinery, rather than merely playing a structural role (34).

Pol II is a key enzyme of eukaryotic gene expression, transcribing both protein-coding genes and ncRNAs (2,41). As an integral component of the Pol II complex, POLR2L plays essential roles throughout all stages of transcription, including initiation, elongation, and termination (3). Although POLR2L primarily maintains transcriptional efficiency and stability, the subunit is also involved in various cellular processes (34), including the regulation of growth, differentiation, the stress response, and metabolic pathways, demonstrating its broader biological significance (15).

Role of POLR2L in transcription. POLR2L contributes to both transcription initiation and elongation (3). POLR2L stabilizes RNA-DNA hybrids, ensuring that Pol II remains securely attached to the DNA template (40). POLR2L also maintains the structural integrity of Pol II, supporting efficient RNA synthesis via transcription and elongation (34). POLR2L function is prominent near the promoters of actively transcribed genes, where the subunit facilitates transcriptional initiation even in the presence of transcriptional repressors (3), which allows cells to adapt swiftly to environmental changes, enhancing transcriptional flexibility under stress (15).

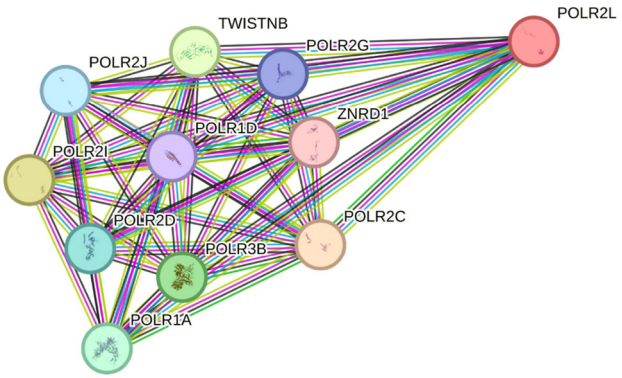

Figure 2. STRING analysis and POLR2L-associated genes. STRING analysis indicates that POLR2L interacts with genes involved in RNA polymerase I, II and II subunit proteins. These interactions play a crucial role in catalyzing the transcription of DNA into RNA by utilizing four ribonucleoside triphosphates as substrates. The POLR2L centered interaction network highlights connections with core Pol I, II and III subunits, supporting a role for POLR2L as an integral component of the general transcription machinery and suggesting potential points of crosstalk between different polymerase complexes. POLR2, RNA polymerase II, I and III subunit; STRING, Search Tool for the Retrieval of Interacting Genes/Proteins.

POLR2L function in cell growth and differentiation. POLR2L participates in the regulation of cell growth and differentiation (34). Its expression is elevated in highly proliferative tissues, suggesting that POLR2L functions as a key transcriptional regulator during the S and G2/M phases of the cell cycle (15). This function highlights the importance of POLR2L in facilitating the production of proteins and RNAs essential for cell proliferation (2). Additionally, POLR2L is required for cellular differentiation associated with both development and tissue regeneration (3). POLR2L inhibition disrupts the transcriptional patterns of differentiating cells, potentially reducing the expression of proteins required for appropriate differentiation and cell survival (34).

POLR2L and stress responses. Cells regulate gene expression when adapting to oxidative stress or hypoxia, among other conditions (15). POLR2L then plays a crucial role during transcription by controlling the expression of stress response genes (1). POLR2L stabilizes Pol II complexes at the promoters of stress-inducible genes, enabling cells to respond rapidly to damage (3). This function is particularly significant when cells such as cancer cells become adapted to stress. Thus, POLR2L promotes survival by enhancing cellular resilience under adverse conditions (16).

POLR2L in cellular metabolism and energy regulation. POLR2L regulates cellular metabolism and the energy balance. Many genes transcribed by Pol II are essential for energy production and metabolism. POLR2L facilitates the transcription of genes that regulate metabolism, thereby maintaining ATP production and the equilibrium among metabolic intermediates. Disrupted POLR2L expression is associated with metabolic imbalances, potentially affecting the metabolic adaptation of cancer cells (16).

