LIM domain only 1: an oncogenic transcription cofactor contributing to the tumorigenesis of multiple cancer types

Guo-Fa Zhao¹, Li-Qin Du², Lei Zhang¹, You-Chao Jia³

¹Department of Medical Oncology, Hebei Key Laboratory of Cancer Radiotherapy and Chemotherapy, Affiliated Hospital of Hebei University, Baoding, Hebei 071000, China; ²Department of Chemistry and Biochemistry, Texas State University, San Marcos, TX 78666, USA.

Abstract

The LIM domain only 1 (LMO1) gene belongs to the LMO family of genes that encodes a group of transcriptional cofactors. This group of transcriptional cofactors regulates gene transcription by acting as a key "connector" or "scaffold" in transcription complexes. All LMOs, including LMO1, are important players in the process of tumorigenesis. Unique biological features of LMO1 distinct from other LMO members, such as its tissue-specific expression patterns, interacting proteins, and transcriptional targets, have been increasingly recognized. Studies indicated that LMO1 plays a critical oncogenic role in various types of cancers, including T-cell acute lymphoblastic leukemia, neuroblastoma, gastric cancer, lung cancer, and prostate cancer. The molecular mechanisms underlying such functions of LMO1 have also been investigated, but they are currently far from being fully elucidated. Here, we focus on reviewing the current findings on the role of LMO1 in tumorigenesis, the mechanisms of its oncogenic action, and the mechanisms that drive its aberrant activation in cancers. We also briefly review its roles in the development process and non-cancer diseases. Finally, we discuss the remaining questions and future investigations required for promoting the translation of laboratory findings to clinical applications, including cancer diagnosis and treatment.

Keywords: LIM domain only 1; Cancer; Single-nucleotide polymorphisms; T-cell acute lymphoblastic leukemia; Neuroblastoma

Background

The gene LIM domain only 1 (LMO1), which is located on human chromosome 11p15.4, also known as T-cell translocation gene 1 (TTG-1) or rhombotin, belongs to the LMO gene family, which consists of four members (LMO1, LMO2, LMO3, and LMO4). The protein products of the LMO gene family share a common LIM domain, which is a cysteine-rich zinc-binding motif, in their protein structures. They are a group of transcription cofactors that regulate the transcription of target genes by forming transcription complexes with other proteins. Due to their structural similarity, LMO proteins unsurprisingly share some common cellular biological functions. In the context of tumorigenesis, studies have demonstrated strong links of all four LMO gene family members to the occurrence and development of various types of cancers.¹ For example, LMO1 and LMO2 are both found to play a role in T-cell acute lymphoblastic leukemia (T-ALL).² LMO3 and LMO1 are both linked to neuroblastoma,³ and the overexpression of LMO4 is a marker of poor prognosis in breast cancer.⁴ Despite their structural similarity and certain common functions, there is strong evidence showing that each of the LMO proteins also has its own unique biological features, such as tissue-specific expression patterns, interacting proteins, gene targets, and pathological consequences. These differences that have been increasingly recognized in recent studies are intriguing to researchers and strongly indicate that the functions of the LMO family are far more diverse and complicated than initially assumed. For this reason, LMO family proteins are still under intensive investigation.

LMO1 was first described as a gene disrupted by a t(11;14) (p15;q11) genetic translocation event involving the TCRβ locus in RPMI-8402, a cell line derived from a patient with T-ALL.⁶ Compared to that of other LMO family members, the function of LMO1 is far less characterized. This is most likely due to the more restricted tissue-specific expression relative to other members. The oncogenic function of LMO1 was first identified in T-ALL and neuroblastoma.¹,³ In later investigations, it was increasingly recognized that the LMO1 gene plays an essential role in tumorigenesis.
role in the normal development process, and its aberrant expression is likely to contribute to a variety of human diseases, including various types of cancers. For example, the expression of LMO1 at the physiological level has been suggested to play a role in normal forebrain development.[1] LMO1 gene polymorphisms were found to be closely related to the susceptibility of Wilms’ tumor.[8] Overexpression of the LMO1 gene in lung cancer and colorectal cancer reduces sensitivity to cetuximab.[9,10] The high expression of LMO1 in gastric cancer may be an indicator of poor prognosis.[11] The current knowledge of its oncogenic role strongly suggests that developing LMO1-based diagnostic and therapeutic tools would be beneficial to cancer patients.

At the beginning of this article, we summarize the basic knowledge of the LMO family and concisely review the physiological roles of LMO1 in normal developmental processes and the mechanism in non-cancer diseases. We then systematically review the findings on its role in oncogenesis. We hope this review will give researchers an inclusive overview of LMO1 regarding its various functions, especially its oncogenic functions. We hope that our review will promote further investigations into this important gene and facilitate the translation of the knowledge on this gene into clinical applications.

The LMO1 and LMO Gene Family

The LMO gene family shares a common LIM domain structure, which is a highly conserved cysteine-rich zinc-binding motif that consists of ∼55 amino acid residues. The LIM domain participates in the interaction with other DNA-binding proteins, but it does not directly bind to DNA. At present, the crystal structures of LMO proteins alone have not been successfully isolated or characterized.[12] However, the structures of complexes formed by some LMOs (e.g., LMO2 and LMO4) have been reported.[13] The term “LMO” was generated from “LIM only,” which refers to a family of LIM domain-containing proteins that comprise two tandem LIM domains but contain no additional defined functional domains or motifs in their structure.[14] Other LIM proteins, such as the cysteine-rich intestinal protein and the particularly interesting new cysteine-histidine-rich protein, are also composed of LIM domains but with one or more additional defined domains or motifs and therefore do not belong to the LMO family.[15] The LIM domain can interact with a variety of proteins, including basic helix-loop-helix (bHLH) transcription factors T-cell acute lymphocytic leukemia 1/ stem cell leukemia protein (TAL1/SCL), LIM domain-binding protein 1 (LDB1)/ nuclear LIM interactor (NLI), and GATA family of transcription factors.[16,17] The conserved core of LIM domains consisting of N- and C-terminal Zn2+ coordination modules provides a platform upon which sequence variations that can lead to variations in target binding specificity and affinity.[18] The pairwise sequence identity between the four LMO proteins has been determined and their sequence similarity was schematically summarized by Matthews et al.[1] [Figure 1]. The four LMOs are involved in the occurrence or progression of a variety of cancers by modulating a variety of key oncogenic processes, including proliferation, differentiation, and hematopoiesis.[19]

LMO1 was the first LMO family member that was identified. It was first identified as a cysteine-rich protein with a molecular weight of 18 kDa, and the cysteine-rich region of LMO1 was subsequently identified as the LIM domain.[2,20] Physiological levels of LMO1 were found to be expressed in a highly tissue- and stage-specific pattern during development. Using a transgenic mouse model, Greenberg et al.[21] first found that LMO1 was expressed in a segmental and developmental manner in rhombomeres of the developmental hindbrain. During the developmental process, the gene became more widely expressed but was still confined to the central nervous system in precisely defined regional patterns. A more detailed analysis of LMO1 expression showed that LMO1 was expressed in the forebrain, hindbrain, eyes, olfactory system, and spinal cord in developing mouse embryos, while its expression in adult mouse tissues was mainly concentrated in the bladder and certain nerve tissues, such as the retina and hippocampus.[22]

Studies have suggested that LMO1 plays a role in development-related diseases, especially development-related diseases in the nervous system. The expression of LMO1 is limited to specific areas of the central nervous system during development.[23] LMO1 is one of the target genes of the transcription factor Aristless-related homeobox (ARX). ARX binds to a specific site (TAATTA) in the promoter region of the LMO1 gene and downregulates the expression of LMO1 in migrating cortical interneurons.[24] ARX expression is mainly restricted to populations of GABA-containing neurons and plays multiple roles in brain patterning, neuronal proliferation and migration, cell maturation and differentiation, and axonal outgrowth and connectivity.[24] The loss of repression activity of ARX can lead to different degrees of inter-neuronopathy in both humans and mice.[25] LMO1 was found to be upregulated in an ARX mutant in the subpallium.[17] Normally, LMO1 is expressed at very low levels in the ventral telencephalon. However, it was found to be highly expressed in ARX mutant medial, lateral, and caudal ganglionic eminences.[26] These findings, together with the tissue-specific
expression of LMO1 in the central nervous system observed in other studies,[23] strongly suggest that LMO1 plays an important role in GABAergic neurons, and its aberrant expression may result in mental retardation and epilepsy. However, this speculation needs to be verified in further studies.

