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

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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,[3,4] and the overexpression of *LMO4* is a marker of poor prognosis in breast cancer.[5] 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 TCRδ 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.[2,3] In later investigations, it was increasingly recognized that the *LMO1* gene plays an essential

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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.[7] *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* (*eg*, *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 Zn^{2+} 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]

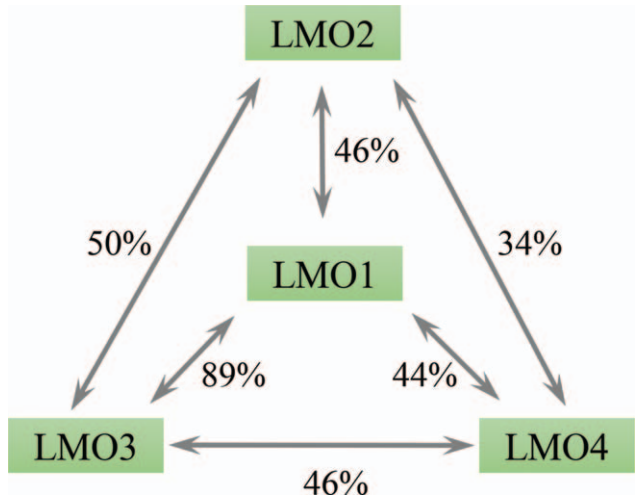

Figure 1: The pairwise sequence identity of LMO proteins. *LMO1*: LIM domain only 1; *LMO2*: LIM domain only 2; *LMO3*: LIM domain only 3; *LMO4*: LIM domain only 4.

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 Aristaless-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.[7] *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.[7] 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%.[2]*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.[27] 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.[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 Jδ 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* (*eg*, 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*[45] 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 proportional to 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.[48] 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 *TAL/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.[48] In addition, the number of immature $CD44^{+}$ $CD25^{-}$ cells dramatically increased in *TAL1/SCL-LMO1* mice compared with those in single transgenic mice or normal mice.[48] 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*.[28] These interactions are mediated by the binding of the LIM domains in *LMO1* and *LMO2* to the bHLH sequences in the bHLH proteins.[28] 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*.[28] The oncogenic role of the interplay between *TAL1/SCL* and *LMO1* was verified in *in vivo* 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.[36,48] 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.[36,48,49] The direct interaction between *TAL1/SCL* and *LMO1* was confirmed in an additional study conducted by Gerby *et al*[46]. 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*.[46] 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-κB 1 (*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

