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Review Article

Role of the zinc finger and SCAN domain-containing transcription factors in cancer

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Abstract: Transcription factors are key determinants of gene expression that recognize and bind to short DNA sequence motifs, thereby regulating many biological processes including differentiation, development, and metabolism. Transcription factors are increasingly recognized for their roles in cancer progression. Here, we describe a subfamily of zinc finger transcription factors named zinc finger and SCAN domain containing (ZSCAN) transcription factors. In this review, we summarize the identified members of the ZSCAN family of transcription factors and their roles in cancer progression. Due to the complex regulation mechanisms, ZSCAN transcription factors may show promotive or prohibitive efforts in angiogenesis, cell apoptosis, cell differentiation, cell migration and invasion, cell proliferation, stem cell properties, and chemotherapy sensitivity. The upstream regulation mechanisms of their varied expression levels may include gene mutation, DNA methylation, alternative splicing, and miRNA regulation. What's more, to clarify their diverse functions, we summarize the modulation mechanisms of their activity in downstream genes transcription, including protein-protein interactions mediated by their SCAN box, recruitment of co-regulating molecules and post-translational modifications. A better understanding of the widespread regulatory mode of these transcription factors will provide further insight into the mechanism of transcriptional regulation and suggest novel therapeutic strategies against tumor progression.

Keywords: ZSCAN transcription factor, transcriptional regulation, SCAN domain, cancer progression

Introduction

Transcription factors play a crucial role in controlling gene expression from DNA to mRNA by recognizing specific DNA sequences. Transcription factors are classified into families according to their conserved DNA-binding domains. New technologies such as large-scale chromatin immunoprecipitation (ChIP)-seq and DNase protection assays have revealed that promoters overlap with transcription factors. Transcription factors can turn genes on or off in specific environments and at specific times as part of their accurate transcriptional regulation [1]. They can also function as promoters and/or suppressors of downstream gene expression, and therefore possess a broad range of properties [2].

Zinc finger (ZNF) transcription factors, which form the largest transcription factor family, are characterized by finger-like DNA binding domains that require one or more zinc ions to stabilize the structure; they play an important role in many biological processes [3]. ZNF family transcription factors are divided into several classes according to the manner in which the zinc ions bind to the cysteine or histidine residues of the finger-like domain motif, such as C2H2 and Cys6 among others [4]. ZNF transcription factors contain N-terminal domains that interact with other proteins to regulate expression, subcellular localization, and transcriptional activity [5], including the Kruppel-associated box domain (KRAB) [6], the poxvirus and zinc finger domain (POZ) [7], the insect zinc finger associated domain (ZAD) [8], and the SCAN domain [9]. In this review, we will focus on zinc finger and SCAN domain-containing (ZSCAN) transcription factors, which comprise the smallest and most recently defined subfamilies [9]. The members of the mouse SCAN fam-

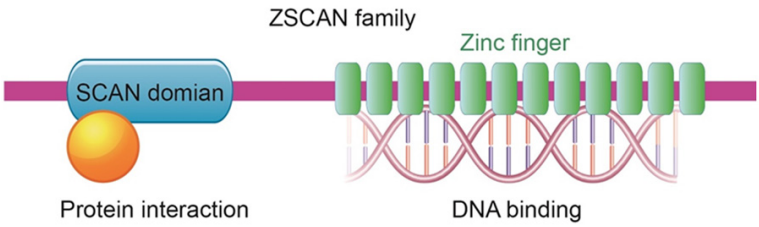


Figure 1. Model of the structures of the ZSCAN family. The ZSCAN family of transcription factors shares a similar DNA binding domain consisting of three or more zinc fingers (green). At the N-terminus, the SCAN domain (blue) functions as an interaction domain.

ily, a highly conserved protein family, were previously described [5], whereas the human ZSCAN transcription factors are not well-organized. Providing additional insight into their roles and regulatory function is important as an increasing number of studies have reported the relationship between the ZSCAN transcription factors and cancer progression.

In this review, we phylogenetically classified the ZSCAN family and summarized the role of all the well-studied members in cancer. In addition, we described the potential underlying mechanisms from several aspects, namely, upstream regulation of these transcription factors, modulation of the transcriptional activity through protein interactions, and regulation of downstream genes.

The structure and members of the ZSCAN transcription factor family

ZSCAN transcription factors contain two main domains, the zinc finger domain and the SCAN box (**Figure 1**).

The zinc finger domain

The zinc finger domain in the ZSCAN transcription factor contains a C2H2 motif. The C-terminus of the ZSCAN transcription factor contains three or more fingers consisting of two conserved cysteine residues and two histidine residues coordinated with a zinc ion [10]. The C2H2 ZNF transcription factors are the main type of ZNF transcription factors. According to the Inter Pro database (updated on February 2018), there are approximately 2,443 genes in the human genome encoding proteins with a C2H2 motif (http://www.ebi.ac.uk/interpro/entry/IPR036236/proteins-matched?species=9606). This zinc finger domain functions as a DNA binding domain and helps the ZSCAN transcription factor target specific cis-acting elements.

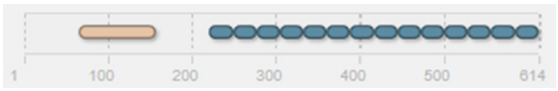
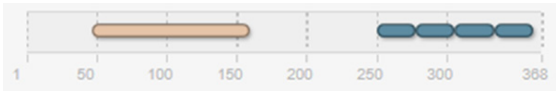
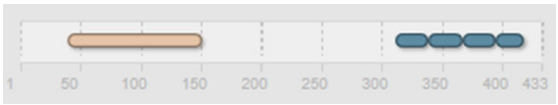
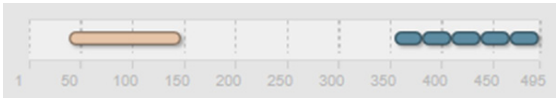
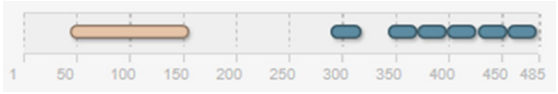
The SCAN domain

