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REVIEW

Zinc fingers and homeoboxes family in human diseases

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The zinc-fingers and homeoboxes (ZHX) family is a group of nuclear homodimeric transcriptional repressors that interact with a subunit of nuclear factor-Y (NF-YA) and contain two C2H2-type zinc fingers and five homeobox DNA-binding domains. The members of ZHX family form homodimers or heterodimers with other members or a subunit of NF-YA to repress transcription. ZHX family members function in hematopoietic cell development and differentiation, and neural progenitor maintenance. Dysfunction of ZHX family members correlates with the development and progression of various diseases, including hepatocellular carcinoma (HCC), hematological diseases, neurological diseases and glomerular diseases. Furthermore, low expression of ZHX is associated with poor prognosis in malignancies. This review provides an update on the role of ZHX family in development and its function in cancer, with special emphasis on HCC and hematological malignant diseases.

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THE ZHX FAMILY

The zinc-fingers and homeoboxes (ZHX) family includes ZHX1, ZHX2, and ZHX3.[1–3] All ZHX family members contain two Cys-Xaa2-Cys-Xaa12-His-Xaa4-His-type zinc-finger motifs and four or five HOX-like homeodomains (HDs), and function as transcriptional repressors (Figure 1a).[3,4] The type and component of homeodomains in the ZHX family are restricted to vertebrate lineage. The human ZHX1 and ZHX2 are on chromosome 8, whereas ZHX3 is on chromosome 20.

ZHX1 was firstly identified in a bone marrow stromal cell complementary DNA (cDNA) library by yeast two-hybrid library screen in 1999.[1,5] The 873 amino acid ZHX1 protein contains two N-terminal zinc fingers, five central and C-terminal homeodomains, a C-terminal acidic region, and two putative nuclear localization signals (NLSs). The expression of ZHX1 is high in brain and low in liver and kidney, whereas nearly undetectable in heart and muscle.[1,5,6] The human and mouse ZHX1 proteins share 91% amino acid identity.

Human ZHX2 was cloned from a size-fractionated brain cDNA library in 1998.[7] It contains two C2H2-type zinc-finger motifs and five HDs, with a unique proline-rich region (P domain) between HD1 and HD2 (Figure 1a).[3] ZHX2 expression was detected in all kinds of tissues with highest levels in ovary, followed by lung, heart, kidney, brain and liver. Intermediate expression was detected in pancreas, spleen, testis and skeletal muscle.[7] Mouse and rat ZHX2 were cloned in 2003 by database analysis, respectively.[2] The mouse and human ZHX2 proteins share 87% amino acid identity. Besides, some ZHX2 variants have been identified. G779A polymorphism of ZHX2 has been identified (Figure 1b).[8] However, further function studies are required for this polymorphism. A polymorphism of ZHX2 in intron 2 has also been identified. Individuals with this polymorphism have been demonstrated with the strong response to smallpox vaccine in a genome-wide association study.[9]

A partial human ZHX3 cDNA, KIAA0395, was identified in 1997.[10] Three full-length human ZHX3 cDNA were subsequently identified in a testis cDNA library. ZHX3 protein was eventually cloned by screening rat liver and granulose cell cDNA libraries using yeast two-hybrid analysis with ZHX1 as bait in 2003.[4] ZHX3 encodes a 956 amino acid protein with two zinc-finger domains, five homeodomains, a glu-rich region (E domain), and two NLS (Figure 1a). ZHX3 and ZHX1 share 34.4% amino acid identity.

ZHXS SIGNALING

ZHX family molecules are involved in the development and differentiation in different types of cells, and always act as transcriptional repressors by binding with the promoter regions to regulate the transcription of target genes in human tissues. Current studies demonstrated that a direct interaction between ZHX1 and ZHX2 could not only form heterodimer, but also form homodimers *in vivo* and *in vitro* to repress transcription.[2,3,11] All interactions required an extensive region around HD1. ZHX proteins also interact with nuclear factor-Y (NF-Y) subunits to have transcriptional suppression roles. NF-Y family contains three subunits NF-YA, NF-YB and NF-YC. NF-YA subunit includes two activation domains, a serine/threonine-rich region and a glutamine-rich region. ZHX proteins interact with different activation domains of NF-YA. Another transcriptional co-repressor of ZHX1, BS69, has also been identified.[12] ZHX1 interacts with the glutamine-rich region, whereas ZHX2 and ZHX3 interact with the serine/threoonine-rich region.[3,13] Meanwhile, the NLS of ZHX proteins are different. The NLS of ZHX1 is located in the amino acid sequence between residues 734 and 768,[14] which contains an arginine-rich basic region. The NLS of ZHX2 is sited at a proline-rich basic region, corresponding to the amino acid sequence between residues 317 and 446 (ref. 3; Figure 1a). In contrast, ZHX3 contains two NLSs that are located in the N-terminal zinc-finger 1 and HD2 region.[4] The repressor domain of ZHX1 is the C-terminal acidic region, which corresponds to the amino acid sequence between residues 831 and 873.[14] Both ZHX2 and ZHX3 contain a transcriptional repressor domain in the HD1, corresponding to the