POLR2L and regulation of gene expression. The roles played by POLR2L in transcription aside, the subunit also contributes

to epigenetic regulation (42). As part of the Pol II complex, POLR2L interacts with histone-modifying enzymes and DNA methyltransferases, as well as transcription factors and co-activators that regulate gene expression (43,44). Such epigenetic functions underscore the fact that POLR2L modifies the transcriptional programs of specific cell types that respond to changed environmental conditions. In addition to maintaining transcriptional efficiency and stability, POLR2L is actively involved in cell growth, differentiation, stress responses, and metabolic regulation. POLR2L dysregulation has been linked to the development of various diseases, yielding valuable research insights and identification of potentially therapeutic targets (16).

POLR2L and ncRNA regulation. In addition to its role in protein-coding gene transcription, POLR2L may influence the regulation of ncRNAs through Pol II-mediated transcriptional control. RNA polymerase II is responsible for the transcription of numerous long ncRNAs and microRNA precursors, suggesting that POLR2L participates indirectly in ncRNA biogenesis (52-54). The dysregulation of POLR2L expression may be linked with altered transcriptional programs involving oncogenic long ncRNAs and microRNAs that regulate cancer cell proliferation, metastasis, and drug resistance (53,55). Although direct physical interactions between POLR2L and ncRNAs have not yet been clearly demonstrated, POLR2L-dependent transcriptional regulation likely shapes ncRNA expression landscapes in disease contexts. Further studies employing RNA immunoprecipitation and single-cell transcriptomic analyses will be required to elucidate the mechanistic links between POLR2L and ncRNA networks (8,56,57).

5. POLR2L and disease

POLR2L regulates gene expression during various physiological processes. POLR2L dysregulation has been increasingly associated with pathogenesis, particularly cancer, where increased POLR2L expression may contribute to tumor progression, drug resistance, and modulation of the immune response (16). Transcriptomic data revealed that POLR2L expression was significantly elevated in several tumor types compared to the corresponding normal tissues, including diffuse large B-cell lymphoma (DLBC), glioblastoma multiforme (GBM), liver hepatocellular carcinoma (LIHC), ovarian cancer (OV), thymoma (THYM), prostate adenocarcinoma (PRAD), and stomach adenocarcinoma (STAD) (Fig. 3A). POLR2L expression levels were linked to survival rates of patients with liver hepatocellular carcinoma (HCC), adrenocortical carcinoma, skin cutaneous melanoma, and uveal melanoma (Fig. 3B). POLR2L can thus serve as both a prognostic biomarker of and a possible therapeutic target for cancer.

POLR2L is highly expressed in HCC, promoting tumor cell proliferation and metastasis (45,46). Such overexpression activates the survival pathways of cancer cells, contributing to resistance against chemotherapeutic agents such as cisplatin (17). POLR2L inhibition reduced HCC viability and induced apoptosis, highlighting the fact that POLR2L may serve as a therapeutic target for liver cancer (17).

Increased POLR2L expression has also been observed in gastric cancer, associated with poorer patient prognosis (38). Patients with elevated POLR2L levels often exhibit more rapid tumor progression and enhanced resistance to chemotherapy (16). Targeting of POLR2L structural stability may be useful in the treatment of gastric cancer (16).

POLR2L is a key regulator of prostate cancer malignancy and drug resistance (38,58). POLR2L promotes cell invasiveness by activating TGF-β and epithelial-mesenchymal transition (EMT) pathways (17). POLR2L suppression enhanced sensitivity to anti-androgen therapies such as bicalutamide and chemotherapeutic agents such as docetaxel, further highlighting the potential of POLR2L as a therapeutic target (16,59).