Based on analysis of gene sequence homology, the researchers discovered two other members of the LMO family, LMO2 and LMO3.[2,23] The sequence homology between LMO2 and LMO1 is 50%,[23] LMO2 is widely expressed in various tissues.[23] Despite its universal expression pattern in tissues, LMO2 was found to be particularly important for the early stages of hematopoiesis and angiogenesis, whereas impairment of development in other tissue types was not obvious.[23] The null mutation of the LMO2 gene led to the disturbance of yolk sac erythropoiesis and the loss of definitive hematopoiesis in mice.[27,28] Compared with LMO2, LMO3 has a higher sequence similarity with LMO1. The LIM domain of LMO3 has 98% homology with LMO1. The expression patterns of LMO1 and LMO3 are also similar during mouse development, with both being highly expressed in specific areas of the brain but with little expression in lymphoid tissue.[23] Due to the high sequence identity in the LIM domain of LMO1 and LMO3, it is plausible to speculate that they may share interacting proteins and transcriptional targets. However, it was found that the expression levels of LMO1 and LMO3 appeared in different periods of the porcine fetus, suggesting that LMO1 and LMO3 may play different roles during development.[29]

LMO4 was first identified in gene expression array analyses conducted in breast cancer patients. LMO4 has been suggested to be important in the occurrence and development of breast cancer as an oncogene.[30,31] At the amino acid level, the homology of the LIM domains of LMO1 and LMO4 is only 55%. Similar to LMO2, LMO4 was also found to be widely expressed in a variety of mouse cells and tissues.[32] In the thymus, LMO4 was found to be expressed in both the adult thymus (mainly CD4+ CD8- T cells) and embryonic thymus (mainly CD4+CD8- T cells).[33] LMO4 was also found to be required for neural tube development.[34] Similar to LMO1, many questions regarding the function and mechanisms of action of LMO4 remain to be answered.

LMO proteins do not have DNA-binding activity; they can only mediate protein–protein interactions in transcriptional complexes. The diversity of interacting proteins of LMOs suggests that LMOs may control gene expression by regulating the formation of many transcriptional complexes. It was speculated that the similar structures of LMOs may cause them to bind to the same proteins to produce similar effects, and therefore, the LMOs can compensate for the functions of each other. For example, a study showed that combined null mutations of LMO1 and LMO3 led to perinatal fetal death in mice, while null mutations of any one of them did not cause this outcome,[35] suggesting that LMO1 and LMO3 can compensate each other to perform their functions in directing normal tissue development. However, full functional compensation between LMOs only occurs in some but not all circumstances. Studies have demonstrated that the depletion of a single LMO protein could lead to severe developmental defects in diseases. For example, LMO2-null mutant mice die on embryonic days 9 to 10.[10,27] Overall, although some biological functions of LMOs overlap, each LMO has its own unique protein interactome and performs certain unique functions, highlighting the importance of individually characterizing the functions and mechanisms of action of each LMO in future investigations.

**LMO1 in Blood Cancers**

The role of LMO1 in blood cancers was first characterized in T-ALL,[23] an invasive malignant blood cancer. Studies have indicated that activation of the LMO1 and LMO2 genes is among the main oncogenic mechanisms that drive the initiation and progression of T-ALL.[23] Since its first identification in T-ALL, LMO1 has been intensively investigated, and it was found that LMO1 forms an interplay network with multiple key oncogenic players in T-ALL, including TAL1/SCL,[36] lymphoblastic leukemia 1 (LYL1), LDB1, oligodendrocyte lineage transcription factor 2 (OLIG2), and NOTCH1[37] and coordinately drives the process of oncogenesis. More recently, LMO1 was found to contribute to the oncogenesis of other types of blood cancers, such as precursor T-cell lymphoblastic lymphoma/leukemia (pre-TLBL),[38] suggesting that LMO1 may have a universal oncogenic role in blood cancers.

**LMO1 gene alterations in human T-ALL**

An alteration in the LMO1 gene in T-ALL was first found in a T-ALL patient and the T-cell line RPMI8420 as a gene affected by a chromosomal translocation event that occurred between the T-cell receptor joining J6 segment (TCRδ) at 14q11 and 11p15.[39,40] The translocation splits the TCRδ locus and results in pathogenic activation of genes in the 11p15 locus, including LMO1.[41,42] The aberrant activation of LMO1 gene transcription is likely caused by truncation (ie, removal) of a promoter/control segment on the LMO1 gene that is normally involved in the transcriptional control of LMO1[2,22,43] Later, the activation of the LMO1 gene was found to be oncogenic in T-ALL.[20] Since then, many studies have demonstrated the oncogenic role of LMO1 in blood cancers.[16,38,44,46]

Single-nucleotide polymorphism (SNP) in LMO1 is another type of gene alteration of the LMO1 gene that was identified in ALL.[47] By genotyping, 672 tagged SNP sites located in 29 high-potential candidate genes in a sample of 163 ALL patients and 251 healthy control subjects who were Caucasian children, Beuten et al[47] discovered 15 SNPs in 15 genes that are associated with the risk of ALL. Further stratified analysis of ALL subtypes showed that the SNP rs442264 in the LMO1 locus was significantly associated with the risk of developing precursor-B-cell leukemia. Moreover, a major haplotype within LMO1 comprising 14 SNPs was found to significantly increase the risk of ALL.[47] Overall, these results suggest that SNPs within the LMO1 gene are important risk factors for ALL. Moreover, the identified SNPs of LMO1 were specifically associated with the B-lineage leukemia subtype but not with other types of
leukemia, indicating that the mechanisms of action of LMO1 (e.g., interacting proteins) in different subtypes of ALL might vary significantly. Future investigations are certainly warranted to investigate the clinical significance of subtype-specific genetic variations in the LMO1 gene.

**Investigations on the oncogenic role of LMO1 in both in vitro and in vivo T-ALL models**

To further characterize the carcinogenic role of LMO1 in T-ALL, researchers studied the effect of LMO1 on T-ALL development in LMO1 transgenic mice. McGuire et al. constructed an LMO1 transgenic mouse model by placing the LMO1 gene under the control of the lck proximal promoter. In this model, the abnormal expression of LMO1 specifically occurs in immature thymocytes. They found that the thymus and spleen of LMO1 transgenic mice were significantly enlarged, that transgenic mice frequently developed immature, aggressive T-cell leukemia/lymphomas, and that tumor incidence was proportionally larger than the level of LMO1 expression. They further found that the tumors from these mice were usually composed of immature CD4−CD8+ and CD4+CD8+ T cells. In the premalignant state, the thymuses and spleens of the LMO1 transgenic mice were significantly larger than those in the control mice. Further examination showed that transgenic thymuses contained 24% more cells than the control mice and that the percentage of thymocytes in the S phase and G2/M phases of the cell cycle was consistently higher than that of normal thymocytes. However, the percentage of each CD4−CD8+ cell subset in the transgenic mice did not differ from that in the control, suggesting that LMO1 overexpression increases thymocyte numbers at all stages of development. These results together suggest that LMO1 overexpression increases either the proliferation or survival of thymocytes without significantly interfering with the orderly progression of T cell maturation and cell function before driving thymocytes into oncogenic transformation.

Subsequently, the TAL1/SCL and LMO1 double transgenic mouse model was studied, which showed that TAL1/SCL and LMO1 might have synergistic effects on T-ALL occurrence. The TAL1/SCL-LMO1 double transgenic mice develop T-ALL with a short latency of 3 months, which greatly shortens the incubation period for T-ALL occurrence compared with TAL1/SCL or LMO1 single transgenic mice. In addition, the TAL1/SCL-LMO1 mice showed significant premalignant developmental abnormalities in terms of thymocyte number, immunophenotype, cell proliferation, clonality, and thymic architecture compared with those in the other three genotypic groups: the two single transgenic groups and the non-transgenic group. At 4 weeks of age, TAL1/SCL-LMO1 double-transgenic mice showed 70% fewer total thymocytes, and thymocytes had increased rates of both proliferation and apoptosis. At this stage, the clonal populations of thymocytes in TAL1/SCL-LMO1 mice were also different from those in the other three genotypic groups, showing a significant decrease in the number of CD4−CD8+ thymocytes and an increase in the number of CD4+CD8+ thymocytes relative to single transgenic mice or non-transgenic mice. In addition, the number of immature CD4+CD25− cells dramatically increased in TAL1/SCL-LMO1 mice compared with those in single transgenic mice or normal mice. Altogether, this study indicates that the LMO1 gene cooperates with TAL1/SCL to promote the development of T-ALL and that cooperation of TAL1/SCL with LMO1 is also critically important for normal thymus development.