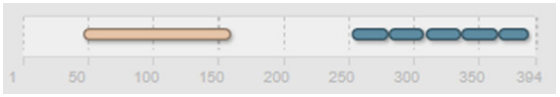
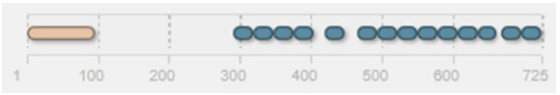
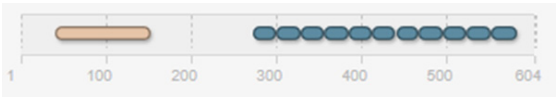
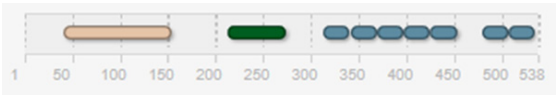
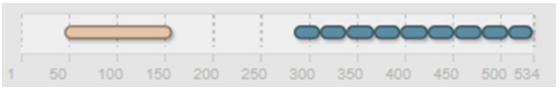
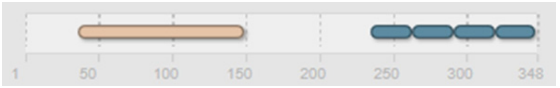
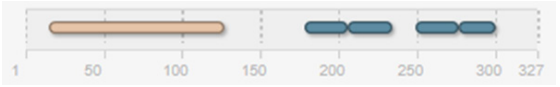
Based on the four members initially identified (SRE-ZBP, CT n-51, AW-1, and Number 18 cDNA), another domain was named the SCAN box [9]. It was described more than 20 years ago. In the human genome, approximately 244 protein products containing the SCAN domain have been identified, among which approximately 50 ZSCAN transcription factors were described (http://www.ebi.ac.uk/interpro/entry/IPR003309/proteins-matched?species=9606). The highly conserved SCAN domain consists of 84 amino acids rich in leucine residues; therefore, this domain is also known as the leucine rich region (LeR) [11]. The SCAN domain has an amphipathic secondary structure and is involved in protein-protein interactions, in particular for self-association and to mediate oligomerization [12-14]. Increasing research on this domain revealed that it can interact with an isolated SCAN domain, such as SCAN domain protein 1 (SDP1), or with other family members with the SCAN domain [15]. Furthermore, this interaction is selective, indicating that not all the family members can form oligomers. These varied interactions between transcription factors lead to diverse transcriptional activities.

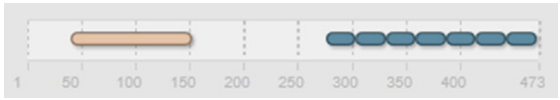
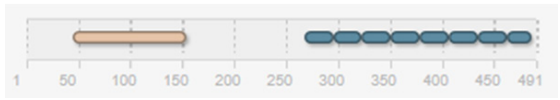
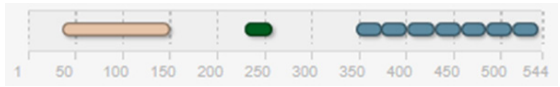
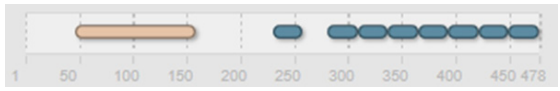
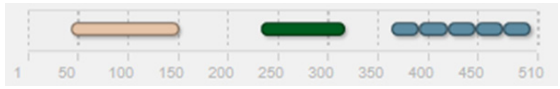
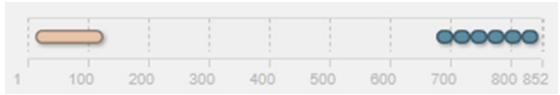
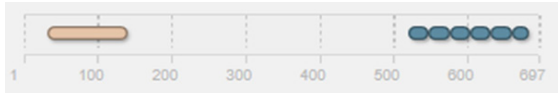
The human ZSCAN transcription factor family

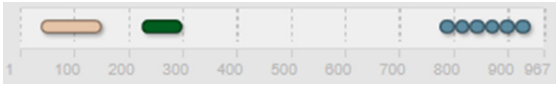
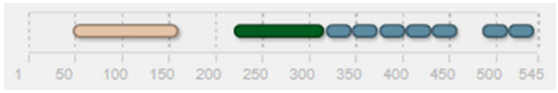
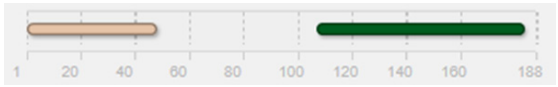
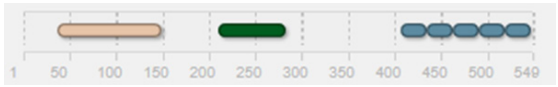
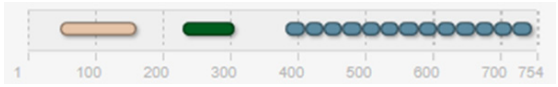
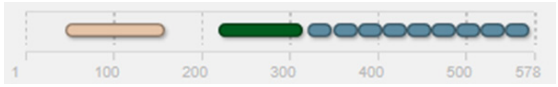
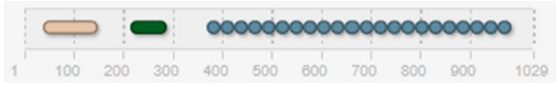
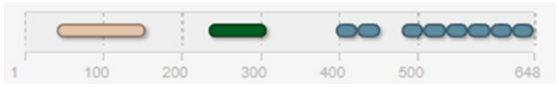
There are 54 identified members of the human ZSCAN transcription factor family, and because they are all zinc finger proteins, they are referred to as ZNF proteins. In addition, specific proteins may have several special names according to their domains. Examination of the NCBI gene database revealed that family members have unified names ranging from ZSCAN1 to ZSCAN54 (**Table 1**). In this family, 24 members containing both the KRAB domain and the SCAN domain are named ZKSCAN proteins. In addition, certain proteins have unique names such as myeloid zinc finger 1 (MZF1) and paternally expressed 3 (PEG3).

Table 1. ZSCAN family members and protein structures

Approved Symbol	Approved Name	Previous Symbols	Synonyms	Chromosome	Protein domain
ZSCAN1	Zinc finger and SCAN domain containing 1		FLJ33779, ZNF915, MZF-1	19q13.43	
ZSCAN2	Zinc finger and SCAN domain containing 2	ZFP29	FLJ20595, ZNF854	15q25.2	
ZNF24	Zinc finger protein 24	ZNF191	ZSCAN3, Zfp191, KOX17	18q12.2	
ZSCAN4	Zinc finger and SCAN domain containing 4	ZNF494	FLJ35105	19q13.43	
ZSCAN5A	Zinc finger and SCAN domain containing 5A	ZNF495, ZSCAN5	MGC4161	19q13.43	
ZSCAN5B	Zinc finger and SCAN domain containing 5B		ZNF495B, ZNF371	19q13.43	
ZSCAN5C	Zinc finger and SCAN domain containing 5C	ZSCAN5CP	ZNF495C	19q13.43	
ZSCAN5DP	Zinc finger and SCAN domain containing 5D pseudogene	ZSCAN5DP, ZSCAN5D	ZNF495D	19q13.43	
MZF1	Myeloid zinc finger 1	ZNF42	ZSCAN6, MZF1B, MZF-1, Zfp98	19q13.43	
ZNF165	Zinc finger protein 165		ZSCAN7, CT53	6p22.1	
ZNF174	Zinc finger protein 174		ZSCAN8	16p13.3	