POLR2L in viral infections. POLR2L facilitates viral transcription and modulation of host immune responses. POLR2L enhances hepatitis B virus gene expression by allowing the virus to use host transcriptional machinery for replication (60). POLR2L inhibition reduced hepatitis B virus replication, suggesting that POLR2L targeting may exert antiviral effects (60). POLR2L is also essential for herpes simplex virus gene expression. POLR2L knockdown significantly impaired replication, underscoring its critical role in the viral life cycle and potential as a therapeutic target.

POLR2L in immune disorders. POLR2L regulates the immune responses of autoimmune and inflammatory diseases by controlling inflammatory signaling and cytokine production. POLR2L overexpression was associated with excessive immune activation (61). POLR2L modulated the expression of various inflammatory cytokines including interleukins (ILs) and tumor necrosis factor (TNF) that contribute to the pathogenesis of autoimmune diseases (62). POLR2L modulated the expression of immune checkpoint proteins including PD-1 and CTLA-4 that control immune cell activation (63). POLR2L therefore serves as a promising target for novel immunotherapies, particularly for patients with cancer (64).

POLR2L and DNA damage repair. POLR2L plays a crucial role in terms of DNA damage repair by maintaining genomic stability. POLR2L coordinates expression of the transcriptional and DNA repair mechanisms to ensure that damage is rapidly remedied. POLR2L deficiencies impair DNA repair and induce genomic instability, increasing the risk of tumorigenesis. The involvement of POLR2L in the preservation of genomic integrity indicates that POLR2L may serve as a therapeutic target for cancers associated with defective DNA repair (65).

Thus, POLR2L plays critical roles in various pathological processes, including cancer, viral infections, immune disorders, and DNA damage repair. POLR2L dysregulation contributes to both disease onset and progression, highlighting its potential as a therapeutic target (66). A deeper understanding of how POLR2L affects disease could lead to the development of novel diagnostic tools and personalized treatment strategies, thus advancing the field of precision medicine (67).

POLR2L as a diagnostic and prognostic biomarker. Accumulating transcriptomic and clinical evidence supports