**The mechanism of action of LMO1 in blood cancers**

As introduced above, due to the lack of inherent DNA-binding activity, LMO1 regulates target gene transcription by forming complexes with other transcriptional factors. Studies conducted in blood cancers have identified multiple transcriptional complexes associated with LMO1 [Figure 2]. LMO1 may change the gene expression pattern by affecting the balance of proteins in transcriptional complexes. A study conducted in Jurkat T-ALL cells showed that the transcriptional activity of LMO1 and LMO2 was achieved by forming a transcriptional complex with a group of unique bHLH proteins that share exceptional homology in their bHLH sequences, which include TAL1/SCL, T-cell acute lymphocytic leukemia 2 (TAL2), and LYL1. These interactions are mediated by the binding of the LIM domains in LMO1 and LMO2 to the bHLH sequences in the bHLH proteins. The LIM–bHLH interactions were found to be highly specific to this group of bHLH proteins since LMO1 and LMO2 did not interact with other bHLH proteins such as E12 and MYC. The oncogenic role of the interaction between TAL1/SCL and LMO1 was verified in in vitro studies. Mice with transgenic co-overexpression of LMO1 and TAL1/SCL in the thymus developed aggressive T-cell leukemia/lymphoma with a high degree of penetrance, generally within 6 months. However, mice transgenic for LMO1 alone or TAL1/SCL alone only occasionally developed T-ALL and had a much longer incubation period for T-ALL development, with none of the mice developing the disease within 6 months. The direct interaction between TAL1/SCL and LMO1 was confirmed in an additional study conducted by Gerby et al. By the double transgenic expression of TAL1/SCL and LMO1 in mice, the authors found that the direct TAL1/SCL-LMO1 interaction could activate the transcription of the self-renewal program in thymocytes. They further found that LYL1 could substitute for TAL1/SCL to reprogram thymocytes in concert with LMO1. Intriguingly, this study also showed that NOTCH1 acted as a strong enhancer of TAL1/SCL-LMO1 self-renewal activity but lacked intrinsic reprogramming activity in the absence of the oncogenic transcription factors TAL1/SCL, LMO1, and LYL1. These findings together demonstrated that the function of LMO1 in regulating the self-renewal of thymocytes required coordinative interactions with TAL1/SCL, LYL1, and NOTCH1. Further investigations are needed to elucidate the molecular mechanism by which NOTCH1 participates in this self-renewal signaling network.

Additional mechanisms underlying TAL1/SCL-LMO1 oncogenic signaling have been discovered. A study revealed a significant negative correlation of nuclear factor-κB1 (NF-κB1) with TAL1/SCL and LMO1 expression in primary human TAL1/SCL-LMO1 double-positive T-ALL samples, suggesting that NF-κB1 is a downstream transcriptional
target of \textit{TAL1/SCL-LMO1} mediating the oncogenic function of \textit{TAL1/SCL-LMO1} \[50\]. However, the function of \textit{TAL1/SCL-LMO1} in regulating \textit{NF-κB1} expression needs to be confirmed experimentally in \textit{in vitro} and/or \textit{in vivo} studies. In a study aimed at examining the cellular and molecular targets of the \textit{TAL1/SCL-LMO1} complex at the preleukemic stage, the authors found that maturation of primitive thymocytes to the pre-T cell stage was associated with the downregulation of \textit{TAL1/SCL}, \textit{LMO1}, and \textit{LMO2} and the concomitant upregulation of the expression of two bHLH proteins, \textit{E2A} and \textit{HEB}. \[16\] This finding suggested the function of the \textit{TAL1/SCL-LMO1} complex in regulating T-cell differentiation since both \textit{HEB} and \textit{E2A} have been well demonstrated to be important players in T cell differentiation during development. \[51,52\] Indeed, the authors further showed that enforced expression of \textit{TAL1/SCL} and \textit{LMO1} recapitulated a loss of \textit{HEB} function and inhibited T cell differentiation. \[16\] Together, these results suggest that \textit{E2A} and \textit{HEB} are two important downstream effectors that mediate the function of the \textit{TAL1/SCL-LMO1} complex in T cell differentiation and T-ALL development. \[16\] Another study showed that \textit{TAL1/SCL-LMO1} double transgenic mice had decreased expression of \textit{P16INK4A} upon the development of leukemia. Forced expression of \textit{P16INK4A} in thymocytes of these mice drastically reduced T-cell differentiation and blocked leukemogenesis in the majority of the mice. These findings strongly suggest that the downregulation of \textit{P16INK4A} expression is an important player in \textit{TAL1/SCL-LMO1}-directed leukemogenesis pathways. \[53\]

\textit{OLIG2} is another bHLH transcription factor that has been identified to participate in oncogenic pathways together with \textit{LMO1}. \[38\] This study showed that nearly 60\% of the transgenic mice that ectopically overexpressed both \textit{OLIG2} and \textit{LMO1} in the thymus developed pre-TLBL with large thymic tumor masses, whereas overexpression of \textit{OLIG2} alone was only weakly oncogenic, with only 2 of 85 mice developing pre-TLBL. \[38\] However, the physical interaction between \textit{LMO1} and \textit{OLIG2} was not investigated in this study. Interestingly, gene expression profiling analysis conducted in this study showed that \textit{NOTCH1} as well as Deltex1 (\textit{DTX1}) and pre-T-cell antigen receptor A (\textit{PTCRA}), the two genes downstream of \textit{NOTCH1}, were upregulated in thymic tumors. \[38\] The proliferation of leukemia cell lines established from \textit{OLIG2-LMO1} transgenic mice was inhibited by inhibitors of γ-secretase, a protease complex required for the proteolytic processing of \textit{NOTCH1}, further demonstrating that \textit{NOTCH1} plays an important role in mediating the function of \textit{OLIG2-
Moreover, thymocytes from clinically healthy TAL1/SCL-LMO1 mice aged 5 weeks did not have NOTCH1 mutations, whereas thymocytes from clinically healthy TAL1/SCL-LMO1 mice aged 8–12 weeks gained NOTCH1 mutations and formed tumors upon transplantation into nude mice. These results suggest that concurrent overexpression of TAL1/SCL and LMO1 is sufficient to induce genetic instability, at least within the NOTCH1 gene sequence. The findings of the involvement of NOTCH1 and its downstream proteins in multiple independent studies conducted in TAL1/SCL-LMO1 transgenic mice strongly support that NOTCH1 signaling functions as a critical downstream effector in mediating the oncogenic mechanisms of LMO1-associated transcriptional complexes.

Aside from binding with bHLH transcription factors, additional protein-binding partners of LMO1 have been identified. For example, LMO1 was found to form a heterodimer with LDB1. The LMO1-LDB1 interaction is likely to be involved in tumorigenesis after LMO1 is ectopically expressed in T cells. The importance of the LMO1-LDB1 interaction in oncogenesis needs to be further characterized in the future.

**LMO1 and Neuroblastoma**

Neuroblastoma is a childhood cancer of the sympathetic nervous system that accounts for approximately 10% of all pediatric oncology deaths. Although LMO1 was first found in the chromosomal translocation of T-ALL cells, it was subsequently found to play an important role in the development of the nervous system, suggesting that LMO1 is sufficient to induce genetic instability, at least within the NOTCH1 gene sequence. The findings of the involvement of NOTCH1 and its downstream proteins in multiple independent studies conducted in TAL1/SCL-LMO1 transgenic mice strongly support that NOTCH1 signaling functions as a critical downstream effector in mediating the oncogenic mechanisms of LMO1-associated transcriptional complexes.