ZSCAN9	Zinc finger and SCAN domain containing 9	ZNF193	PRD51	6p22.1	
ZSCAN10	Zinc finger and SCAN domain containing 10	ZNF206		16p13.3	
ZNF232	Zinc finger protein 232		ZSCAN11	17p13.2	
ZSCAN12	Zinc finger and SCAN domain containing 12	ZNF305, ZNF96	KIAA0426, ZNF29K1, ZFP96, dJ29K1.2	6p22.1	
ZKSCAN3	Zinc finger with KRAB and SCAN domains 3	ZNF306, ZNF309	Zfp47, ZF47, ZSCAN35	6p22.1	
ZNF396	Zinc finger protein 396		ZSCAN14, FLJ31213	18q12.2	
ZNF397	Zinc finger protein 397	ZNF47	ZSCAN15, MGC13250	18q12.2	
ZSCAN16	Zinc finger and SCAN domain containing 16	ZNF392, ZNF435	FLJ22191, dJ265C24.3	6p22.1	
ZNF444	Zinc finger protein 444		ZSCAN17, FLJ11137, EZF2	19q13.43	
ZSCAN18	Zinc finger and SCAN domain containing 18	ZNF447	FLJ12895	19q13.43	
ZNF449	Zinc finger protein 449		ZSCAN19, FLJ23614	Xq26.3	
ZSCAN20	Zinc finger and SCAN domain containing 20	ZNF360, ZNF31	KOX29	1p35.1	

ZSCAN21	Zinc finger and SCAN domain containing 21	ZNF38	DKFZp434L134, NY-REN-21, Zipro1	7q22.1	
ZSCAN22	Zinc finger and SCAN domain containing 22	ZNF50, HKR2		19q13.43	
ZSCAN23	Zinc finger and SCAN domain containing 23	ZNF453, ZNF390	dJ29K1.3.1	6p22.1	
PEG3	Paternally expressed 3		ZKSCAN22, KIAA0287, ZNF904, ZSCAN24	19q13.4	
ZSCAN25	Zinc finger and SCAN domain containing 25	ZNF498	FLJ32468	7q22.1	
ZSCAN26	Zinc finger and SCAN domain containing 26	ZNF187	SRE-ZBP	6p22.1	
ZNF75D	Zinc finger protein 75D	ZNF82, ZNF75	ZKSCAN24, D8C6, ZSCAN28	Xq26.3	
ZSCAN29	Zinc finger and SCAN domain containing 29	ZNF690	FLJ35867, Zfp690	15q15.3	
ZSCAN30	Zinc finger and SCAN domain containing 30	ZNF397OS	ZNF917	18q12.2	
ZSCAN31	Zinc finger and SCAN domain containing 31	ZNF310P, ZNF323		6p22.1	
ZSCAN32	Zinc finger and SCAN domain containing 32	ZNF434	FLJ20417	16p13.3	
ZKSCAN1	Zinc finger with KRAB and SCAN domains 1	ZNF139, ZNF36	KOX18, PHZ-37, ZSCAN33	7q22.1	

ZKSCAN2	Zinc finger with KRAB and SCAN domains 2	ZNF694	FLJ23199, ZSCAN34	16p12.1	
ZKSCAN4	Zinc finger with KRAB and SCAN domains 4	ZNF307, ZNF427	p373c6.1, P1P373C6, FLJ32136, ZSCAN36	6p22.1	
ZKSCAN5	Zinc finger with KRAB and SCAN domains 5	ZFP95	ZNF914, ZSCAN37	7q22.1	
ZNF18	Zinc finger protein 18		ZKSCAN6, KOX11, HDSG1, Zfp535, ZNF535, ZSCAN38	17p12	
ZKSCAN7	Zinc finger with KRAB and SCAN domains 7	ZNF64, ZNF448, ZNF167	FLJ12738, ZSCAN39	3p21.31	
ZKSCAN8	Zinc finger with KRAB and SCAN domains 8	ZNF192	LD5-1, ZSCAN40	6p21	
ZNF197	Zinc finger protein 197	ZNF166	P18, D3S1363E, ZKSCAN9, ZSCAN41	3p21.31	
ZNF202	Zinc finger protein 202		ZKSCAN10, ZSCAN42	11q23.3	
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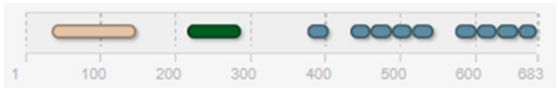
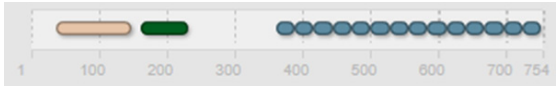
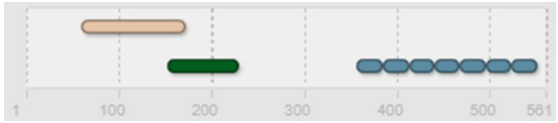
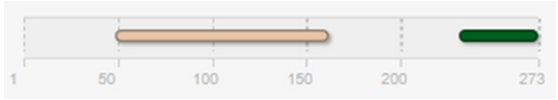
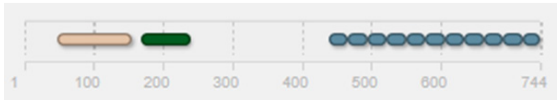
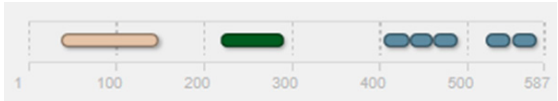
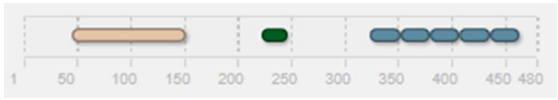
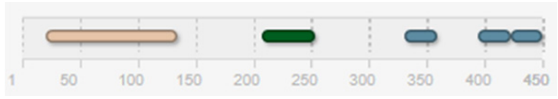
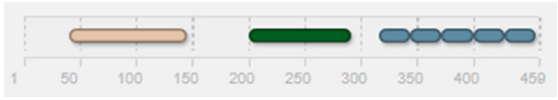
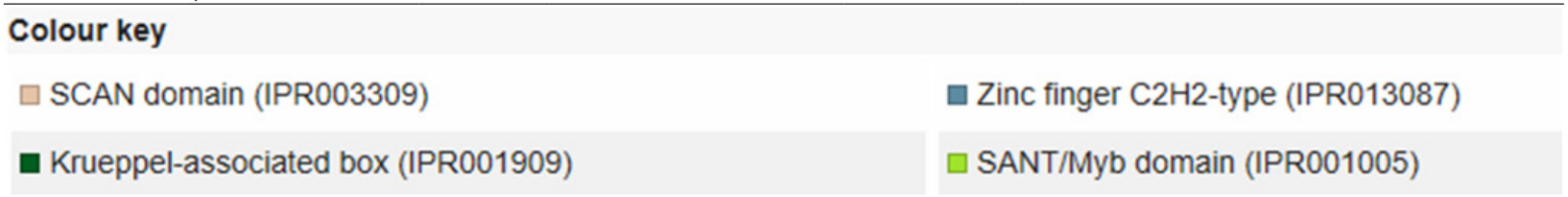
ZNF263	Zinc finger protein 263		FPM315, ZKSCAN12, ZSCAN44	16p13.3	
ZNF287	Zinc finger protein 287		ZKSCAN13, ZSCAN45	17p11.2	
ZNF394	Zinc finger protein 394		ZKSCAN14, FLJ12298, ZSCAN46	7q22.1	