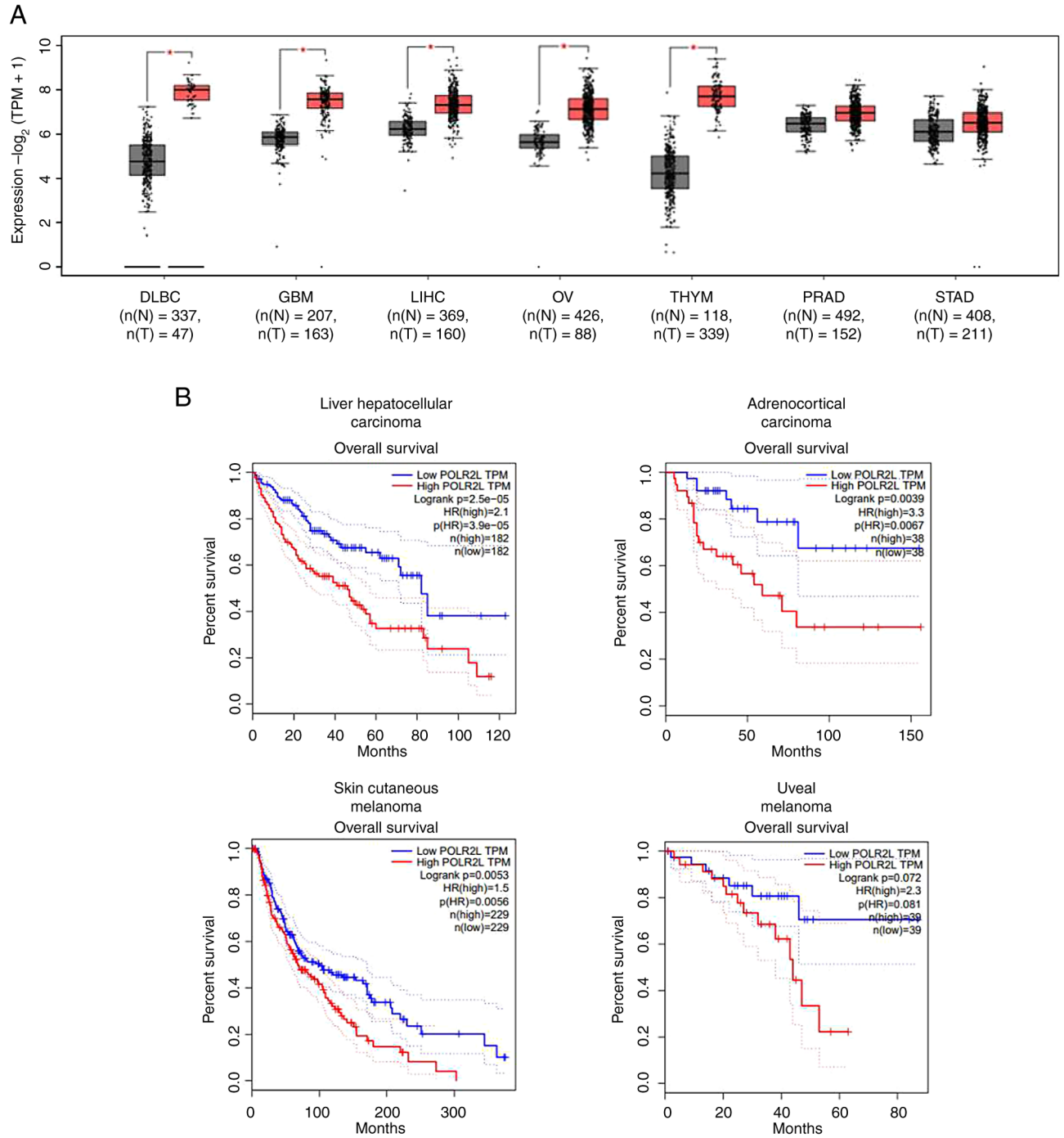

Figure 3. POLR2L expression in various tumors and its impact on survival rates. In cancer research, POLR2L expression was found to be significantly elevated or showed an increasing trend in seven types of cancer. (A) The expression levels of POLR2L in normal tissues (gray) and tumor tissues (red) in seven cancer types in which POLR2L expression was relatively high (DLBC, GBM, LIHC, OV, THYM, PRAD and STAD). (B) Survival rates are shown in relation to POLR2L expression across different tumor types. *P<0.05. DLBC, lymphoid neoplasm diffuse large B-cell lymphoma; GBM, glioblastoma multiforme; LIHC, liver hepatocellular carcinoma; OV, ovarian serous cystadenocarcinoma; THYM, Thymoma; PRAD, prostate adenocarcinoma; STAD, stomach adenocarcinoma; ACC, adrenocortical carcinoma; SKCM, skin cutaneous melanoma; UVM, uveal melanoma; POLR2L, RNA polymerase II, I and III subunit L.

the potential of POLR2L as a diagnostic and prognostic biomarker in cancer (17,68). Elevated POLR2L expression has been consistently associated with advanced tumor stage, poor prognosis, and reduced overall survival in multiple malignancies, including hepatocellular carcinoma, gastric cancer, and prostate cancer (Table I). These associations suggest that POLR2L expression levels may reflect tumor aggressiveness and transcriptional dependency (38,59,69,70).

Importantly, POLR2L may also be applicable in non-invasive clinical settings. Advances in liquid biopsy technologies have enabled the detection of tumor-derived RNA signatures in circulating blood, raising the possibility that POLR2L mRNA levels could be monitored using circulating tumor RNA or exosomal RNA (56). Although direct clinical validation remains limited, these approaches highlight the translational potential of POLR2L as a minimally invasive

Table I. POLR2L as a biomarker in human cancer.