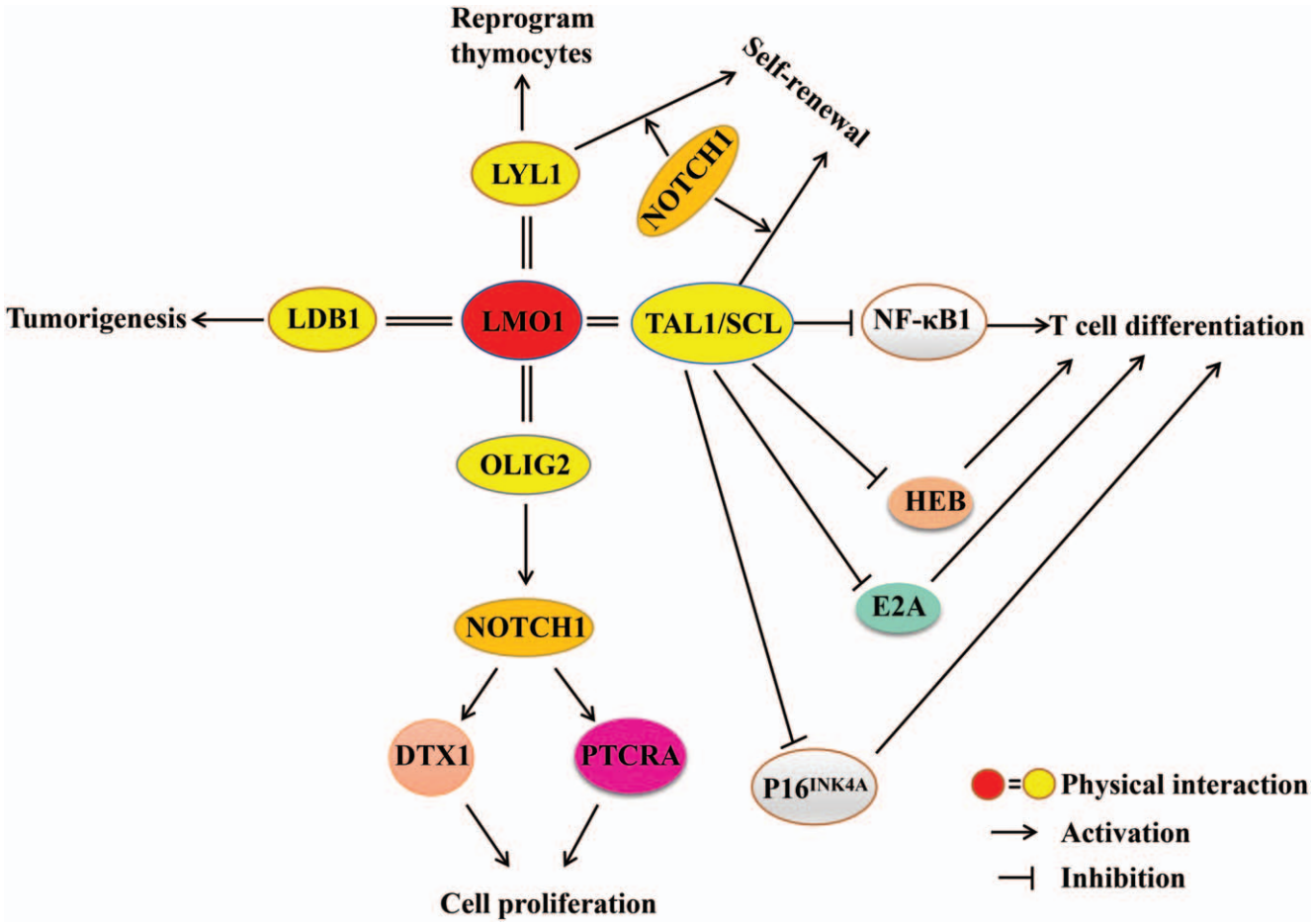

Figure 2: Interaction between *LMO1* and multiple transcription factors in blood cancers and their roles in tumorigenesis. *DTX1*: Deltex1; *LMO1*: LIM domain only 1; *LDB1*: LIM domain-binding protein 1; *LYL1*: Lymphoblastic leukemia 1; *NF-κB1*: Nuclear factor-κB 1; *OLIG2*: Oligodendrocyte lineage transcription factor 2; *PTCRA*: Pre-T-cell antigen receptor A; *SCL*: Stem cell leukemia protein; *TAL1*: T-cell acute lymphocytic leukemia 1.

target of *TAL1/SCL-LMO1* mediating the oncogenic function of *TAL1/SCL-LMO1*.[50] However, the function of *TAL1/SCL-LMO1* in regulating *NF-κB1* expression needs to be confirmed experimentally in *in vitro* and/or *in vivo* studies. In a study aimed at examining the cellular and molecular targets of the *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 *TAL1/SCL*, *LMO1*, and *LMO2* and the concomitant upregulation of the expression of two bHLH proteins, *E2A* and *HEB*.[16] This finding suggested the function of the *TAL1/SCL-LMO1* complex in regulating T-cell differentiation since both *HEB* and *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 *TAL1/SCL* and *LMO1* recapitulated a loss of *HEB* function and inhibited T cell differentiation.[16] Together, these results suggest that *E2A* and *HEB* are two important downstream effectors that mediate the function of the *TAL1/SCL-LMO1* complex in T cell differentiation and T-ALL development. Another study showed that *TAL1/SCL-LMO1* double transgenic mice had decreased expression of $P16^{INK4A}$ upon the development of leukemia. Forced expression of $P16^{INK4A}$ 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 $P16^{INK4A}$ expression is an important player in *TAL1/SCL-LMO1*-directed leukemogenesis pathways.[53]

OLIG2 is another bHLH transcription factor that has been identified to participate in oncogenic pathways together with *LMO1*.[38] This study showed that nearly 60% of the transgenic mice that ectopically overexpressed both *OLIG2* and *LMO1* in the thymus developed pre-TLBL with large thymic tumor masses, whereas overexpression of *OLIG2* alone was only weakly oncogenic, with only 2 of 85 mice developing pre-TLBL.[38] However, the physical interaction between *LMO1* and *OLIG2* was not investigated in this study. Interestingly, gene expression profiling analysis conducted in this study showed that *NOTCH1* as well as Deltex1 (*DTX1*) and pre-T-cell antigen receptor A (*PTCRA*), the two genes downstream of *NOTCH1*, were upregulated in thymic tumors.[38] The proliferation of leukemia cell lines established from *OLIG2-LMO1* transgenic mice was inhibited by inhibitors of γ-secretase, a protease complex required for the proteolytic processing of *NOTCH1*, further demonstrating that *NOTCH1* plays an important role in mediating the function of *OLIG2*-