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amino acid sequence between residues 263 and 446, and between residues 303 and 502, respectively.[3,4] The dimerization with ZHX1, ZHX2 or ZHX3 is requested for full repressor activities.[4,14]

The upstream regulators and downstream targets of ZHX2 have been demonstrated. As shown in Figure 2a, FoxC1 and ephrin-B1/B2 are identified as upstream regulators of ZHX2. Specifically, FoxC1 represses the expression of ZHX2, whereas ephrin-B1/B2 activates the ZHX2 signaling pathways.[15,16] In the downstream signaling of ZHX2, ZHX2 represses the expression of AFP, Cyclin A and Cyclin E. *In vitro*, cellular studies also demonstrated that ZHX2 induces the activity of lipoprotein lipase (Lpl).[17] However, most of the studies about ZHX2 signaling are very preliminary. Further studies are required to demonstrate more details about ZHX2 signaling.

It has been shown that ZHX family can regulate alpha-fetoprotein (AFP) expression in liver development. The expression of ZHX2 protein is absent in the fetal liver but upregulated in the normal adult liver. However, the expression of ZHX2 in hepatocellular carcinoma (HCC) exhibits an opposite tendency, which is dramatically repressed.[18,19] This tendency is different with the expression of AFP protein in liver development and diseases.[20] Studies in mice also demonstrated that ZHX2 is a negative transcriptional regulator of AFP in liver.[18,21] The molecular mechanism that ZHX2 repressed AFP expression has also been demonstrated. Specifically, AFP regulator 1 is an important regulatory factor of AFP and targets to AFP promoter to repress the transcription of AFP. Furthermore, Perincheri *et al.*[18] used the positional cloning approach to demonstrate that AFP regulator 1 protein binds with ZHX2 protein to forma complex. They also found that AFP expression in BALB/cJ mouse liver was caused by the ZHX2 mutation. Shen *et al.*[22] found ZHX2 interacted with hepatocyte NF-1 binding sites to repress AFP transcription in HCC cell lines. Furthermore, a clinical study demonstrated that ZHX2 expression is negatively related with AFP expression in HCC samples.[23] Other genes, such as *Gpc3* and *H19* were also demonstrated to regulate AFP expression controlled by ZHX2.[18,24] These results were further confirmed by partial hepatectomy in mouse. The level of ZHX2 was repressed at 24 and 48 h after partial hepatectomy, whereas the levels of AFP and GPC3 increased significantly. Similar to AFP and GPC3, the ZHX2 expression recovered to normal level after 48 h.[25]

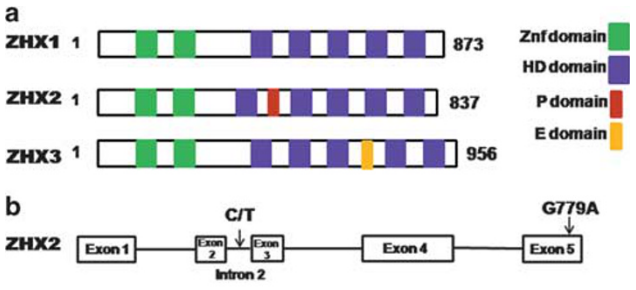

Figure 1. Diagram of zinc fingers and homeoboxes (ZHX) family. (**a**) Protein structures of ZHX family. (**b**) Gene structure of the polymorphisms of *ZHX2*.

ZHX FAMILY MEMBERS IN HUMAN DISEASES

Increasing evidence confirms important roles of ZHX family in the development of human diseases. Several studies indicated that the low expression of ZHX was bound up with the process of tumorigenesis and development. As a tumor suppressor gene, *ZHX2* is of great significance in the diagnosis of tumor diseases (Figure 2b).