Cancer type	POLR2L expression	Clinical association	Potential application
Hepatocellular carcinoma	Upregulated	Poor prognosis, chemoresistance	Prognostic biomarker
Gastric cancer	Upregulated	Advanced stage, reduced survival	Prognostic marker
Prostate cancer	Upregulated	EMT, drug resistance	Predictive biomarker
Glioblastoma multiforme	Elevated	Tumor aggressiveness	Diagnostic support
Multiple cancers	Increased in tumors	Survival correlation	Liquid biopsy (potential)

EMT, epithelial-mesenchymal transition; POLR2L, RNA polymerase II, I and III subunit L.

biomarker for cancer diagnosis, prognosis, and therapeutic response monitoring (46,71).

6. POLR2L and signaling pathways

POLR2L regulates multiple signaling pathways via transcriptional control, impacting cell survival, differentiation, stress responses, and cancer progression (16). Therefore, POLR2L involvement in key signaling pathways has gained increasing attention, particularly in the context of cancer and other pathological conditions (17).

PI3K-Akt signaling pathway. The PI3K-Akt pathway is a key regulator of cell survival, growth, and transcription, and plays critical roles in both cancer cell proliferation and therapy resistance (72). POLR2L activates the pathway by modulating Pol II-mediated gene expression. POLR2L regulates the transcription of genes essential for Akt activation, thereby supporting cancer cell survival and metabolism (72) (Fig. 4). POLR2L overexpression enhances PI3K-Akt signaling, promoting the G1/S cell cycle transition and driving cancer cell proliferation (73). In patients with HCC and gastric cancer, POLR2L has been implicated in the development of chemoresistance mediated by the PI3K-Akt pathway (74). POLR2L suppression deactivates the pathway and triggers cancer cell apoptosis, further highlighting the key role played by POLR2L as a regulator of PI3K-Akt signaling (75).

Wnt/β-catenin signaling pathway. The Wnt/β-catenin pathway is essential for cell differentiation and tissue homeostasis, and plays major roles in cancer development and metastasis (76). POLR2L modulates this pathway by regulating β-catenin transcription and activating downstream target genes. POLR2L enhanced the transcription of Wnt target genes, including CCND1 and MYC (76). Activation of β-catenin via POLR2L-dependent transcription promoted cancer cell proliferation and motility (77) (Fig. 4). POLR2L regulated the Wnt/β-catenin pathways of prostate and liver cancers (78). POLR2L inhibition triggered pathway deactivation, reducing cancer cell invasiveness and metastasis (77). These findings suggest that POLR2L could serve as a promising therapeutic target when seeking to block Wnt/β-catenin signaling in cancer patients (77).

TGF-β signaling pathway. The TGF-β signaling pathway plays key roles in various biological processes, including growth inhibition, immune regulation, and epithelial-to-mesenchymal transition (EMT). POLR2L regulates the expression of TGF-β-induced transcription factors, promoting the EMT and enhancing cancer invasiveness (17). Via TGF-β signaling, POLR2L facilitates the EMT, enabling cancer cells to acquire metastatic properties and develop drug resistance (17) (Fig. 4). POLR2L inhibition downregulated the expression of EMT-related genes such as ZEB1 and SNAI1, thereby reducing prostate and gastric cancer cell migration and invasiveness (79). POLR2L increased the activation of immunosuppressive cells, including regulatory T cells and M2 macrophages, in the tumor microenvironment, in turn promoting immune evasion (80). These findings highlight the potential of POLR2L as a cancer immunotherapy target (80).