LMO1.[38] 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.[54,55] 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*.[17] The *LMO1-LDB1* interaction is likely to be involved in tumorigenesis after *LMO1* is ectopically expressed in T cells.[17] 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.[56] 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,[21] suggesting that abnormal expression of *LMO1* in the nervous system may also play a critical role in the development of cancers with a neuronal origin, including neuroblastoma. Indeed, genetic variations in *LMO1* were found to be closely associated with susceptibility to neuroblastoma and the prognosis of neuroblastoma patients. Interestingly, current findings have suggested that *LMO1* may function as an oncogene in neuroblastoma through mechanisms distinct from those that have been defined in T-ALL. For example, although *LMO1* frequently co-occupies target loci with GATA-binding protein 3 (*GATA3*) in both neuroblastoma and T-ALL cells, there was little overlap of the genomic regions associated with the *LMO1-GATA3* complex between these two cancer types.[57] Similarly, the genes and pathways altered by *LMO1* knockdown in neuroblastoma cells are distinct from those in T-ALL cells.[57] We, therefore, review the findings of *LMO1* in neuroblastoma in a separate section.

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*[58] applied GWAS to the study of neuroblastoma in individuals of European descent for the first time. They found that a genetic variation 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.

rs110419

The rs110419 was first identified to be associated with neuroblastoma susceptibility at the first intron of *LMO1* by Wang *et al*[3] in 2011. In this study, GWAS was performed

Table 1: LMO1 SNPs identified in neuroblastoma.

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	[66]
					Eastern Chinese children	[65]
					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 2251 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*.[59] 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 531 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*[60] 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.

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*[65] 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.

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*[65] 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.

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.

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.[60,62-65] A recent meta-analysis performed by Hashemi *et al*[68] 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).[59,62,67] 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*[69] 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*.[69,70] 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.[69] 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.[69] 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.[69] Therefore, these findings support that members of the LOX family are critical downstream targets