HEPATOCELLULAR CARCINOMA

Several independent groups have demonstrated that overexpression of ZHX2 inhibited the growth of HCC cells *in vivo* and *in vitro*.[18,21] Furthermore, high level of ZHX2 expression was correlated with low expression of Cyclin A and Cyclin E in HCC samples, suggesting that ZHX2 induces cell cycle arrest at G1 phase.[21] Mechanistic studies indicated that ZHX2 protein directly bound with the promoter regions of Cyclin A and Cyclin E to repress their transcriptions.[21]

Repression of ZHX2 in HCC has also been identified. Lv *et al.*[26] reported that hypermethylation of the ZHX2 promoter was higher in HCC than in adjacent non-tumor issues using methylation-sensitive restriction fingerprinting. They also found that the expression of ZHX2 was silenced in liver of HCC patients. These results suggest that ZHX2 is a tumor suppressor. Wang *et al.*[27] have confirmed the similar results independently. However, Hu *et al.*[28] demonstrated that the expression of ZHX2 was upregulated in HCC samples comparing with the adjacent non-tumor issues, especially in poorly differentiated and metastasis samples. It's a controversial problem that needs to be explored.

The clinical significance of ZHX2 expression in HCC has been demonstrated. The overexpression of ZHX2 was detected in well-differentiated liver tissues than in poor-differentiated tissues.[21] Furthermore, nuclear ZHX2 expression was also correlated with the overall survival times of patients and was correlated with the inhibition of hepatocyte proliferation and tumor microvascularization.[21]

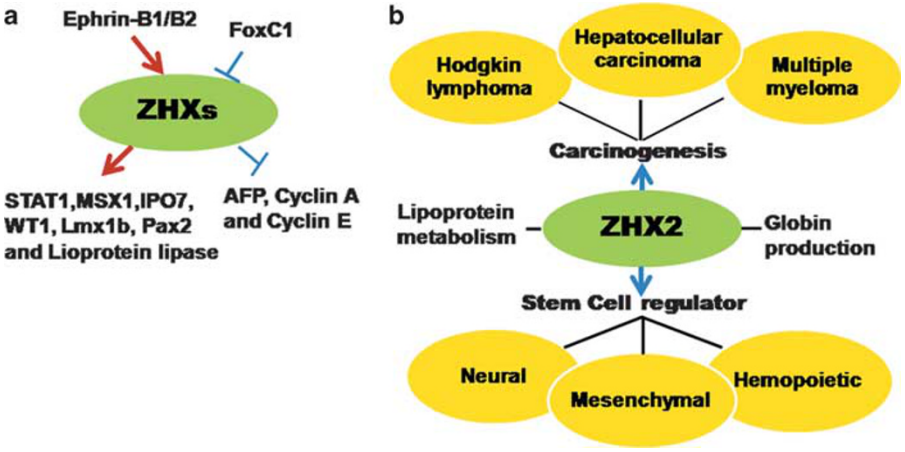

Figure 2. ZHX2 in different kinds of human disease. (**a**) ZHX2 signaling. (**b**) ZHX2-related diseases.

HEMATOLOGICAL DISEASES

ZHX2 gene coincides on the quantitative trait loci that have been reported to influence the absolute fetal hemoglobin levels.[29] de Andrade *et al.*[30] demonstrated that the expressed transcripts of ZHX2 in reticulocytes from a normal and a hereditary persistence of fetal hemoglobin-2 patients were different. Some of the detectable transcripts were involved in globin gene regulation.[30] Downregulation of ZHX2 was detected in two hereditary persistence of fetal hemoglobin-2 patients and in a carrier of the Sicilian δβ-thalassemia trait. These results suggest that ZHX2 represses the expression of globin, particularly γ-globin.[30] The clinical manifestations of β-thalassemia are extremely variable in severity. It has been reported that there is no apparent relationship among G779A polymorphism of *ZHX2* gene and severity of thalassemia and the level of HbF8. It has also been found that ZHX2 protein was involved in red blood cell differentiation and its expression was influenced by erythropoietin.[31]

Recent study also confirmed that ZHX2 was aberrantly expressed in multiple myeloma (MM).[32] The critical role of ZHX2 in MM was initially identified in studies of gene-expression profiles. Shaughnessy *et al.*[33] found that low expression of ZHX2 was associated with a risk of progression in a selected series of 221 transplanted patients with MM. In addition, lower expression of ZHX2 protein was detected in high-risk proliferative MM than in low-risk proliferative MM,[34] and the expression level of ZHX2 protein was closely related with the invasion ability of MM.[35] Some properties of ZHX2 are taken into an important prognostic marker for MM. The increased ZHX2 mRNA level was associated with beneficial prognostic index like β_2-microglobulin $< 5.5\ mg\ l^{-1}$, albumin $> 35\ g\ l^{-1}$ or a better cytogenetics.[34] Furthermore, high expression level of ZHX2 correlated with prolonged duration of response and overall survival of patients.[34] In addition, the patients with low ZHX2 levels had a higher rate of resistance to chemotherapy.[34]