**SNPs in LMO1 associated with the susceptibility to neuroblastoma**

Genome-wide association study (GWAS) is a powerful tool to identify disease-related genomic loci, and GWAS is widely used to explore the genetic mechanisms of diseases, including cancer. In 2008, Maris et al.[3] performed a GWAS to the study of neuroblastoma in individuals of European descent for the first time. They found that a genetic variant at chromosome band 6p22 is associated with susceptibility to neuroblastoma. Since then, multiple GWASs on neuroblastoma have identified that SNPs in several genes are associated with the risk of developing neuroblastoma.[3,59-61] LMO1 was one of the genes identified in these studies. The LMO1 SNPs identified in neuroblastoma are collectively summarized in Table 1.

| LMO1 SNP | Risk allele | Non-risk allele | Nucleotide position | Location | Population | Reference |
|----------|-------------|-----------------|---------------------|----------|------------|-----------|
| rs110419 | A           | G               | 8231306             | Intron 1 | Italian, British, and European American | [3]       |
|          |             |                 |                     |          | Italian and European American           | [59]      |
|          |             |                 |                     |          | Chinese children                          | [62]      |
|          |             |                 |                     |          | Southern Chinese children                 | [63]      |
|          |             |                 |                     |          | Chinese children                          | [64]      |
|          |             |                 |                     |          | Eastern Chinese children                  | [65]      |
| rs4758051| G           | A               | 8217092             | 3’ UTR   | Italian, British, and European American   | [3]       |
|          |             |                 |                     |          | Chinese children                          | [64]      |
|          |             |                 |                     |          | Eastern Chinese children                  | [65]      |
| rs10840002| A           | G               | 8221479             | 3’ UTR   | British and European American             | [3]       |
|          |             |                 |                     |          | Chinese children                          | [64]      |
|          |             |                 |                     |          | Eastern Chinese children                  | [65]      |
| rs2168101| G           | T               | 8233861             | Intron 1 | Italian, British, and European American   | [3]       |
|          |             |                 |                     |          | Eastern Chinese children                  | [66]      |
|          |             |                 |                     |          | Northern and southern Chinese children    | [67]      |
| rs204926 | C           | T               | 8255106             | Intron 1 | Chinese children                          | [62]      |
| rs110420 | T           | C               | 8253049             | Intron 1 | Chinese children                          | [62]      |
| rs3750952| G           | C               | 8230374             | Exon 2   | Northern and southern Chinese children    | [67]      |
| rs204938 | C           | T               | 8256650             | Intron 1 | British and European American             | [3]       |

3’ UTR: 3’ untranslated coding region; LMO1: LIM domain only 1; SNP: Single-nucleotide polymorphism.
on 2231 patients and 6097 cancer-free control subjects of European descent and included four case series (the Discovery case and the subsequent US, UK, and Italian replications). A total of 1627 neuroblastoma patients and 3254 genetically matched control subjects were genotyped in the Discovery case, and four SNPs (rs110419, rs4758051, rs10840002, and rs204938) in the LMO1 locus were found to be significantly associated with neuroblastoma ($P < 1 \times 10^{-4}$). The US and UK replications were performed by genotyping all four SNPs, while the Italian replication genotyped the two most significant LMO1 SNPs (rs110419 and rs4758051). These three replications draw similar conclusions as those in the Discovery case. Combined analysis indicated that the LMO1 polymorphism rs110419 A$>$G was strongly related to a reduced risk of neuroblastoma development. Given that the LMO1 SNP has been enriched in a subgroup of patients with more aggressive diseases, this research group further analyzed the alterations in genomic DNA copy number in 701 patients with primary tumors, and they found that the risk allele A in rs110419 increased LMO1 expression in neuroblastoma primary tumors and increased the risk of developing the more aggressive disease.\(^{[3]}\) Later, a study of 370 neuroblastoma patients and 809 control subjects of Italian ancestry and an additional dataset of 1627 patients with European ancestry and 2575 children of cancer-free Caucasian ancestry were analyzed by Capasso et al.\(^{[39]}\) A total of 14 SNPs were assessed, including 2 SNPs at the LMO1 locus (rs110419 and rs4758051), to detect their association with neuroblastoma risk. Only rs110419 was found to have a significant association with neuroblastoma susceptibility. Lu et al.\(^{[62]}\) studied 127 SNPs in nine target genes in 244 Chinese neuroblastoma patients and 305 healthy control subjects. Among the 21 SNPs associated with neuroblastoma susceptibility at the two-sided $P < 0.05$ level, 11 SNPs were located in the LMO1 locus, in which only rs204926 was the most significantly different after multiple corrections. However, they found that a major haplotype, which contains rs110419, rs204926, and rs110420, had a positive correlation with neuroblastoma. Later, a study was conducted by He et al.\(^{[63]}\) in southern Chinese children. Four LMO1 SNPs (rs110419 A$>$G, rs4758051 G$>$A, rs10840002 A$>$G, and rs204938 A$>$G) were genotyped in 256 neuroblastoma patients and 331 control subjects. Only LMO1 gene rs110419 A$>$G was found to have a protective effect against neuroblastoma. Zhang et al.\(^{[64]}\) performed another small sample test containing 118 neuroblastoma patients and 281 control subjects in northern Chinese children. They found that rs110419 A$>$G, rs4758051 G$>$A, and rs10840002 A$>$G were associated with decreased neuroblastoma risk. He et al.\(^{[65]}\) conducted a three-center case-control study in eastern Chinese children. Five SNPs were genotyped in 313 patients and 716 cancer-free controls to evaluate the association of five LMO1 SNPs (rs110419 A$>$G, rs4758051 G$>$A, rs10840002 A$>$G, rs204938 A$>$G, and rs2168101 G$>$T) with neuroblastoma risk. Four of five polymorphisms (rs110419 A$>$G, rs4758051 G$>$A, rs10840002 A$>$G, and rs2168101 G$>$T) were found to significantly reduce neuroblastoma risk. Overall, based on the available data, the LMO1 rs110419 A$>$G variant was the most common genetic variation that occurred in the LMO1 locus in neuroblastoma patients. However, the study reported by Latorre et al.\(^{[66]}\) in African Americans, which investigated 390 neuroblastoma patients and 2500 control subjects, did not find an association of this polymorphism with susceptibility to neuroblastoma, which suggests that ethnic differences might be a vital factor in the relationship between SNPs and neuroblastoma susceptibility.

\textbf{rs4758051 and rs10840002}

These two SNPs are located at the 3’ untranslated coding region (3’ UTR) of LMO1 mRNA. rs4758051 G$>$A and rs10840002 A$>$G were first discovered by Wang et al.\(^{[3]}\) to be associated with decreased neuroblastoma risk. Zhang et al.\(^{[64]}\) and He et al.\(^{[63]}\) then verified the role of these two SNPs in reducing neuroblastoma risk in northern and eastern Chinese children. Although there are many subsequent studies involving these two SNPs,\(^{[59,60,62,63,66]}\) only the three studies mentioned above have shown a significant correlation of these two SNPs with neuroblastoma susceptibility. Therefore, the significance of these two SNPs in determining neuroblastoma susceptibility needs to be further evaluated.

\textbf{rs2168101}

This SNP was first reported by Oldridge et al.\(^{[66]}\) in 2015. Three case series [European American (Americans of European ancestry), Italian, and British] identified that rs2168101 G$>$T was associated with reduced neuroblastoma susceptibility.\(^{[66]}\) However, this association was not identified in the African-American patients.\(^{[66]}\) The risk allele G is involved in a conserved GATA transcription factor binding motif. The polymorphism rs2168101 G$>$T changed “GATA” to “TATA,” which destroyed the binding motif and led to decreased LMO1 expression.\(^{[66]}\) Studies by He et al.\(^{[63]}\) and He et al.\(^{[67]}\) in Chinese subpopulations further supported the above findings. He et al.\(^{[67]}\) genotyped five polymorphisms (rs2168101 G$>$T, rs1042359 A$>$G, rs11041838 G$>$C, rs2071458 C$>$A, and rs3750952 G$>$C) in the LMO1 locus in two Chinese populations. They confirmed that rs2168101 G$>$T was significantly associated with decreased neuroblastoma susceptibility. These studies revealed that disruption of the transcription factor binding site caused by polymorphisms might be an important oncogenesis mechanism in neuroblastoma.

\textbf{rs204926, rs110420, and rs3750952}

rs204926 C$>$T and rs110420 T$>$C were identified to be significantly associated with reduced neuroblastoma susceptibility by Lu et al.\(^{[62]}\) in Chinese children in 2015. The association of rs3750952 G$>$C with reduced neuroblastoma susceptibility was found in northern and southern Chinese populations by He et al.\(^{[67]}\). However, the association between these variations and neuroblastoma susceptibility has not been identified in other ethnic populations to date.

\textbf{rs204938}

Contradictory results were observed for this SNP. rs204938 T$>$C was first reported by Wang et al.\(^{[3]}\) to be
associated with increased susceptibility to neuroblastoma in the British and European American populations. Interestingly, other studies involving rs204938 did not observe this association in either the Chinese or African American populations. A recent meta-analysis performed by Hashemi et al. in 2020 confirmed most of the results on LMO1 SNPs from previous studies. They reported that the LMO1 polymorphisms rs110419 A>G, rs4758051 G>A, rs10840002 A>G, rs2168101 G>T, and rs204938 C>T were associated with decreased susceptibility to neuroblastoma.