ZNF445	Zinc finger protein 445	ZNF168	ZKSCAN15, ZSCAN47	3p21.31	
ZNF483	Zinc finger protein 483		ZKSCAN16, KIAA1962, ZSCAN48	9q31.3	
ZNF496	Zinc finger protein 496		ZKSCAN17, MGC15548, ZSCAN49	1q44	
ZNF500	Zinc finger protein 500		ZKSCAN18, KIAA0557, ZSCAN50	16p13.3	
ZNF274	Zinc finger protein 274		ZKSCAN19, ZSCAN51	19q13.43	
ZNF446	Zinc finger protein 446		ZKSCAN20, FLJ20626, ZSCAN52	19q13.43	
ZNF213	Zinc finger protein 213		CR53, ZKSCAN21, ZSCAN53	16p13.3	
ZFP69	ZFP69 zinc finger protein	ZNF642	ZKSCAN23A, FLJ16030, ZFP69A, ZSCAN54A	1p34.2	
ZFP69B	ZFP69 zinc finger protein B	ZNF643	ZKSCAN23B, FLJ34293, ZSCAN54B	1p34.2	



Involvement of ZSCAN transcription factors in cancer

Although these family members share a similar structure (**Figure 1**), ZSCAN transcription factors show great diversity of biological functions, especially in cancer progression. Recently, an increasing number of studies detected aberrant expression of ZSCAN transcription factors in different kinds of cancer. Notably, in different cancer types or even in the same cancer type, ZSCAN transcription factors can lead to opposite outcomes. Next, we discuss the well-researched members and their impacts on cancer. To summarize, ZSCAN transcription factors may take part in angiogenesis, cell apoptosis, cell differentiation, cell migration and invasion, cell proliferation, stem cell properties, and chemotherapy sensitivity (**Figure 2**). We list all the members and their functions in **Table 2** (sorted by biological process).

MZF1

MZF1, also known as ZNF42, ZFP98, or ZSCAN6, was first reported in myeloid differentiation and leukemia [16]. Since then, it has attracted increasing attention for its involvement in several mammalian cancers [15, 17, 18]. Data from the TCGA database show significant alterations of MZF1 gene copy numbers in several tumors such as breast, lung, bladder, glioma, and colon cancer. However, whether MZF1 acts as a tumor promoter or suppressor remains unclear because of its specific expression in different tissues and the complexity of its function. We will then discuss the roles of MZF1 in different biological processes during tumorigenesis from two aspects: the promoters or the inhibitors of tumors.

Tumor promoter

Cell apoptosis: MZF1 is associated with poor prognosis in gliomas, where MZF1 directly binds to the promoter of LIM domain only protein 3 (LMO3), which induces apoptosis by upregulating the expression of the caspase signal pathway [19].

Cell migration and invasion: In cervical cancer, the induction of forkhead box M1 (FOXM1) by the MZF1/NK2 homeobox 1 (NKX2-1) axis is involved in cell invasion [20]. It is consistent with another aspect of cervical cancer, in which MZF1 binds directly to the AXL receptor tyrosine kinase (AXL) promoter, which promotes cervical cell invasion, and the expression of MZF1 is closely correlated with the clinical stage in cervical cancer [21]. In colon cancer, MZF1 regulates the expression of AXL, leading to enhanced migratory, invasive, and metastatic potentials, as demonstrated in vivo and in vitro [22]. A research team from Taiwan suggested that MZF1 cooperates with Elk-1 and significantly upregulates protein kinase C alpha (PKCα), promoting cell migration and invasion in hepatocellular, breast, and bladder transitional cell carcinoma [23-25]. In breast cancer, MZF1 is a key transcription factor mediating the expression of transforming growth factor beta 1 (TGF-β) and it is involved in the transformation of mesenchymal stem cells to cancer associated fibroblasts [26]. Similarly, another group found that in ErbB2-driven invasion of breast cancer, MZF1 plays a decisive role by activating the downstream gene cathepsin B (CTSB) [27-29]. In non-small cell lung cancer, MZF1 is an important prognostic marker in early stage patients [30]. Microarray analysis of the c-Myc regulatory gene network in lung adenocarcinoma identified MZF1 as a putative indirect target of c-Myc action, and its involvement in the Myc tumorigenic phenotype was demonstrated [31]. The involvement of the MZF1/c-Myc axis in migration, invasion, and soft agar growth of lung adenocarcinoma cells was also confirmed in another study [32]. Research in esophageal cancer cells found that MZF1 may upregulates N-cadherin during epithelial-mesenchymal transition [33].

Cell proliferation: The cooperation of MZF1 and Elk-1 may also promote cell proliferation in hepatocellular, breast, and bladder transitional cell carcinomas [24-26]. In melanoma cells, MZF1 binds to the hypomethylated promoter of the tumor antigen preferentially expressed antigen of melanoma (PRAME) and transactivates the expression of PRAME, increasing cell proliferation [34]. Hepatocyte growth factors (HGFs), whose expressions are elevated in multiple myeloma cells, are potential targets of MZF1. Mechanistic studies have shown that DNA mutations in the promoter alleles of HGF provide new functional binding sites for MZF1 [35]. Another group found that MZF1 transcriptionally activates p55PIK and increases the proliferation of colorectal cancer cells [36]. In lung