Expression analysis in hematopoietic cell lines and primary cells indicated that B-cell-specific homeobox gene *ZHX2* is a tumor suppressor gene in Hodgkin lymphoma. t(4;8)(q27;q24) is a novel chromosomal rearrangement in Hodgkin lymphoma.[36] Target genes at *4q27* or *8q24* were shortlisted. Expression analysis of candidate target genes revealed that the inhibition of homeobox gene *ZHX2* was located at 8q24.[36] ZHX2 is a critical factor in development and differentiation of early B cells. The expression of ZHX2 was upregulated during the process from hematopoietic stem cells to early B stage or from early B to pro-B transitions.[37] The repression of ZHX2 is caused by the upregulation of FoxC1.[38] Aberrantly expressed FoxC1 leads to activation of IPO7 and repression of the transcription factors MSX1, and subsequently repressed the activation region of *ZHX2* gene.[15] IPO7 also contributes to ZHX2 repression by increasing nuclear levels of co-repressor histone H1C.[38]

OTHERS

ZHX2 functions in lipoprotein metabolism *in vivo*. Gargalovic *et al.*[17] demonstrated that mutation of ZHX2 regulates the lipoprotein alterations, especially the expression of Lpl in the mouse models. Lpl is a critical enzyme in the metabolism of triglyceride-rich lipoproteins.[39] Some ZHX2 variants activate the expression of Lpl.[17] However, it remains unclear how ZHX2 protein regulates Lpl expression. There is no evidence to indicate that ZHX2 binds with Lpl promoter directly. It's possible that ZHX2 forms heterodimers with other family members, such as ZHX3, to indirectly interact with the promoter regions of Lpl.[40] Moreover, a mass of ZHX3 mutations were found in both hypertriglyceridemia patients and healthy people.[41] Thus, the role of different ZHX proteins in lipoprotein metabolism should be further investigated.

ZHX2 protein was specifically detected in the ventricular and subventricular zone of the cortex during various stages of cortical neurogenesis. Blocking ZHX2 signaling in cortical neural progenitor cells by the expression of ZHX2-VP16 causes neuronal differentiation, whereas overexpression of ZHX2 in the cortex interrupts the normal differentiation of cortical neural progenitor cells.[42] Overexpression of ZHX2 was identified in neural progenitor cell and correlated with the expression of nestin protein.[42] ZHX2 is also a candidate NF for the intracellular fragment of ephrin-B, a critical factor in regulating cortical neural progenitors.[16,43,44] Introduction of an ephrin-B1 intracellular domain can activate ZHX2 activity.[42] Theephrin-B1 binding domain of ZHX2 is at the N-terminal portion (263–294) of the ephrin-B1 cytoplasmic domain, a region adjacent to the transmembrane domain and conserved between ephrin-B1 and ephrin-B2.[42] In addition, ZHX2 variants have also been identified in two corticobasal degeneration patients. These results further indicate that ZHX2 participates in the genesis and development of human neurological disease.[45]

Recent studies suggest that ZHX3 is a marker of osteogenic differentiation in mesenchymal stem cell. Suehiro *et al.*[46] found that ZHX3 has an important role in the early stages of osteogenic differentiation. ZHX3 mRNA expression was upregulated after incubation with mesenchymal stem cell in the osteogenic induction medium, which was 3- to 5-fold higher compaerd with that in undifferentiated mesenchymal stem cell,[46] but not upregulated during chondrogenic or adipogenic differentiation of mesenchymal stem cell.

The role of ZHX proteins in glomerular diseases was indicated in animal models[40,47] and human kidney biopsies.[40] ZHX proteins are mostly located in non-nuclear regions in normal podocyte in heterodimer way and a minority of them are located in normal nuclear regions. Furthermore, ZHX3 protein was transiently downregulated before the onset of proteinuria. The recovery of ZHX3 expression was associated with migration of ZHX3 protein into the nucleus and the development of proteinuria in minimal change disease.[40] ZHX3 regulates the expression of podocyte gene directly or indirectly via other ZHX proteins.[40] Sustainable downregulation of ZHX3 protein causes the reduction of *WT1*, *Lmx1b* and *Pax2* genes. All these genes are crucial in focal glomerulopathy sclerosis.[40,48]

FUTURE DIRECTIONS

Current studies indicate that ZHX family members are crucial in the development and progression of human diseases. However, studies of ZHX family members are still premature and further studies are required. First of all, to further identify the role of ZHX family members in the development of diseases, genetically engineered mouse models should be generated. Transgenic, knockout and knockin ZHX mouse models are still not available. Second, it is still unclear about the signaling pathway of ZHX family. The downstream targets and upstream regulators of ZHX proteins are required to be further investigated. Finally, it's also unclear whether ZHX family members are therapeutic targets in HCC and other kinds of diseases. Some preclinical experiments are required to be performed to identify the potential ZHX-targeted therapies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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