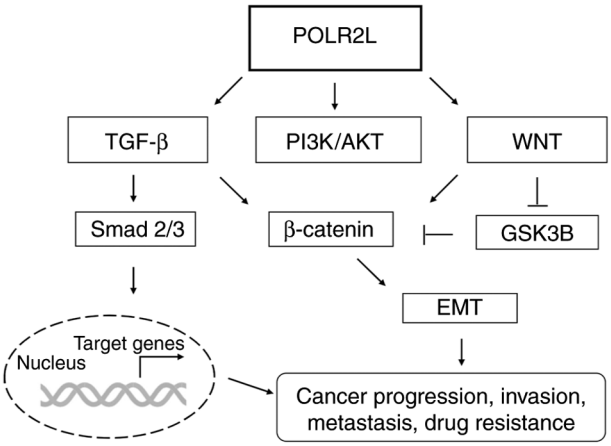

Figure 4. POLR2L function in TGF-β, WNT and PI3K/AKT signaling pathways. POLR2L enhances cell survival and metabolism through the PI3K/AKT pathway and facilitates the transcription of target genes in the nucleus by promoting Smad2/3 phosphorylation via the TGF-β pathway. Additionally, POLR2L contributes to the activation of β-catenin through the WNT pathway, thereby increasing EMT, a process also influenced by TGF-β signaling. By promoting ETM through these pathways, POLR2L plays a significant role in enhancing cancer proliferation, metastasis, invasion and drug resistance. EMT, epithelial-mesenchymal transition; POLR2L, RNA polymerase II, I and III subunit L.

NF-κB signaling pathway. POLR2L also regulates the NF-κB signaling pathway, which plays essential roles in both inflammation and cancer progression (81). NF-κB controls the expression of cytokines, inflammatory proteins, and survival genes (36), and POLR2L facilitates transcription of these genes (82). Elevated POLR2L expression has been linked to NF-κB

activation, which has intensified inflammatory responses and contributed to the development of tumor-promoting inflammatory microenvironments (83). POLR2L inhibition reduced the expression of inflammation-related genes, such as those encoding TNF and IL6, suggesting that POLR2L knockdown may exert an anti-inflammatory effect (82). Interactions between POLR2L expression and NF-κB signaling have been observed in patients with gastric cancer and HCC (17,84). POLR2L suppression inhibited the signaling pathway, reducing tumor growth and metastasis, again indicating that POLR2L may be a valuable therapeutic target (83).

POLR2L interacts with various signaling pathways via transcriptional regulation. Such pathways include the PI3K-Akt, Wnt/β-catenin, TGF-β, and NF-κB pathways, which play crucial roles in pathological conditions such as cancer (16). POLR2L dysregulation distorts these signaling networks, promoting tumor survival and metastasis (17). These findings position POLR2L as both a potential therapeutic target and a diagnostic biomarker, opening up new possibilities for understanding and treating disease (16).

7. Therapeutic potential of POLR2L

POLR2L plays a vital role in transcriptional regulation and significantly impacts the progression of cancer and other diseases (16). POLR2L dysregulation is strongly associated with tumor cell survival, metastasis, and drug resistance, highlighting the potential of POLR2L as a promising candidate for both disease diagnosis and therapeutic intervention (17).

POLR2L inhibition may exert anticancer effects. POLR2L is overexpressed in cancer cells; POLR2L suppression reduced cell viability, inhibited metastasis, and induced apoptosis (16). Advanced technologies such as RNA interference (siRNA, shRNA) and CRISPR-Cas9 have been used to downregulate POLR2L expression (85), in turn impairing transcriptional efficiency followed by cell cycle arrest and apoptosis (16). Such effects have been particularly pronounced in models of HCC, gastric cancer, and prostate cancer (16). In the HCC context, POLR2L inhibition suppressed cell proliferation and enhanced the effectiveness of anti-POLR2L therapies in combination with chemotherapeutic agents (17). Similarly, POLR2L suppression reduced metastatic potential in gastric and prostate cancers by inhibiting TGF-β and Wnt/β-catenin signaling. These findings highlight the therapeutic promise of POLR2L targeting in various cancer cells (16).