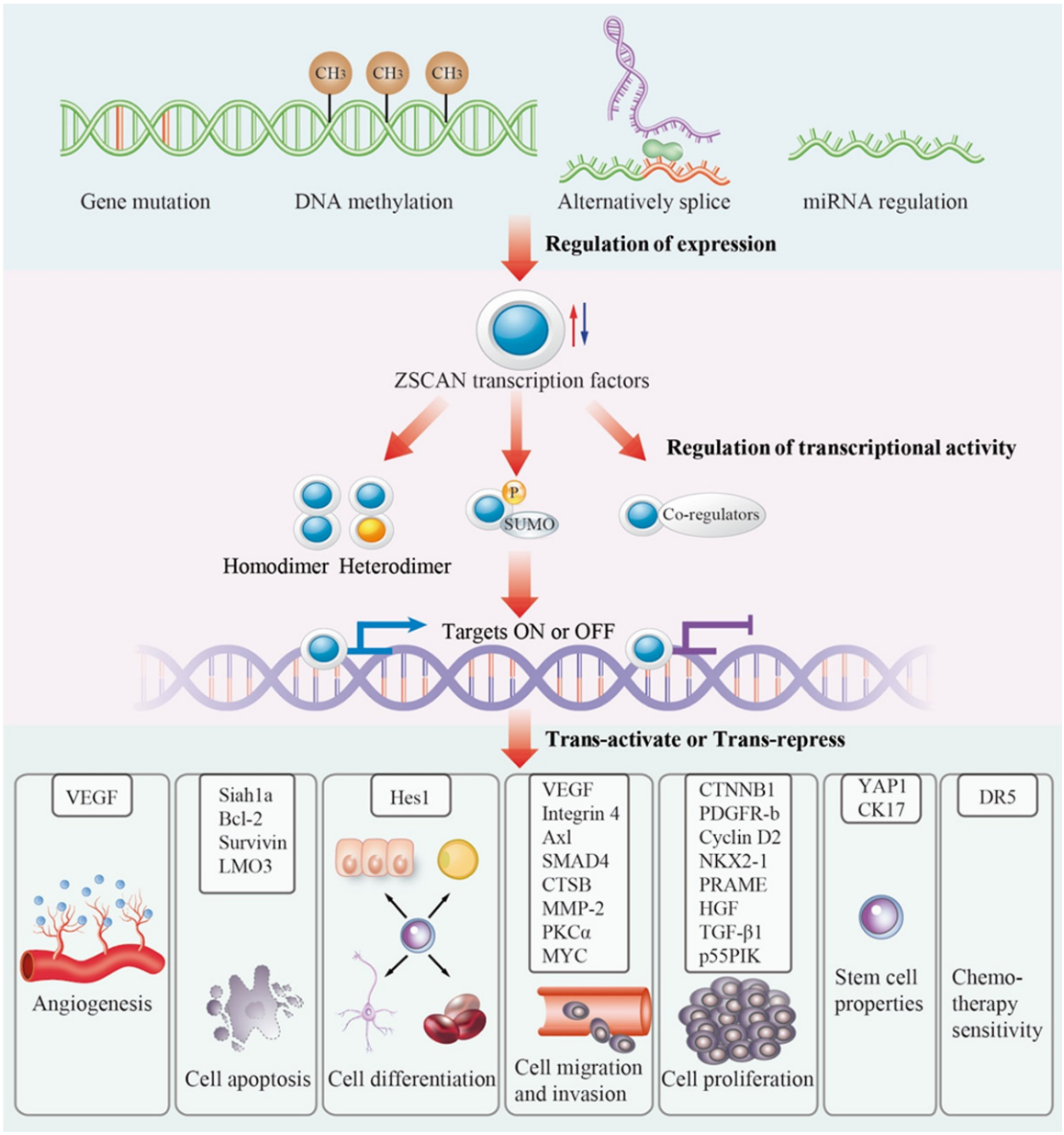


Figure 2. Roles of ZSCAN transcription factors in cancer and the potential mechanism. Regulation of the expression of ZSCAN transcription factors: gene mutation, DNA methylation, alternative splicing, or microRNA regulation may up- or down-regulate the expression of ZSCAN transcription factors. Regulation of transcriptional activity: according to the context of the environment, ZSCAN transcription factors function as transcriptional activators or repressors: i) they may interaction through the SCAN domain to form a homodimer or heterodimer; ii) post-translational modifications, such as phosphorylation and SUMOylation, may affect transcription, resulting in different outcomes; and iii) they may recruit co-regulators including SETDB1, NSD1, H2A.Z, and HDAC1 to form transcriptional complexes. Transactivation or transrepression of a wide variety of downstream genes: by targeting different genes, ZSCAN transcription factors are involved in i) angiogenesis; ii) cell apoptosis; iii) cell differentiation; iv) cell migration and invasion; v) cell proliferation; vi) stem cell properties; and vii) chemotherapy sensitivity.

squamous cell carcinoma, MZF1 acts as an oncogene to promote cell proliferation and invasion [37].

Stem cell properties: MZF1 is amplified in osteosarcoma and may promote stem cell properties by inducing yes associated protein 1 (YAP1) expression, whereas silencing of MZF1 promotes cell differentiation [38]. In cervical cancer, MZF1 is a key transcriptional activator of CK17, which promotes the stemness of cervical cancer cells [39]. In vivo and in vitro experi-

Table 2. ZSCAN family target genes and biological progress

Member	Target	Cancer type	Biological process	Tumor suppresser or promoter	Reference
ZNF24	VEGF	Breast cancer	Angiogenesis	Inhibitor	[61, 62]
ZKSCAN3	VEGF	Colorectal cancer	Angiogenesis	Promoter	[53]
PEG3	Siah1a	Fibroblast cell	Cell apoptosis	Inhibitor	[48]
ZKSCAN1	Bcl-2 and survivin	Gastric cancer	Cell apoptosis	Promoter	[67, 69]
MZF1	LMO3	Glioma	Cell apoptosis	Promoter	[19]
ZNF206		Neuroblastoma	Cell differentiation	Promoter	[63]
ZKSCAN4	Hes1	Basal cell carcinoma	Cell differentiation	Promoter	[64]
ZNF24	VEGF	Gastric cancer	Cell migration and invasion	Inhibitor	[44]
ZKSCAN3		Colorectal cancer	Cell migration and invasion	Promoter	[73]
ZKSCAN3	Integrin 4	Colorectal cancer	Cell migration and invasion	Promoter	[74]
ZKSCAN3		Prostate cancer	Cell migration and invasion	Promoter	[76]
MZF1	Axl	Cervical cancer	Cell migration and invasion	Promoter	[21]
MZF1	Axl	Colorectal cancer	Cell migration and invasion	Promoter	[22]
MZF1	SMAD4	Gastric cancer	Cell migration and invasion	Inhibitor	[41]
MZF1	CTSB	Breast cancer	Cell migration and invasion	Promoter	[27-29]
MZF1	N-cadherin	Esophageal cancer	Cell migration and invasion	Promoter	[33]
MZF1	MMP-2	Cervical cancer	Cell migration and invasion	Inhibitor	[40]
ZNF24	PDGFR-b	Breast cancer	Cell proliferation	Inhibitor	[63]
ZNF24	CTNNB1 (β-catenin)	Hepatocellular carcinoma	Cell proliferation	Promoter	[65]
ZKSCAN3		Colorectal cancer	Cell proliferation	Promoter	[74]
ZKSCAN3	Cyclin D2	Multiple myeloma	Cell proliferation	Promoter	[75]
ZKSCAN3		Breast cancer	Cell proliferation cell migration and invasion	Promoter	[79]
ZKSCAN1		Hepatocellular carcinoma	Cell proliferation cell migration and invasion	Inhibitor	[71]
PEG3	β-catenin	Glioma	Cell proliferation	Inhibitor	[53]
PEG3		Ovarian cancer	Cell proliferation	Inhibitor	[56]
ZNF496		Breast cancer	Cell proliferation	Inhibitor	[102]
MZF1	NKX2-1	Cervical cancer	Cell proliferation	Promoter	[20]
MZF1	PRAME	Melanoma	Cell proliferation	Promoter	[34]
MZF1	HGF	Multiple myeloma	Cell proliferation	Promoter	[35]
MZF1	TGF-β1	Breast cancer	Cell proliferation	Promoter	[26]
MZF1	p55PIK	Colorectal cancer	Cell proliferation	Promoter	[36]
MZF1	PKCα	Hepatocellular carcinoma	Cell proliferation cell migration and invasion	Promoter	[23]
MZF1	PKCα	Bladder transitional cell carcinoma	Cell proliferation cell migration and invasion	Promoter	[24]
MZF1	PKCα	Breast cancer	Cell proliferation cell migration and invasion	Promoter	[25]
MZF1	MYC	Lung adenocarcinomas	Cell proliferation cell migration and invasion	Promoter	[31, 32]
MZF1		Lung squamous cell carcinoma	Cell proliferation cell migration and invasion	Promoter	[37]
MZF1	NFKB	Gastric cancer	Cell proliferation cell migration and invasion	Inhibitor	[42]
MZF1	DR5	Colorectal cancer	Chemotherapy sensitivity	Inhibitor	[44]
MZF1	YAP1	Osteosarcomas	Stem cell properties	Promoter	[38]
MZF1	CK17	Cervical cancer	Stem cell properties	Promoter	[39]

ments demonstrated that the MZF1/NKX2-1/FOXM1 axis mentioned above is also responsible for cell stemness in human papilloma virus 16/18 (HPV16/18)-infected cervical cancer [20].