Overall, current findings have supported that polymorphisms within the LMO1 gene region are a strong factor associated with susceptibility to neuroblastoma. Some SNPs, such as rs110419, are consistently associated with neuroblastoma susceptibility in multiple populations, strongly supporting their critical role in determining neuroblastoma susceptibility. The value of these SNPs in clinical diagnosis is certainly worth exploring in the future. On the other hand, some SNPs are associated with neuroblastoma susceptibility in just a single ethnic population. These SNPs need to be further investigated in the future.

**The oncogenic mechanism of LMO1 in neuroblastoma**

The genetic variations of LMO1 are not only related to the tendency to develop neuroblastoma but also closely related to the occurrence of high-risk diseases (metastasis, advanced age, and poor pathological tumor grade). The mechanisms underlying the oncogenic function of LMO1 in neuroblastoma have been investigated by several research groups. The findings are summarized in Figure 3. Zhu et al. proved the critical role of MYCN in the LMO1 oncogenic cascade in vivo for the first time by establishing a zebrafish neuroblastoma model. They found that transgenic coexpression of MYCN and LMO1 in zebrafish resulted in widespread tumor masses in multiple regions, which were not observed in transgenic zebrafish [MYCN-only or MYCN-ALK (anaplastic lymphoma kinase) double transgenic overexpression]. These results indicated that LMO1 has a strikingly strong synergistic impact in potentiating the oncogenic function of MYCN. To identify key genes affected by LMO1 overexpression, RNA sequencing was used to compare the global gene expression profiles in BE(2)-C cells expressing LMO1 to cells transfected with a control vector. The LMO1-expressing cells showed enrichment for a gene signature encoding “matrisome-associated proteins,” which consist of structural extracellular matrix (ECM) proteins and ECM-associated enzymes, as well as for the related gene signatures “ECM regulators” and “integrins.” Among these enriched genes, increased expression of lysyl oxidase-like 3 (LOXL3), integrin-α2b (ITGA2B), integrin-α3 (ITGA3), and integrin-α5 (ITGA5) was further validated by RT-PCR in BE(2)-C cells overexpressing LMO1. These representative genes were also upregulated in neuroblastomas cells overexpressing both LMO1 and MYCN relative to those expressing MYCN alone. Among the upregulated ECM-associated genes, those in the LOX family encode enzymes that crosslink collagen. It was found that both the number and thickness of the picrosirius red-stained collagen fibers were significantly increased in tumors from animals co-expressing MYCN and LMO1 compared with the tumors from animals expressing MYCN alone. Furthermore, treatment of LMO1-expressing BE(2)-C cells with the LOX enzyme inhibitor β-aminopropionitrile significantly reduced the invasion of LMO1-expressing BE(2)-C cells. Therefore, these findings support that members of the LOX family are critical downstream targets for a gene signature encoding “matrisome-associated proteins,” which consist of structural extracellular matrix (ECM) proteins and ECM-associated enzymes, as well as for the related gene signatures “ECM regulators” and “integrins.” Among these enriched genes, increased expression of lysyl oxidase-like 3 (LOXL3), integrin-α2b (ITGA2B), integrin-α3 (ITGA3), and integrin-α5 (ITGA5) was further validated by RT-PCR in BE(2)-C cells overexpressing LMO1. These representative genes were also upregulated in neuroblastomas cells overexpressing both LMO1 and MYCN relative to those expressing MYCN alone. Among the upregulated ECM-associated genes, those in the LOX family encode enzymes that crosslink collagen. It was found that both the number and thickness of the picrosirius red-stained collagen fibers were significantly increased in tumors from animals co-expressing MYCN and LMO1 compared with the tumors from animals expressing MYCN alone. Furthermore, treatment of LMO1-expressing BE(2)-C cells with the LOX enzyme inhibitor β-aminopropionitrile significantly reduced the invasion of LMO1-expressing BE(2)-C cells. Therefore, these findings support that members of the LOX family are critical downstream targets.
of LMO1, which contribute to metastasis in neuroblastoma by promoting tumor cell invasion and migration.

Subsequently, it was found that ASCL1, a bHLH transcription factor, is a high confidence target gene downstream of LMO1 and MYCN in neuroblastoma cells.\[57\] Using ChIP-seq analysis, the authors found that LMO1, GATA3, and MYCN, which are members of the adrenergic neuroblastoma core transcriptional regulatory circuitry (CRC), occupied the transcription regulatory element of ASCL1 in the neuroblastoma cell line KELLY\[57\] and that the same loci were associated with element of ASCL1 circuitry (CRC), occupied the transcription regulatory adrenergic neuroblastoma core transcriptional regulatory LMO1 transcription factor, is a high con... LMO1 expression of miR-3648.\[74\] However, there is no suf... LMO1 expression to drive the overexpression of LMO1 in T-ALL. For example, a study reported that a C-to-T single-nucleotide transition upstream of the LMO1 transcriptional start site from patients with T-ALL created a MYB-binding motif of LMO1, leading to the formation of an aberrant transcriptional enhancer complex comprising GATA3, runt-related transcription factor 1 (RUNX1), SCL, and LMO1. This aberrant transcriptional enhancer complex drives the overexpression of LMO1.\[55\] Although the gain of LMO1 function to oncogenic level was first identified to be associated with genetic variations, overexpression of LMO1 occurs in approximately 50% of human T-ALL patients in the absence of any known mutations in its locus,\[122\] indicating that there are additional regulatory mechanisms other than genetic mutations that can increase the expression of LMO1. Transcriptional regulation of LMO1 expression has been investigated. Oram et al\[23\] found that LMO1 has two promoters that drive the expression of LMO1. They observed that both promoters were able to drive reporter gene expression in transgenic mice. The promoters display chromatin modification marks in multiple blood cells, including T cells. The promoters have a 3′ flanking enhancer region, which is the binding site of TAL1/SCL and GATA3, to enhance LMO1 expression [Figure 4B]. Therefore, the authors speculated that the ectopic transcriptional activation of LMO1 expression that contributes to T-ALL oncogenesis involves both a breakdown of epigenetic repression in the chromatin modification site and the binding of TAL1/SCL and/or GATA3 to the enhancer.

A regulatory pathway of LMO1 expression that involves microRNA let-7 and fibroblast growth factor (FGF) was established.\[76\] In this study, Wang et al\[76\] found that FGF regulated the expression of let-7 through FGF receptor substrate 2 (FRS2); let-7 subsequently suppresses the expression of transforming growth factor-beta receptor 1 (TGFβRI) by directly targeting the 3′ UTR of TGFβRI. These findings are consistent with the results from a separate study conducted in human umbilical artery endothelial cells.\[77\] Wang et al further investigated the downstream targets of TGF-β1/TGFβRI signaling and found that the expression levels of TGFβRI and LMO1 were decreased after treating neuroblastoma cells with the let-7c mimic and that their expression levels were increased when cells were transfected with the let-7 inhibitor. Based on these results, they speculated that let-7 functioned as an indirect repressor of LMO1 expression by directly inhibiting TGF-β1/TGFβRI signaling through a let-7 target site in the 3′ UTR of TGFβRI. Interestingly, they found that decreased let-7 expression upregulated the expression of both LMO1 and MYCN, while knocking down TGFβRI...

Mechanisms that Regulate LMO1 Expression and Function

As reviewed above, genetic variation has been identified as a very common mechanism that results in the gain-of-function of LMO1 in cancers. Genetic variations either raise the expression level of the LMO1 protein or lead to a mutated LMO1 protein with enhanced protein-binding and transcriptional activity, both of which could increase the LMO1 function to a pathological level that leads to malignant transformation.\[35\] Increased LMO1 expression level can be caused by the gain of the LMO1 gene copy number. For example, in a study of 701 neuroblastoma specimens, it was found that an increased copy number of the LMO1 gene locus was found in 12.4% of neuroblastoma tumors and that this event was associated with more advanced disease and poor survival.\[33\] SNPs have been one of the most common genetic variations that have been identified to drive the overexpression of LMO1 in T-ALL. For example, a study reported that a C-to-T single-nucleotide transition upstream of the LMO1 transcriptional start site from patients with T-ALL created a MYB-binding motif of LMO1, leading to the formation of an aberrant transcriptional enhancer complex comprising GATA3, runt-related transcription factor 1 (RUNX1), SCL, and LMO1. This aberrant transcriptional enhancer complex drives the overexpression of LMO1.\[55\] Although the gain of LMO1 function to oncogenic level was first identified to be associated with genetic variations, overexpression of LMO1 occurs in approximately 50% of human T-ALL patients in the absence of any known mutations in its locus,\[122\] indicating that there are additional regulatory mechanisms other than genetic mutations that can increase the expression of LMO1. Transcriptional regulation of LMO1 expression has been investigated. Oram et al\[23\] found that LMO1 has two promoters that drive the expression of LMO1. They observed that both promoters were able to drive reporter gene expression in transgenic mice. The promoters display chromatin modification marks in multiple blood cells, including T cells. The promoters have a 3′ flanking enhancer region, which is the binding site of TAL1/SCL and GATA3, to enhance LMO1 expression [Figure 4B]. Therefore, the authors speculated that the ectopic transcriptional activation of LMO1 expression that contributes to T-ALL oncogenesis involves both a breakdown of epigenetic repression in the chromatin modification site and the binding of TAL1/SCL and/or GATA3 to the enhancer.