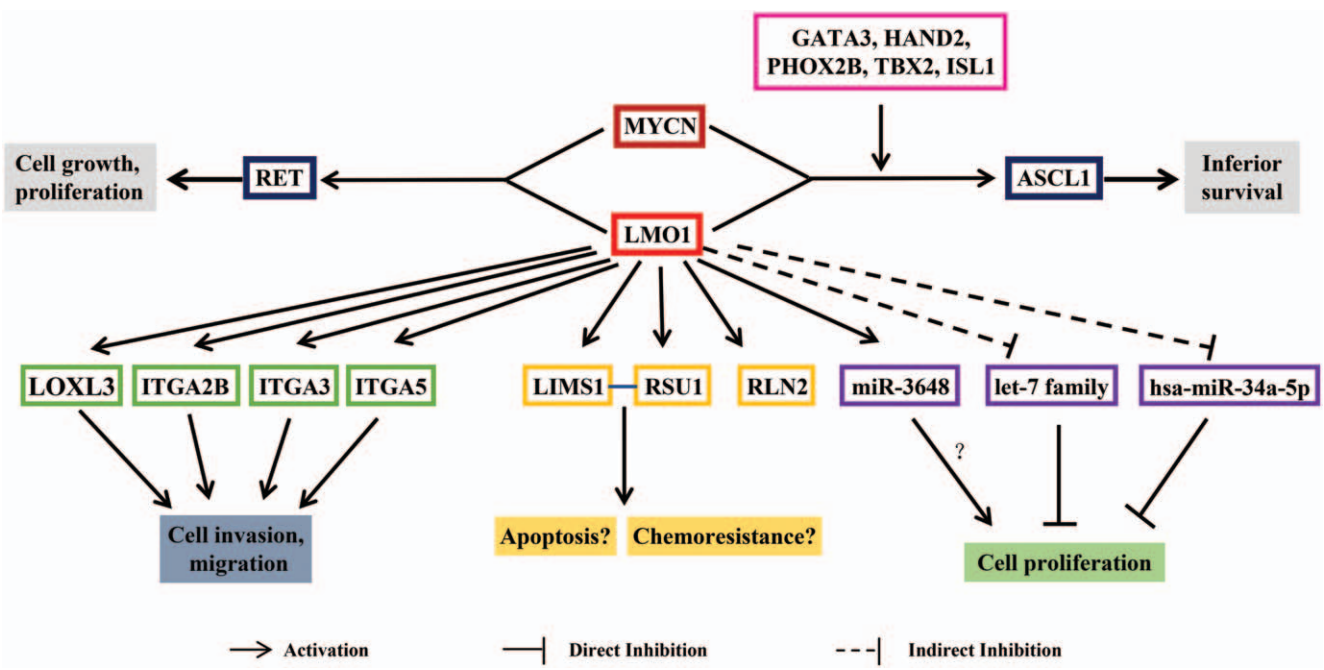

Figure 3: The downstream cascades of *LMO1* in neuroblastoma. *GATA3*: GATA-binding protein 3; *HAND2*: Heart- and neural crest derivatives-expressed transcript 2; *ISL1*: Islet-class LIM-homeodomain 1; *ITGA2B*: Integrin alpha 2b; *ITGA3*: Integrin-α3; *ITGA5*: Integrin-α5; *LIMS1*: LIM and senescent cell antigen-like domains 1; *LMO1*: LIM domain only 1; *LOXL3*: Lysyl oxidase-like 3; *PHOX2B*: Paired-like homeobox 2b; *RLN2*: Relaxin 2; *RSU1*: Ras suppressor protein 1; *TBX2*: T-box 2.

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 the enrichment of four other CRC members, including paired-like homeobox2b (*PHOX2B*), heart- and neural crest derivatives-expressed transcript 2 (*HAND2*), T-box 2 (*TBX2*), and islet-class LIM-homeodomain 1 (*ISL1*), suggesting that *LMO1* collaborates with all these CRC proteins to coordinately regulate *ASCL1* expression.[57] In addition to *ASCL1*, the authors found that the receptor tyrosine kinase *RET*, which has been implicated in neuroblastoma tumorigenesis,[71,72] was also positively regulated by *LMO1* and *MYCN* in neuroblastoma cells. *LMO1* and *MYCN* directly upregulate *RET* gene expression, and this upregulation is correlated with increased cell proliferation.[57] Similarly, the authors identified and validated multiple binding sites of the *LMO1*, *GATA3*, and *MYCN* proteins upstream of the *RET* gene locus.[57] However, it was found that several *LMO1*-high cell lines did not express *RET*, whereas some *LMO1*-low cell lines expressed this protein.[57] Therefore, *LMO1* or *MYCN* may not be the essential determinants of *RET* expression, but when combined with other factors, they can actively promote *RET* gene expression.[57]

Additional downstream genes of *LMO1* have been identified. Saeki *et al*[73] identified three genes directly regulated by *LMO1* at the transcriptional level. These three genes are LIM and senescent cell antigen-like domains 1 (*LIMS1*), Ras suppressor protein 1 (*RSU1*), and relaxin 2 (*RLN2*). In this study, ChIP-seq analysis demonstrated the direct association of *LMO1* protein with these three genes in two neuroblastoma cell lines SK-N-SH and LAN-5.[73] The authors further showed that knocking down *LMO1* expression suppressed the expression of the three genes.[73] In subsequent studies conducted by the same research group, it was found that *LMO1* indirectly downregulates 18 tumor-suppressive microRNAs in SK-N-SH cells, including hsa-miR-34a-5p and 7 members of the let-7 family,[74] suggesting that downregulating the expression of those miRNAs is one of the mechanisms underlying the oncogenic function of *LMO1*. This research group also reported that *LMO1* directly upregulates the expression of miR-3648.[74] However, there is no sufficient evidence supporting the role of this miRNA in mediating the oncogenic function of *LMO1*.