Another therapeutic strategy involves POLR2L targeting to overcome cancer-associated drug resistance. POLR2L is a key contributor to chemoresistance, and POLR2L inhibition may therefore be valuable. POLR2L enhances resistance to chemotherapeutic agents such as cisplatin and bicalutamide by activating PI3K-Akt and NF-κB signaling. POLR2L suppression restored the drug sensitivity of drug-resistant cancer cells, suggesting a novel approach toward improvement of therapeutic efficacy (16). POLR2L also upregulates immune checkpoint proteins, including PD-1 and PD-L1, in turn allowing cancer cells to evade immune detection (86). POLR2L targeting enhanced the effectiveness of immune checkpoint inhibitors, suggesting that anti-POLR2L agents might be useful components of combination therapies (86).

POLR2L exhibits significant potential as both a diagnostic and prognostic biomarker of cancers and other diseases (16). POLR2L expression levels are strongly correlated with tumor progression, rendering POLR2L a valuable disease severity indicator (17). For example, POLR2L expression has predicted the tumor size and metastatic status of HCC and gastric cancer (17). Analyzing POLR2L expression levels may aid non-invasive diagnosis. Its overexpression has been linked to lower survival rates and increased risk of metastasis, both of which are critical to patient outcomes (17). Thus, POLR2L expression levels may guide the development of personalized therapeutic strategies, in turn enhancing precision medicine (16).

Direct POLR2L targeting is emerging as a promising cancer treatment (16). The structural characteristics of POLR2L, particularly the atypical zinc finger domain, render it an ideal target of small-molecule inhibitors (2) that selectively block POLR2L function to suppress tumor growth and metastasis (16). Combining POLR2L inhibitors with existing chemotherapies or immune checkpoint inhibitors has enhanced therapeutic efficacy. For example, an anti-POLR2L agent and cisplatin exhibited synergistic effects against HCC and gastric cancer (17). POLR2L is a key regulator of transcription in cancer and other diseases, and is therefore promising as both a therapeutic target and a biomarker (16). POLR2L inhibition reduced tumor cell survival, overcame drug resistance, and enhanced the efficacy of immunotherapy (87). Drugs that specifically target POLR2L as part of new combination therapies may become a new cancer treatment paradigm, paving the way for more effective personalized therapeutic strategies (88).

Small-molecule-targeting strategies for POLR2L. Although direct small-molecule inhibitors specifically targeting POLR2L are not yet clinically available, emerging evidence suggests that POLR2L represents a pharmacologically tractable target (25,89). Structural analyses have indicated that the atypical zinc finger domain of POLR2L plays a critical role in stabilizing Pol II assembly, making this motif a potential site for structure-guided inhibitor design. Small molecules that disrupt zinc coordination or POLR2L-mediated subunit interactions may impair transcriptional stability in POLR2L-dependent cancer cells (25,90).

Indirect pharmacological approaches have also been proposed. Cancer cells exhibiting POLR2L overexpression appear to display heightened dependency on Pol II transcriptional stress. Thus, transcriptional inhibitors or compounds that destabilize Pol II assembly may exert selective anticancer effects in tumors with high POLR2L expression (91). These findings support the rationale for developing POLR2L-centered therapeutic strategies, either through direct inhibition or via synthetic lethality-based approaches (37,91).

8. Discussion and future perspectives

POLR2L, a crucial Pol II component, plays fundamental roles in cell growth, differentiation, stress responses, metabolic regulation, and disease progression (1). This review comprehensively analyzed POLR2L in terms of its structural characteristics, physiological functions, dysregulated expression in disease, interactions with key signaling pathways, and