A regulatory pathway of LMO1 expression that involves microRNA let-7 and fibroblast growth factor (FGF) was established.\[76\] In this study, Wang et al\[76\] found that FGF regulated the expression of let-7 through FGF receptor substrate 2 (FRS2); let-7 subsequently suppresses the expression of transforming growth factor-beta receptor 1 (TGFβRI) by directly targeting the 3′ UTR of TGFβRI. These findings are consistent with the results from a separate study conducted in human umbilical artery endothelial cells.\[77\] Wang et al further investigated the downstream targets of TGF-β1/TGFβRI signaling and found that the expression levels of TGFβRI and LMO1 were decreased after treating neuroblastoma cells with the let-7c mimic and that their expression levels were increased when cells were transfected with the let-7 inhibitor. Based on these results, they speculated that let-7 functioned as an indirect repressor of LMO1 expression by directly inhibiting TGF-β1/TGFβRI signaling through a let-7 target site in the 3′ UTR of TGFβRI. Interestingly, they found that decreased let-7 expression upregulated the expression of both LMO1 and MYCN, while knocking down TGFβRI...
only decreased the expression of LMO1, suggesting that MYCN is regulated by let-7 through a separate mechanism independent of the TGF-β/TGFβRI signaling pathway. Overall, this study establishes a novel mechanism that controls LMO1 expression in neuroblastoma cells. The disrupted balance of the elements in this pathway can cause the aberrant overexpression of both LMO1 and MYCN.

**LMO1 in Other Cancer Types**

Aside from its role in T-ALL and neuroblastoma, the oncogenic function of LMO1 is increasingly recognized in several other cancer types. The expression of LMO1 in human prostate cancer was found to be significantly higher than that in benign prostatic hyperplasia. In addition, the expression of LMO1 in poorly differentiated prostate cancer was found to be significantly higher than that in well-differentiated and moderately differentiated prostate cancer. These results suggest that the expression level of LMO1 is related to the severity of prostate cancer and that LMO1 may be a prognostic indicator and potential molecular target of prostate cancer. To understand its mechanisms of action in prostate cancer, the authors found that LMO1 may act as an androgen receptor (AR) coactivator by forming a complex with AR. The association of LMO1 with AR subsequently upregulates the expression of P21 and prostate-specific antigen (PSA). The AR-mediated upregulation of P21 and PSA expression has been demonstrated to play an important role in the progression of prostate cancer.

In the gastric cancer cell line MKN45, the expression of Bcl-2 decreased while Bax increased after knocking down LMO1. Bcl-2 plays an important role in the mitochondrial apoptosis pathway and can inhibit apoptosis. Bax, as a proapoptotic gene, can induce apoptosis when overexpressed. The effect of LMO1 knockdown on Bcl-2 and Bax expression therefore strongly suggests that LMO1 may play an important role in gastric cancer growth by regulating Bcl-2 and Bax. Additionally, Sun et al. found that the expression level of LMO1 in gastric cancer was significantly higher than that in adjacent tissues. Furthermore, the LMO1 protein was related to tumor stages and lymph node metastasis of gastric cancer and was regarded as an independent prognostic factor for gastric cancer.

LMO1 plays a role in reducing the responsiveness of patients to the EGFR tyrosine kinase inhibitor cetuximab in lung cancer and colorectal cancer. LMO1 expression was correlated with elevated AKT phosphorylation in non-small cell lung cancer and colorectal cancer, while AKT phosphorylation was required for the oncogenic effects of LMO1. The role of LMO1 in lung cancer was investigated in additional studies. LMO1 was found to be expressed at significantly higher levels in small cell lung cancer cells than in both non-small lung cancer cells and immortalized normal lung cells. The expression level of LMO1 mRNA was significantly correlated with the neuroendocrine differentiation of lung cancer, and a high tumor level of LMO1 mRNA was an independent predictor of poor patient survival. TTK/MPS1, a dual-specificity protein kinase with the ability to phosphorylate tyrosine, serine, and threonine residues which plays an important role in controlling centrosome duplication and accurate segregation of chromosomes during mitosis, acts as a downstream mediator of LMO1 function in lung cancer cells.

Liu et al. found that LMO1 gene polymorphisms may contribute to Wilms' tumor risk. Among the four SNPs
Similarly, another study performed by Li et al.\[83\] found that the LMO1 super-enhancer rs2168101 G>T polymorphism reduces the susceptibility to Wilms’ tumor, which is consistent with findings in neuroblastoma.\[67\] Therefore, these studies suggest that LMO1 is also an important contributor to the oncogenesis of Wilms’ tumor.

Overall, emerging evidence has strongly suggested that LMO1 is a universal oncogene that is involved in the oncogenesis of various types of cancers, highlighting the importance of further understanding this important oncogene in the future.

**Conclusion**

Because LMO1 itself has no direct DNA-binding activity, the transcriptional targetome of LMO1 is defined by its DNA-binding protein partners. It is known that the interactome of the LIM domain is large and diverse, which suggests that the actual transcriptome of LMO1 is likely to be far larger than what is currently recognized. In the future, the development of high-throughput approaches that can be used to systematically identify the LMO1 interactome and transcriptome would be the key to define the complete profile of proteins that interact with LMO1 and reveal the complete list of genes that are under the transcriptional control of LMO1. In addition, given the cellular context specificity that has been widely observed for many oncogenes and tumor suppressor genes, the LMO1 interactome and transcriptome should be investigated separately in each individual cancer type, which is essential for translating the laboratory findings on LMO1 to the diagnosis and treatment of each specific type of cancer.

The tissue-specific expression pattern of LMO1 has been shown in several studies.\[10,44,78,83\] However, since the transcriptional targets of LMO1 are determined by its direct DNA-binding partners, the actual tissue-specific transcriptional activity of LMO1 is expected to be additionally refined by the tissue-specific expression pattern of its binding partners. In the future, each of the LMO1-interaction factor complexes identified from cells needs to be further finely dissected for their transcriptional activity in different types of cancers by the combined investigation of the tissue-specific expression pattern of both LMO1 and its binding partners.

The epigenetic modulation of gene expression has been demonstrated to play an important role in tumorigenesis. However, there is still a lack of investigations into the epigenetic mechanisms that regulate LMO1 expression. On the other hand, the role of epigenetic modification of the LMO1 target sites, as determined by its binding partners, in determining the transcriptional activation of these genes by LMO1 should also be investigated.

Multiple SNPs of the LMO1 gene are related to the susceptibility to certain cancer types, especially in neuroblastoma, as reviewed above. SNPs are one of the common genetic mechanisms that contribute to tumorigenesis. Both SNPs that lead to loss of function of key tumor-suppressive genes and SNPs that cause a gain of functions of oncogenes are evidenced in cancers. Since the association of LMO1 SNPs with neuroblastoma and T-ALL has been observed, it is plausible to speculate that LMO1 SNPs contribute to other types of cancer, which warrants further investigations.

As reviewed above, the overexpression of LMO1 is significantly correlated with poor patient prognosis in several types of cancers, implicating the diagnostic value of LMO1. However, many questions need to be answered for applying LMO1 to clinical diagnosis. For example, more practical quantification approaches that can be used in clinical laboratories to examine new patients need to be developed. In addition, the quantitative cut-off value of LMO1 expression and the combination of this value with other well-established prognostic risk factors need to be established and validated in prospective studies.