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.[75] 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.[3] 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 an 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* [Figure 4A]. This aberrant transcriptional enhancer complex drives the overexpression of *LMO1*.[75]

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,[22] 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*[22] 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 I (*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*[76] further investigated the downstream targets of *TGF-βI/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-βI/TGFβRI via* 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*

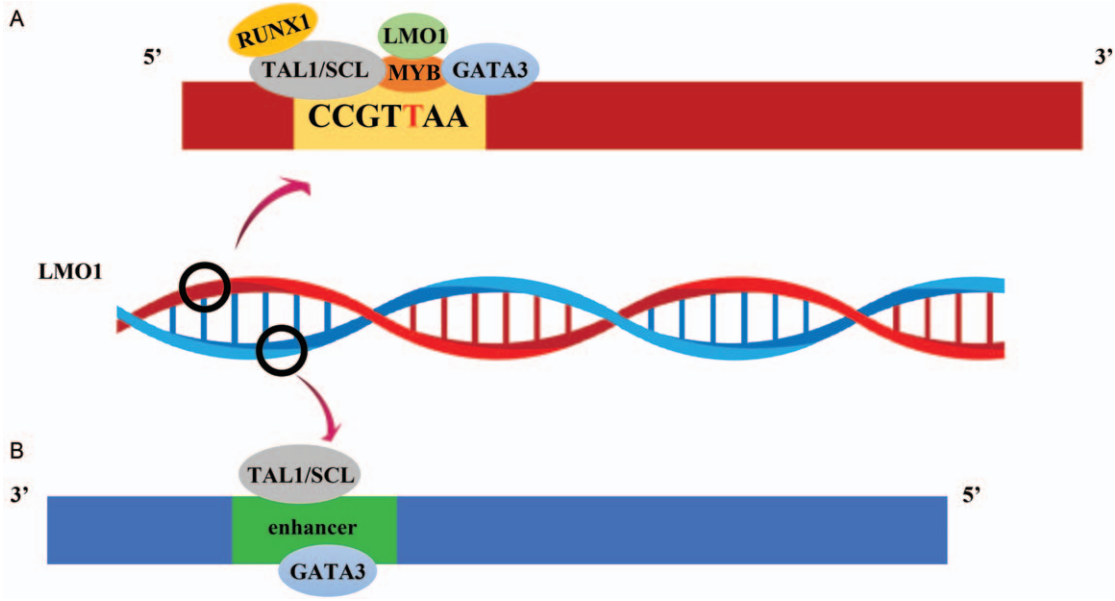

Figure 4: Mechanisms that regulate the transcription of *LMO1*. **A.** The C-to-T mutation upstream of the transcription start site of *LMO1* found in T-ALL patients created a *MYB* binding motif. The binding of *MYB* to this site leads to the formation of an aberrant transcriptional enhancer complex comprising *GATA3*, *RUNX1*, *SCL* and *LMO1*, which activates *LMO1* gene expression. **B.** The 3' flanking enhancer region in the *LMO1* promoter contains *TAL1/SCL* and *GATA3* binding sites. The binding of *TAL1/SCL* and *GATA3* promotes *LMO1* gene transcription. *GATA3*: GATA-binding protein 3; *LMO1*: LIM domain only 1; *RUNX1*: Runt-related transcription factor 1; SC*L*: Stem cell leukemia protein; *TAL1*: T-cell acute lymphocytic leukemia 1.

only decreased the expression of *LMO1*, suggesting that *MYCN* is regulated by let-7 through a separate mechanism independent of the *TGF-βI/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.[78] 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.[78] 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.[78] The association of *LMO1* with AR subsequently upregulates the expression of *P21* and prostate-specific antigen (*PSA*).[78] The AR-mediated upregulation of *P21* and *PSA* expression has been demonstrated to play an important role in the progression of prostate cancer.[79,80]

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.[81] *Bax*, as a proapoptotic gene, can induce apoptosis when overexpressed.[82] 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*[11] 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 may play a role in reducing the responsiveness of patients to the *EGFR* tyrosine kinase inhibitor cetuximab in lung cancer and colorectal cancer.[9,10] *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*.[9,10] 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.[83] 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,[84,85] which plays an important role in controlling centrosome duplication and accurate segregation of chromosomes during mitosis,[86] acts as a downstream mediator of *LMO1* function in lung cancer cells.[83]

Liu *et al*[87] found that *LMO1* gene polymorphisms may contribute to Wilms' tumor risk. Among the four SNPs

(rs110419 A>G, rs4758051 G>A, rs10840002 A>G, and rs204938 A>G) studied, the rs110419 A>G polymorphism in *LMO1* may reduce the tumor susceptibility of Wilms' tumor in the southern Chinese population. Similarly, another study performed by Li *et al*[8] 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*-transcription 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 three-dimensional 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.

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