Tumor suppressor

Although its oncogenic function has been well-studied, many studies describe an opposite role for MZF1 in cancer. In human cervical cancer, MZF1 may suppress matrix metalloproteinase-2 (MMP2) and repress cell migration and invasion [40]. Recently, a study in gastric cancer cells showed that overexpression of MZF1 upregulates the tumor suppressor SMAD family member 4 (SMAD4), which directly suppresses Wnt/β-catenin signaling and inhibits cell migration [41]. This finding indicates that MZF1 can act as a negative regulator of tumorigenesis. Another study of gastric cancer found that MZF1 suppressed cell proliferation and migra-

tion through targeting NFKB associated with MT2A [42]. Immunohistochemical analysis of 274 patients with oral squamous cell carcinoma using tissue microarrays concluded that low expression of MZF1 is associated with advanced clinical stage and lower overall survival rates [43]. Different roles of MZF1 were even found in the same cancer. Although MZF1 acts as an oncogene in colon cancer, upregulation of MZF1 by sulindac sulfide induces the expression of the receptor for tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), sensitizing cancer cells to TRAIL-based therapy [44].

PEG3

PEG3 is an imprinted gene with tumor suppressor activity, and it interacts with many well-known proteins. Recently, a transcriptional amplification system aimed to improve PEG3 was developed to target Androgen Receptor+ and Androgen Receptor-prostate cancer cells [45]. In a study of cervical cancer, 213 women from Tanzania with cervical intraepithelial neoplasia I/II/III or invasive cervical cancer (ICC) were analyzed to identify DNA methylation markers associated with cancer persistence or progression. The study showed that a 5% increase in PEG3 DNA methylation was associated with a 1.6-fold increase of ICC risk [46]. Downregulation of PEG3 is found in glioma cell lines and glioma tissues, and its expression correlates with glioma subtype or grade [47]. PEG3 can also affect other cancers with the following biological behaviors.

Cell apoptosis

PEG3 is a potential regulator of p53/c-Myc mediated apoptosis through cooperating with Siah1 to regulate Tax translocation in fibroblast cell lines [48]. Other studies found that PEG3 is upregulated in response to DNA damage in a p53-dependent manner, leading to decreased neuronal survival [49].

Angiogenesis

PEG3 is also involved in endothelial cell autophagy, which is related to angiogenesis and tumorigenesis, by regulating transcription factor EB (TFEB) induction and nuclear translocation [50]. Another study investigating its role in endothelial cell autophagy showed that PEG3 increases Beclin 1 promoter activity and expression, which concurrently inhibits endothelial cell migration and invasion [51].

Cell proliferation

PEG3 regulates the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signal transduction pathway related with cell growth by interacting with tumor necrosis factor receptor-associated factor 2 (TRAF2) [52]. Because of its high expression in glioma [47, 53], it may lead to increased Wnt/β-catenin signaling and promote proliferation [53]. In vitro experiments showed that transfection of PEG3 inhibited colony forming ability in glioma cell lines [54]. In addition, low expression of PEG3 was reported in ovarian and endometrial cancers by global gene expression analysis [55]. Pyrosequencing demonstrated that hypermethylation of the CpG island may account for its silence, and re-expression of PEG3 inhibited the growth and proliferation of ovarian cancer cells [56]. A different study confirmed that PEG3 functions as a tumor suppressor in ovarian cancer because of hypermethylation of the PEG3-CpG island [57].

Stem cell properties

A recent study showed that PEG3 is related to mesoangioblast stem cell differentiation and migratory potential by acting as a transcription factor repressing target genes [58].

ZNF protein 24 (ZNF24)

ZNF24, also known as ZNF191 or KOX17, is located on chromosome 18q12.1, which is frequently deleted in colorectal cancer [59, 60]. Microarray analysis after overexpression or knockdown of ZNF24 showed that ZNF24 may modulate numerous genes associated with tumor growth, including inhibitory and positive effects [59].

Tumor suppressor

The expression of vascular endothelial growth factor (VEGF), a stimulator of angiogenesis, is inversely correlated with that of ZNF191 in human breast and colon carcinoma cells [61]. This indicates that ZNF24 may act as a negative regulator in cancer by inhibiting angiogenesis. In vitro, electrophoretic mobility shift

assays and chromatin immunoprecipitation assays showed that ZNF24 binds to the VEGF promoter to repress its transcription. In vivo, a transgenic zebrafish model confirmed the inhibitory effect of ZNF24 on tumor angiogenesis [62]. Another transcriptional target of ZNF24 is the receptor protein tyrosine kinase platelet-derived growth factor receptor-b (PDGFR-b), which affects cellular proliferation, migration, and survival [63]. In gastric cancer, ZNF24 acts as a potential suppressor in the microRNA-940 mediated epithelial mesenchymal transition process [64].

Tumor promoter

In hepatocellular carcinoma, ZNF24 binds directly to the promoter of β-catenin, activating its transcription and promoting cell proliferation [65]. Similarly, a positive role of ZNF24 in the regulation of proliferation and angiogenesis was reported in human primary microvascular endothelial cells [60]. Investigation of the underlying mechanism showed that silencing of ZNF24 upregulates cell cycle inhibitors such as cyclin dependent kinase inhibitor 3 and downregulates cell cycle activators such as cyclin D2. Furthermore, knockdown of ZNF24 decreased the expression of migration promoters such as vascular endothelial growth factor receptor 2 (VEGFR2) and MMP2 [60].