Targeted therapy is the ultimate goal of cancer therapeutics. Targeted therapy allows precision treatment by targeting a specific cancer-driven oncogene or oncogenic mechanism and therefore can be personalized based on the expression level of the targeted gene. Progress has been made in the development of targeted drugs for LMO2 in T-ALL.\[88,89\] The strong ability of LMO1 to promote cell proliferation and metastasis, as well as the close relationship of LMO1 expression level with disease susceptibility and drug resistance, all suggest that LMO1 may be an effective target for cancer therapy. However, targeted therapy against LMO1 has not been successfully developed. This is because many aspects of LMO1, including its gene structure, protein structure, and regulatory mechanisms, have not been sufficiently understood. More directed investigations aimed at the potential niches for targeted therapy would help to accelerate the development of therapeutic approaches that target LMO1. For example, the development of small-molecule inhibitors of the LMO1 protein relies on the full characterization of the threedimensional structure of the LMO1 protein and identification of the potential small-molecule binding pockets on its surface.

The mechanisms of the oncogenic function of LMO1 need to be further investigated. Given the structural similarity of LMO proteins, many proteins found to interact with other LMOs are likely to functionally interact with LMO1. However, many of these proteins have not been investigated for their interactions with LMO1. For example, a study showed that the transcription factor forkhead box P3 (FOXP3), which is a known tumor suppressor in T cell leukemia, binds to LMO2, and reduces the possibility of its interaction with TAL1/SCL, resulting in a decrease in the transcriptional activity of the TAL1/SCL-LMO2 complex.\[90\] It remains to be explored whether FOXP3 interacts with LMO1.

Overall, the functions, mechanisms, regulations, and clinical applications of LMO1 in cancers warrant further investigations. Whether the knowledge gained on LMO1 can be translated into clinical applications and make a...
breakthrough to improve cancer patient survival and prognosis should be the focus of researchers and clinical doctors in future investigations.

Conflicts of interest
None.

References
1. Matthews JM, Lester K, Joseph S, Curtis DJ. LIM-domain-only proteins in cancer. Nat Rev Cancer 2013;13:111–122. doi: 10.1038/nrc3418.
2. Boehm T, Forloni L, Kaneko Y, Perutz MF, Rabbits TH. The rhombotin family of cysteine-rich LIM-domain oncogenes: Distinct members are involved in T-cell translocations to human chromosom es11p15 and 11p13. Proc Natl Acad Sci U S A 1991;88:4367–4371. doi: 10.1073/pnas.88.10.4367.
3. Wang K, Diskin SJ, Zhang H, Attiyeh EF, Winter C, Hou C, et al. Integrative genomics identifies LMO1 as a neuroblastoma oncogene. Nature 2011;469:216–220. doi: 10.1038/nature09609.
4. Aoyama M, Ozaki T, Inuzuka H, Tomotsune D, Hirato J, Okamoto et al. Bivalent promoter marks and a latent enhancer may prime the leukaemia oncogene LMO1 for ectopic expression in T-cell leukemia. Leukemia. 2014;28:1812–1820. doi: 10.1038/leu.2013.28.
5. Colasante G, Sessa A, Crisi S, Calogero R, Mansouri A, Collombat P, et al. LMO2 interacts with a regional key selector gene in the ventral telenencephalon mainly through its transcriptional repression activity. PLoS Biol 2009;7:53–61. doi: 10.1371/journal.pbio.0070053.
6. Yang J, Bane AS, Liu J, Lavenir I, Forster A, Aplan PD, Wu C, et al. The mechanism of chromosomal translocation t(11;14) involving the T-cell receptor C delta locus on human chromosome 14q11 and a transcribed region of chromosome 11p15. EMBO J 1998;7:385–394. doi: 10.1002/1460-2075.1998.tb02852.x.
7. Fulp CT, Cho G, Marsh ED, Nasrallah IM, Labosky PA, Golden JA. The LIM domain: Regulation by association. Mech Dev 1998;95:11257–1126. doi: 10.1016/s0925-4773(99)00314-7.
8. Ricevskis J, Dill A, Sparano JA, Ruan H. Molecular cloning of the LMO1 super-enhancer – a bivalent promoter that marks and primes the LMO1 super-enhancer LMO1–α subunit (α GSU) gene. Biosci Rep 2009;30:51 58. doi: 10.1007/s12032-011-9160-6.
9. Aoyama M, Ozaki T, Inuzuka H, Tomotsune D, Hirato J, Okamoto et al. Design, production and characterization of FLIN2 and FLIN4: LIM-domain-only proteins: Multifunctional nuclear transcription coregulators that interact with diverse proteins. Mol Biol Rep 2014;41:1075–1073. doi: 10.1007/s11033-013-2952-1.
10. Sun Y, Ma GJ, Hu XJ, Yin XY, Peng YH. Clinical significance of LMO1 in gastric cancer tissue and its association with apoptosis of cancer cells. Oncol Lett 2017;14:6511–6518. doi: 10.3892/ol.2017.7102.
11. Deane JE, Sum E, Mackay JP, Watanabe M, Vissvader JE, Matthews JM. Structural basis for the recognition of ldb1 by the N-terminal LIM domains of LMO2 and LMO4. EMBO J 2003;22:2224–2233. doi: 10.1093/emboj/cdg196.
12. Deane JE, Mackay JP, Kwan AYH, Sum EYM, Vissvader JE, Matthews JM. Functional characterization of FLIN2 and FLIN4: The engineering of intramolecular lbd1:LMO complexes. Protein Eng 2001;14:493–499. doi: 10.1093/protein/14.7.493.
13. Sum EYM, Segara D, Duscio B, Bath ML, Field AS, Sutherland RL, et al. Overexpression of LMO4 induces mammary hyperplasia, promotes cell invasion, and is a predictor of poor outcome in breast cancer. Proc Natl Acad Sci U S A 2003;102:7639–7664. doi: 10.1073/pnas.1221502.
14. Deane JE, Sum E, Mackay JP, Watanabe M, Vissvader JE, Matthews JM. Structural basis for the recognition of ldb1 by the N-terminal LIM domains of LMO2 and LMO4. EMBO J 2003;22:2224–2233. doi: 10.1093/emboj/cdg196.
15. Deane JE, Sum E, Mackay JP, Watanabe M, Vissvader JE, Matthews JM. Structural basis for the recognition of ldb1 by the N-terminal LIM domains of LMO2 and LMO4. EMBO J 2003;22:2224–2233. doi: 10.1093/emboj/cdg196.
16. Deane JE, Sum E, Mackay JP, Watanabe M, Vissvader JE, Matthews JM. Structural basis for the recognition of ldb1 by the N-terminal LIM domains of LMO2 and LMO4. EMBO J 2003;22:2224–2233. doi: 10.1093/emboj/cdg196.
malignancies in transgenic mice. EMBO J 1997;16:2408–2419. doi: 10.1093/emboj/16.9.2408.
37. Lin YW, Nichols RA, Letterio JJ, Aplan PD. Notch1 mutations are important for leukemic transformation in murine models of precursor-T leukemia/lymphoma. Blood 2006;107:2540–2543. doi: 10.1182/blood-2005-07-3013.
38. Lin YW, Deveney R, Barbara M, Iscove NN, Nimer SD, Slape C, et al. Olig2 (BHLHB1), a BHLH transcription factor, contributes to leukemogenesis in concert with LMO1. Cancer Res 2005;65:7151–7158. doi: 10.1158/0008-5472.CAN-05-1400.
39. Takasaki N, Maseki N, Shimamura K, Takayama S. Hemophagocytic syndrome complicating T-cell acute lymphoblastic leukemia with a novel (t11;14)(p15;q11) chromosome translocation. Cancer Res 1987;57:424–428. doi: 10.1126/cancerres.57.1.424.
40. Le Beau MM, McKeithan TW, Shima E, Goldman-Leikin RE, Chan AB 3rd, et al. Targeted disruption of TCF12 reveals HEB as essential in neuroblastoma. Cancer Res 2001;61:5925–5931. doi: 10.1158/0008-5472.CAN-01-0675.
41. Capasso M, Dishin SJ, Uñiga-Pérez A, Longo F, Longo I, De Marziano M, Russo R, et al. Replication of GNAS–identified neuroblastoma risk loci strengthens the role of BARD1 and affirms the cumulative effect of genetic variations on disease susceptibility. Carcinogenesis 2011;32:1349–1355. doi: 10.1093/carcin/bgr091.
42. Chevinsky DS, Zhao XF, Lam DH, Ellsworth M, Kwok GS, Aplan DP. Disordered T-cell development and T-cell malignancies in LMO1 null mice. Mol Cell Biol 1992;12:4186–4196. doi: 10.1128/MCB.12.8.4186.
43. Gerby B, Tremblay CS, Tremblay M, Raous-Sutterlin S, Herblot M, Hebert J, et al. SCL, LMO1 and Notch1 reprogram thymocytes into self-renewing cells. PLoS Genet 2014;10:e1004768. doi: 10.1371/journal.pgen.1004768.
44. Beuten J, Gelfond JL, Pwikkham D, Pollock BH, Winick NJ, Collier AB 3rd, et al. Candidate gene association analysis of acute lymphoblastic leukemia identifies new susceptibility loci at 11q15 (LMO1) and 20q13.3 (CARK). Cancer Res 2011;71:1349–1353. doi: 10.1158/0008-5472.CAN-10-2577.
45. Chervinsky DS, Zhao XF, Lam DH, Ellsworth M, Kwok GS, Aplan DP. Disordered T-cell development and T-cell malignancies in LMO1 null mice. Mol Cell Biol 1992;12:4186–4196. doi: 10.1128/MCB.12.8.4186.
46. Larson RC, Fisch P, Larson TA, Lavenir I, Langford T, King G, et al. T-cell tumors of disparate phenotype in mice transgenic for Rb–2. Oncogene 1994;9:3675–3681. doi: 10.1038/345673a0.
47. Zhang PY, Draheim K, Killeher MA, Miyamoto S, NFkB1 is a direct target of the TAL1 oncprotein in human T-cell lymphomas. Cancer Res 2006;66:6008–6013. doi: 10.1158/0008-5472.CAN-06-0194.
48. Li Y, Breuer PM, Singh J, Xioku S, Yoganathan K, Zúñiga-Pflucker JC, et al. Targeted disruption of TCF12 reveals HEB as essential in human mesodermal specification and hematopoiesis. Stem Cell Reports 2017;9:779–795. doi: 10.1016/j.stemcr.2017.07.011.
49. Yan W, Young AZ, Soares VC, Kelley R, Benezra R, Zhai J. High incidence of T-cell tumors in E2A-null mice and E2A/Ad1 double-knockout mice. Mol Cell Biol 1997;17:7317–7327. doi: 10.1128/MCB.17.12.7317.
50. Fasseu M, Aplan PD, Chopin M, Boissel N, Bories JC, Soulier J, et al. p16INK4A tumor suppressor gene expression and CD4(+) T-cell deficiency but not pre-TCR deficiency inhibit TAL1-linked T-lineage leukemogenesis. Blood 2007;110:2610–2619. doi: 10.1182/blood-2007-01-666209.
51. Pear WS, Aster JC. T cell acute lymphoblastic leukemia/lymphoma: a human cancer commonly associated with aberrant NOTCH1 signaling. Curr Opin Hematol 2004;11:426–433. doi: 10.1097/01.noh.0000043963.95081.73.
52. Wass WP, Ferrando AA, Lee W, Morris JP 4th, Silverman LB, Sanchez-Irizarry C, et al. Activating mutations of NOTCH1 in human T-cell acute lymphoblastic leukemia. Science 2004;306:2629–2631. doi: 10.1126/science.1102160.
53. Maris JM. Recent advances in neuroblastoma. N Engl J Med 2010;362:2202–2211. doi: 10.1056/NEJMra0907577.
54. Wang L, Tan TK, Durbin AD, Zimmerman MW, Abraham BJ, Tan SH, et al. ASCL1 is a MYCN- and LMO1-dependent member of the adrenergic neuroblastoma core regulatory circuitry. Nat Commun 2019;10:5622. doi: 10.1038/s41467-019-13155-5.
55. Maris JM, Mose YP, Bradford JP, Hou C, Monni S, Scott RH, et al. Chromosome 6p22 locus associated with clinically aggressive neuroblastoma. N Engl J Med 2008;358:2585–2593. doi: 10.1056/NEJMoa0708698.
74. Saeki N, Saito A, Sugaya Y, Amemiya M, Sasaki H. Indirect down-regulation of tumor-suppressive let-7 family MicroRNAs by LMO1 in neuroblastoma. Cancer Genomics Proteomics 2018;15:413–420. doi: 10.21873/cgp.20100.