potential as a therapeutic target. By explicitly placing POLR2L in a structural and evolutionary context with POLR2H and POLR2K, this review refines current models of Pol II subunit organization and suggests testable hypotheses regarding the differential contribution of individual small subunits to complex assembly, transcriptional plasticity, and oncogenic transcriptional dependency (35,92-94). AlphaFold POLR2L structural prediction offers valuable insights into the functional mechanisms in play and potential POLR2L interaction partners, aiding further exploration of their biological significance. The multifunctional nature of POLR2L underscores its critical roles in the development and progression of various diseases. POLR2L has become a key focus of researchers who seek innovative diagnostic and therapeutic strategies (17). POLR2L is thought to support Pol II assembly and transcriptional competence, thereby connecting its structural role to disease associated transcriptional programs (34). POLR2L contains an atypical zinc finger domain that is thought to support efficient transcription and stabilization in RNA-DNA hybrids, although the precise mechanistic contribution of this motif remains incompletely defined (2). POLR2L is highly conserved across all eukaryotic species because POLR2L plays a fundamental role in transcriptional regulation (3). POLR2L is overexpressed in several cancers, including HCC, gastric cancer, and prostate cancer (16). Increased POLR2L expression has been strongly linked to tumor cell proliferation, metastasis, and drug resistance (17). Notably, POLR2L inhibition reduced cancer cell viability and enhanced drug sensitivity, highlighting the potential of POLR2L as a promising therapeutic target (16).

POLR2L contributes to cancer progression and immune regulation by modulating transcription via key signaling pathways, including the PI3K-Akt, Wnt/β-catenin, TGF-β, and NF-κB pathways (16). POLR2L interacts with both upstream and downstream components of these pathways to regulate key disease-related processes including cell survival, metastasis, and immune suppression (17). Thus, POLR2L may represent a valuable diagnostic and prognostic biomarker. POLR2L levels are strongly correlated with cancer progression and predict both patient survival and metastatic potential. Additionally, POLR2L may be useful a non-invasive clinical diagnostic tool, and POLR2L inhibitors may offer novel therapeutics for cancer and other diseases (95). POLR2L targeting may overcome the drug resistance of cancer cells and improve the effectiveness of chemotherapy and immunotherapy. Personalized therapeutic strategies centered on POLR2L are required (88).

Despite these significant advances, the details of how POLR2L interacts with transcriptional networks remain incompletely understood. Further studies, including RNA sequencing and protein-protein interaction network analyses, are essential. Although the role played by POLR2L in cancer is well established, POLR2L involvement in viral infections, immune disorders, and metabolic diseases remains relatively unexplored. More research is essential. Additionally, anti-POLR2L drug development is still at an early stage (16). Further studies must optimize the stability and efficacy of POLR2L inhibitors in both preclinical and clinical settings to ensure that such materials will be therapeutically active (96).

Future research will further elucidate the roles played by POLR2L in cancers, immune disorders, and infectious diseases, and explore whether POLR2L targeting might advance personalized treatment. The details of how POLR2L interacts with key signaling pathways will allow the development of combination therapies that target both POLR2L and other critical components. Preclinical and clinical studies will assess the stability and efficacy of POLR2L inhibitors. POLR2L inhibitors should be combined with existing chemotherapies and immunotherapies. The roles played by POLR2L in viral infections and autoimmune diseases require further study prior to the development of novel POLR2L-targeting therapies (88). CRISPR-Cas9 gene editing, single-cell RNA sequencing, and bioinformatics studies are required (85). to better understand the transcriptional networks of POLR2L and the role played by POLR2L in disease progression (97).

In summary, POLR2L, a crucial component of the Pol II complex, plays central roles in the progression of cancer and other diseases. Research on POLR2L has evolved from study of the structural and functional characteristics of the protein to exploration of whether POLR2L might serve as a valuable therapeutic target and diagnostic biomarker. Future studies will create new therapeutic strategies for cancers and other complex diseases, ultimately transforming treatment and fostering precision medicine.

Acknowledgements

Not applicable.

Funding

This work was financially supported by research fund of Chungnam National University (SH Kim, 2025) and by the National Research Foundation of Korea grant funded by the Korea government (MSIT) (grant no. RS-2025-00514760).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

BL, CS, SE, YL, SK and JS contributed to the study conception and design. The first draft of the manuscript was written by BL and JP, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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