ZKSCAN domain 1 (ZKSCAN1)

ZKSCAN1, also known as ZNF139, is closely associated with gastric cancer. A group from China reported that ZNF139 is overexpressed in gastric cancer tissues and cells, especially in metastatic tissues. Immunohistochemical analysis of 108 gastric cancer tissue samples and paired adjacent tissues showed that ZNF139 was negatively related to prognosis [66]. This finding revealed its role as an independent prognostic factor in gastric cancer [66]. In vitro and in vivo experiments indicated that ZNF139 may promote cell viability and proliferation by modulating the apoptosis pathway [67]. This result was confirmed by another group [68]. Furthermore, small interfering RNA mediated knockdown of ZNF139 expression effectively reduced gastric cancer cell invasion and migration ability [69]. Regarding its role in chemotherapy resistance, this group showed that the expression of ZNF139 was positively correlated with resistance to therapy [66]. In melanoma, a new fusion protein, ZKSCAN1-MET, was predicted through DNA sequence and confirmed by RT-PCR. This fusion transcript includes a scan domain at the N-terminal of the kinase domain of mesenchymal epithelial transition (MET), which is integral for MET to become constitutively active. It was identified that ZKSCAN1-MET may active the mitogen-activated protein kinase (MAPK)/PI3K signaling pathway and may play important roles in tumor progression [70]. However, its inhibition effect on cell growth, migration and invasion is demonstrated in hepatocellular carcinoma [71].

ZKSCAN domain 3 (ZKSCAN3)

ZKSCAN3, a novel "driver" of cancer progression, is located on chromosome 6p22.1, which is amplified in colorectal cancer. Its overexpression in tumor tissues compared with adjacent nonmalignant mucosa was confirmed by qPCR and immunohistochemistry [72]. A recent study demonstrated a direct relationship between ZKSCAN3 and carcinoembryonic antigen, which plays an active role in the development of colorectal cancer liver metastasis. The results indicated that ZKSCAN3 may facilitate hepatic metastasis [73]. Unbiased screening identified many candidate downstream genes of ZKSCAN3, including several genes favoring tumor progression such as integrin β4, which plays an important role in breast and colorectal cancer tumorigenicity by activating phosphatidic 3-kinase [74]. Datasets from Oncomine and the multiple myeloma genomics portal (MMGP) reveal that the mRNA level of ZKSCAN3 is increased in primary patient samples. It may bind directly to the promoter of cyclin D2, inducing its expression and promoting myeloma proliferation [75]. ZKSCAN3 is also highly expressed in prostate cancer, especially in metastatic prostate cancer. Exogenous expression of ZKSCAN3 promotes prostate cancer cell migration and tumor progression [76]. ZKSCAN3 may also act as a transcriptional repressor of autophagy in bladder cancer cells. It transcriptionally modulates the expression of more than 60 genes involved in various steps of autophagy and lysosome biogenesis [77]. In a research of uterine cervical cancer, clinicopathological analysis and immunohistochemistry shows that ZKSCAN3 is strongly overexpressed in cancer samples [78]. What's more, ZKSCAN3

also promotes cell proliferation, migration and invasion in breast cancer [79].

Other family members

In addition to these well-reported ZSCAN transcription factors, other family members involved in tumor progression have been identified.

ZSCAN4, an important gene expressed in embryo development [80], regulates genome maintenance and telomere extension in embryonic stem cells [81]. The interaction between ZSCAN4 and Rap1 or TRF1, telomere-associated proteins, is also confirmed in cancer cells [82, 83]. In a recent report about resistance to anticancer treatments, ZSCAN4 was found to take part in telomeric DNA damage repair [84].

ZSCAN10, also known as ZNF206, functions as a differentiation repressor in mouse embryonic stem cells [85], and it is one of the important factors associated with human neuroblastoma genesis [86].

In basal cell carcinoma, ZNF396 prevents tumor cell differentiation and promotes cell proliferation [87].

Low expression caused by promoter DNA methylation of ZSCAN18 is found in most gastrointestinal cancers, such as colorectal, gastric, and pancreatic cancer [88]. This finding suggests that ZSCAN18 serves as a biomarker in gastrointestinal cancers.

A study on cervical cancer that analyzed microarray gene expression profiles from patients treated with radiotherapy and chemoradiotherapy showed that ZNF449 is involved in the regulation of differentially expressed genes in response to radiotherapy and chemoradiotherapy [89].

ZKSCAN4 is a transcription factor that was identified approximately 10 years ago. ZKSCAN4 inhibits the transcriptional activities of p53 and p21 [90], and it was shown to interact with the glucocorticoid receptor and play a role in cell proliferation [91].

ZSCAN7, also known as ZNF165, is highly expressed in several tumors, such as hepatocellular carcinoma (HCC), gastric cancer, colon cancer, non-small cell lung carcinoma, and urinary bladder cancer [92-94]. In soft tissue myoepithelial carcinoma, a novel fusion gene EWSR1-ZNF444 was identified and shown to contribute to tumorigenesis [95].

Genome-wide methylation analysis shows that ZSCAN12 is hypermethylated in bladder cancer, especially in high-grade disease. This conclusion is validated in other data sets from TCGA [96].

An expression profile signature analysis of oral squamous cell carcinoma (OSCC) using data derived from two different sources shows that ZSCAN16 is differentially expressed between node-positive OSCCs with and without extracapsular spread [97].

A single-nucleotide polymorphism (SNP) analysis of Thyrotropin (TSH)-secreting pituitary adenomas detects a novel DNA candidate driver mutation of ZSCAN23 [98].

To identify novel mutations in endometrial cancer patients, whole-exome sequencing is performed. The results show ZSCAN29 may act as a potential passenger gene [99].

A genome-wide DNA methylation study in lung cancer suggests ZSCAN31 as a novel gene target [100].

Weighted gene co-expression network analysis shows ZNF215 can be used as a biomarker for diagnosis and prognosis of the basal like breast cancer [101].

ZNF496 is found to be an interactor of ERα in breast cancer cells, this interaction selectively represses target genes transcription and so that inhibits cell proliferation [102].

Potential mechanisms underlying the dual function of ZSCAN transcription factors

General patterns of transcriptional regulation by transcription factors

Transcription factors are critical determinants of gene expression. Their transcriptional activities are multivariate, and many factors such as nuclear-plasma transposition, post-translational modifications, and interaction with other cofactors can change transcriptional output. Furthermore, several transcription factors may bind to the same or independent cis element,

including promoter, intron, or enhancer, and work together to regulate transcription.

Diverse roles of ZSCAN transcription factors in transcriptional regulation

ZSCAN transcription factors have different functions and may even elicit opposing effects on cancer progression. The differential transcriptional regulation of various genes may account for the controversial function of these transcription factors. A wide variety of downstream genes can be regulated by ZSCAN transcription factors, and their transcriptional function may be context-dependent. Binding of ZSCAN transcription factors to specific promoter sequences is mediated by their zinc finger motif. By binding to different target sequences, these transcription factors may favor distinct cofactors, thereby activating or repressing transcription in different cell types [103, 104]. The oncogene of gastric cancer, ZNF139, may increase the expression of a large set of genes related to cell migration and invasion, such as MMP-2, MMP-9, and intercellular adhesion molecule 1 (ICAM-1) [68]. The suppressive role of ZNF307 was confirmed by its effect on p53 expression [90].