75. Li Z, Abraham BJ, Berezovskaya A, Farah N, Liu Y, Leon T, et al. APOBEC signature mutation generates an oncogenic enhancer that drives LMO1 expression in T-ALL. Leukemia 2017;31:2057–2064. doi: 10.1038/leu.2017.75.

76. Wang XH, Wu HY, Gao J, Wang XH, Gao TH, Zhang SF. FGF represses metastasis of neuroblastoma regulated by MYCN and TGF-beta1 induced LMO1 via control of let-7 expression. Brain Res 2019;1704:219–228. doi: 10.1016/j.brainres.2018.10.015.

77. Chen PY, Qin L, Barnes C, Charisse K, Yi T, Zhang X, et al. FGF regulates TGF-beta signaling and endothelial-to-mesenchymal transition via control of let-7 miRNA expression. Cell Rep 2012;2:1684–1696. doi: 10.1016/j.celrep.2012.10.021.

78. Gu H, Liu T, Cai X, Tong Y, Li Y, Wang C, et al. Upregulated LMO1 in prostate cancer acts as a novel coactivator of the androgen receptor. Int J Oncol 2015;47:2181–2187. doi: 10.3892/ijo.2015.3195.

79. Gittes RF. Carcinoma of the prostate. N Engl J Med 1991;324:236–245. doi: 10.1056/NEJM199101243240406.

80. Omar EA, Behlouli H, Chevalier S, Aprikian AG. Relationship of p21(WAF-1) protein expression with prognosis in advanced prostate cancer treated by androgen ablation. Prostate 2001;49:191–199. doi: 10.1002/pros.1134.

81. Reddy TL, Garkapatra KR, Reddy SG, Reddy BV, Yadav JS, Bhadra U, et al. Simultaneous delivery of Pachtaxel and Bcl-2 siRNA via pH-Sensitive liposomal nanocarrier for the synergistic treatment of melanoma. Sci Rep 2016;6:35223. doi: 10.1038/srep35223.

82. Zhang Z, Wang H. lncRNA SNHG1 suppresses gastric cancer cell proliferation and promotes apoptosis via Notch1 pathway. J BUON 2020;25:302–307.

83. Du L, Zhao Z, Suraokar M, Shelton SS, Ma X, Hisao TH, et al. LMO1 functions as an oncogene by regulating TTK expression and correlates with neuroendocrine differentiation of lung cancer. Oncotarget 2018;9:29601–29618. doi: 10.18632/oncotarget.25642.

84. Xie Y, Wang A, Lin J, Wu L, Zhang H, Yang X, et al. Mps1/TTK: A novel target and biomarker for cancer. J Drug Target 2017;25:112–118. doi: 10.1080/1061186X.2016.1258568.

85. Mills GK, Schmandt R, McGill M, Amendola A, Hill M, Jacobs K, et al. Expression of TTK, a novel human protein kinase, is associated with cell proliferation. J Biol Chem 1992;267:16000–16006. doi: 10.1016/S0021-9258(19)49633-6.

86. Wang X, Yu H, Xu L, Zhu T, Zheng F, Fu C, et al. Dynamic autophosphorylation of mps1 kinase is required for faithful mitotic progression. PLoS One 2014;9:e104723. doi: 10.1371/journal.pone.0104723.

87. Liu GC, Zhao ZJ, Zhu SB, Zhu J, Jia W, Zhao Z, et al. Associations between LMO1 gene polymorphisms and Wilms’ tumor susceptibility. Oncotarget 2017;8:50665–50672. doi: 10.18632/oncotarget.16926.

88. Nam CH, Lobato MN, Appert A, Drynan LF, Tanaka T, Rabbitts TH. An antibody inhibitor of the LMO2-protein complex blocks its normal and tumorigenic functions. Oncogene 2008;27:4962–4968. doi: 10.1038/onc.2008.130.

89. Appert A, Nam CH, Lobato N, Priego E, Miguel RN, Blundell T, et al. Targeting LMO2 with a peptide aptamer establishes a necessary function in overt T-cell neoplasia. Cancer Res 2009;69:4784–4790. doi: 10.1158/0008-5472.CAN-08-4774.

90. Fleskens V, Mokry M, van der Leun AM, Huppelschoten S, Pals CEGM, Peeters J, et al. FOXF3 can modulate TAL1 transcriprional activity through interaction with LMO2. Oncogene 2016;35:4141–4148. doi: 10.1038/onc.2015.481.

How to cite this article: Zhao GF, Du LQ, Zhang L, Jia YC. LIM domain only 1: an oncogenic transcription cofactor contributing to the tumorigenesis of multiple cancer types. Chin Med J 2021;134(9). doi: 10.1097/CM9.0000000000001487