Many family members function as both transcriptional activator and repressor, such as MZF1 and ZKSCAN3 [5, 105]. ZKSCAN3 transcriptionally activates integrin β4 and VEGF during colorectal tumorigenesis [74]. It can also transcriptionally repress Map1lC3b and Wipi2, which are involved in autophagy and lysosome biogenesis [77]. Four and a half Lim domain protein-3 (FHL3) is a co-repressor of MZF1 and participates in the regulation of genes related to cancer development [106], whereas in osteosarcoma, MZF1 binds to the YAP1 enhancer and upregulates its expression [38].

Elucidating the potential mechanisms underlying the different effects of these transcription factors on transcriptional regulation is important. Many studies show that protein interactions and post-translational modifications play important roles in the modulation of the transcriptional activity.

Potential mechanisms of transcriptional regulation by ZSCAN transcription factors

Interaction through the SCAN domain: homodimer or heterodimer

Several studies indicated that the SCAN domain acts as a protein interaction domain to form homodimers. A yeast two-hybrid assay showed that ZNF174 forms homodimers via the SCAN domain 13. This self-oligomerization can promote DNA binding affinity and specificity, because PEG3 binds to certain target genes as a homodimer [107].

Many family members of the ZSCAN transcription factors have different protein isoforms, among which longer ones have the SCAN domain and DNA-recognition element zinc finger domain, whereas the smaller ones have only the SCAN domain, such as ZNF202 [108] and MZF1. Interestingly, the smaller isoforms interact with the intact form and change its transcriptional capacity [5, 109].

In addition to these interactions, the SCAN domain can also regulate heterodimer formation between different family members, and this interaction affects the activation of transcription factors. For example, co-localization of MZF1 and ZNF24 was found in the nucleus by immunofluorescence, and GST pull-down assays confirmed this interaction. However, the mutant MZF1 without the SCAN domain shows disrupted co-localization with ZNF24 in the nucleus [110]. Moreover, SDP1, which encodes an isolated SCAN domain, abolishes the expressional capacity of ZNF202 by preventing binding of its co-repressor [108]. SDP1 was also reported to interact with a co-activator of peroxisome proliferator activated receptor gamma 2 (PPARg2) [111]. These SCAN-SCAN associations are selective, and not all the family members can interact with each other [5].

Although the interaction is important for transcriptional activity, the mechanisms have not been totally explored.

Interaction with epigenetic chromatin modification enzymes

During the regulation of transcription, transcription factors may recruit many co-regulators to form transcriptional complexes, including histone-modifying enzymes (histone acetyltransferases and histone methyltransferases) and chromatin remodeling factors, among others. ZNF274 recruits the histone methyltransferase SET domain bifurcated 1 (SETDB1) to H3K9me3 sites and represses transcription [112].

The recruitment of nuclear receptor binding SET domain protein 1 (NSD1), a SET-domain histone lysine methyltransferase, may be partly

associated with the ZNF496 repressor properties [113].

H2A.Z, which is involved in chromosome segregation, centromeric function, and transcriptional regulation, was identified as a novel interacting protein of ZNF24 by yeast two-hybrid, GST pull-down, co-immunoprecipitation, and co-localization assays [114].

Post-translational modifications

The post-translational modifications of transcription factors, especially phosphorylation, may also affect the transcription into different outcomes. The SCAN domain is defined as a leucine rich region, and as a result, phosphorylation mediates transcriptional activation. For example, TGFβ-receptor II-associated ErbB2 may activate downstream MZF1 in breast cancer [27]. ErbB2 activation results in phosphorylation of MZF1-S27, which so that results in increased transcriptional activity of MZF1.

SUMOylation is another kind of post-translational modification [115], and it is considered as an inhibitor of gene transcription [116, 117]. The potential mechanism may be that the SUMO interacting motifs (SIM) occur in the co-repressors, such as the HDAC1 complex [117]. Recruitment of these co-repressors to the SUMOylated transcription factors leads to gene repression [106]. SUMOylation also modulates ZSCAN transcription factors. For example, SUMOylated MZF1 is accumulated in promyelocytic leukemia nuclear bodies through this SUMO/SIM interaction, resulting in gene repression [110, 115, 118].

Regulation of the expression of ZSCAN transcription factors

In view of their essential roles in cancer, many studies focused on the regulation of the expression of ZSCAN transcription factors. Studies showed that gene mutation or alterations of gene copy number lead to different expressional levels of the ZSCAN transcription factors. This was reported for EWSR1-ZNF444 in soft tissue myoepithelial carcinoma [95] and ZKSCAN1-MET in melanoma [70]. Moreover, low expression of several members caused by promoter DNA methylation was also reported. For example, hypermethylation of the PEG3-CpG island was detected in many types of cancer [46]. Similarly, ZSCAN18 was found to be frequently methylated in gastrointestinal cancers [88]. Cancer related miRNA regulation or transcriptional regulation also accounts for expression differences. For instance, miRNA-940 may downregulate ZNF24 in gastric cancer [64]. Alternative promoters of PEG3 may change the potential cis-regulatory motifs involved in regulating the expression patterns of PEG3 [119]. Sequence analysis identified alternatively spliced transcripts of ZNF215 involved in congenital growth alterations because its five alternatively spliced transcripts were imprinted in a tissue-specific manner [120]. In summary, gene mutation, DNA methylation, miRNA regulation, and alternative splicing account for various expression levels of the ZSCAN transcription factors.

Discussion

Transcription factors dominate specific gene expression dynamically by recognizing and binding to short DNA sequence motifs. Recently, an increasing number of studies have shown that the ZSCAN transcription factors play important roles in cancer progression. Gene mutation, DNA methylation, alternative splicing, and miRNA regulation result in various expression levels of the ZSCAN transcription factors. ZSCAN transcription factors differentially regulate downstream genes, and therefore have different functions in cancer progression. These target genes may be involved in angiogenesis, cell apoptosis, cell differentiation, cell migration and invasion, cell proliferation, chemotherapy sensitivity, and stem cell properties. And their efforts involve different kinds of cancer, such as breast cancer, colorectal cancer, gastric cancer, glioma, and prostate cancer. In this article, we summarized 54 expressed members of the human ZSCAN family and their effects on cancer, among them several members such as MZF1, PEG3, ZNF24, ZKSCAN1, and ZKSCAN3 are well-reported. In addition to these known effects, the roles of many family members remain to be explored.

Regarding the potential underlying mechanisms, regulation of transcriptional activity seems to be quite important for the ZSCAN transcription factors. Protein-protein interactions are important for transcriptional regulation. The SCAN box, which mediates dimerization, is the

key domain and contributes to the mystery surrounding the ZSCAN transcription factors. It can form a homodimer with the transcription factor itself or a heterodimer with other proteins with SCAN box. Moreover, the recruitment of co-regulating molecules and post-translational modifications including phosphorylation and SUMOylation, may determine the different effects of these factors on transcription. A better exploration of the structure and the potential mechanisms underlying their selection of interacting partners is necessary. Moreover, elucidating the widespread regulatory mode of the ZSCAN transcription factors is essential.

In summary, a better understanding of the ZSCAN transcription factors will provide further insight into the mechanism of transcriptional regulation and suggest novel therapeutic strategies against tumor progression.

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Disclosure of conflict of interest

None.

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