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REVIEW

Cys2His2 Zinc Finger Protein Family: Classification, Functions, and Major Members

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Abstract—Cys2His2 (C2H2)-type zinc fingers are widespread DNA binding motifs in eukaryotic transcription factors. Zinc fingers are short protein motifs composed of two or three β-layers and one α-helix. Two cysteine and two histidine residues located in certain positions bind zinc to stabilize the structure. Four other amino acid residues localized in specific positions in the *N*-terminal region of the α-helix participate in DNA binding by interacting with hydrogen donors and acceptors exposed in the DNA major groove. The number of zinc fingers in a single protein can vary over a wide range, thus enabling variability of target DNA sequences. Besides DNA binding, zinc fingers can also provide protein–protein and RNA–protein interactions. For the most part, proteins containing the C2H2-type zinc fingers are *trans* regulators of gene expression that play an important role in cellular processes such as development, differentiation, and suppression of malignant cell transformation (oncosuppression).

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Many proteins that are capable of binding to distinct DNA sequences have been characterized to date. Bioinformatic analysis of DNA-binding domains of different proteins has identified a number of amino acid motifs capable of recognizing distinct DNA sequences via interaction with hydrogen donors and acceptors located in DNA major and minor grooves. The most widespread elements of various DNA-binding protein domains are so-called Cys2His2 (C2H2)-type zinc fingers (ZFs) [1]. ZFs are found in DNA-binding domains of about half of human transcription factors, both known and predicted from the data of bioinformatic analysis [2-4]. The typical C2H2-ZF is a short protein motif with two histidine and two cysteine residues that hold a zinc ion with coordination bonds. Such ZF is composed of α-helix and antiparallel β-structure (Fig. 1a). Four amino acid residues located in specific positions at the tip of the finger (in the *N*-terminal part of the α-helix) participate in DNA recognition by interacting with hydrogen donors and acceptors exposed in the major groove (Fig. 1b). One zinc finger recognizes a tri- or tetranucleotide sequence [5].

DNA-binding domains of a majority of transcription factors contain a group of tandem ZFs. Specificity of recognition of extended DNA sequences by tandem ZFs are considered to be largely determined by specificity of recognition of short sequences by individual ZFs [5]. However, the situation is complicated due to possible modification of specificity of DNA recognition by an individual ZF by adjacent ZFs [6, 7]. So, both prediction of DNA sequence recognized by tandem ZFs and construction of protein domains recognizing distinct DNA sequences are complex tasks [8, 9]. Nonetheless, several approaches were recently developed allowing construction of ZF tandems recognizing specific DNA sequences. The use of thus constructed DNA-binding protein domains provides a basis for gene-therapeutic approaches, including methods of genome editing. In recent years, many reviews have been published on this topic [10-14], so we do not focus on this. Natural proteins containing tandem ZFs have comparatively weak specificity to DNA sequences they interact with, recognizing motifs rather than strictly determined nucleotide sequences [15-21].

Abbreviations: a.a., amino acid residue; C2H2, Cys2His2; ZF, zinc finger.

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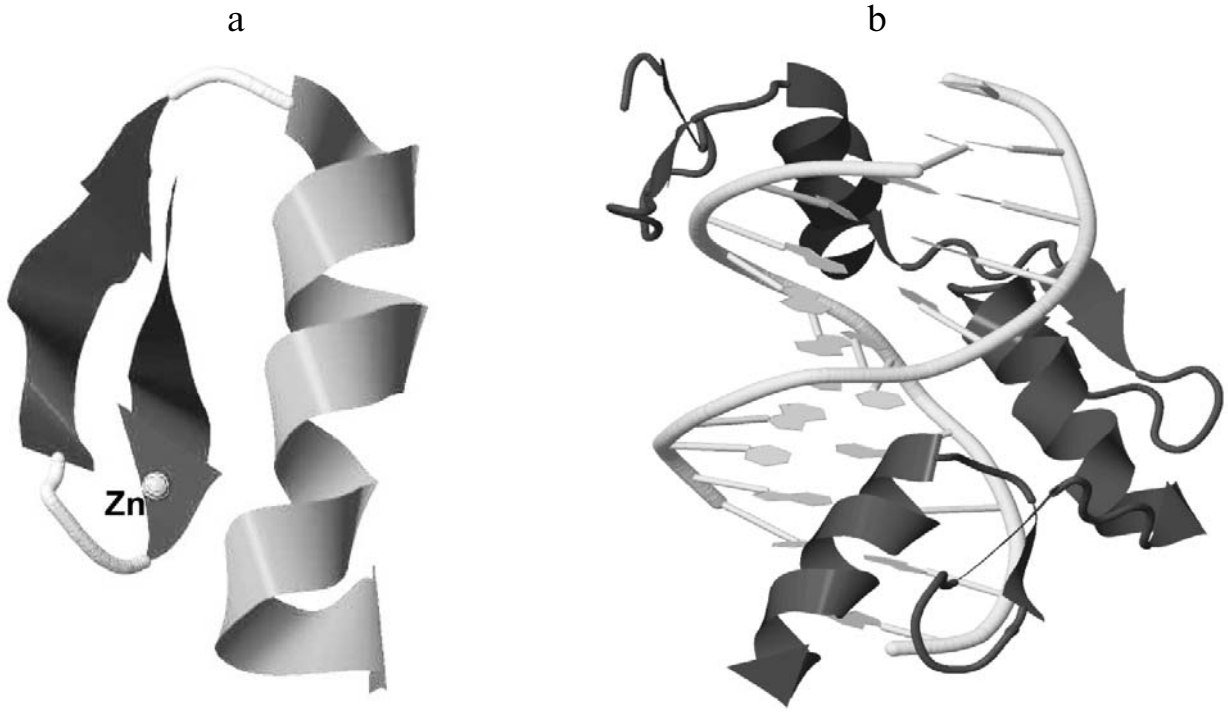

Fig. 1. Structure of zinc finger motif (PDB ID: 1ZNF) (a) and molecular model of the interaction between a domain composed of three zinc fingers and DNA (PDB ID: 1A1J) (b).

Although zinc fingers were first found in DNA-binding domains of various proteins, it is obvious at present that they can also recognize various motifs in RNAs and proteins [22-25]. In the human genome around 1000 genes encode proteins containing zinc fingers (ZF-proteins). As a rule, ZFs are tandemly arranged in blocks composed of 40 or more individual ZFs. Many proteins have several ZF-containing domains. Being capable of specifically interacting with DNA, RNAs, and proteins, ZF-proteins can provide links between these major classes of biological macromolecules.

Besides ZFs, ZF-containing transcription factors contain additional conservative amino acid motifs. These structural domains are implicated in regulation of intracellular localization, DNA binding, and gene expression via control of interaction of these transcription factors with each other and with other cellular targets. The C2H2-type proteins can contain the BTB (Broad-complex, Tram track, and Bric-a-brac proteins)-domain [26], also known as POZ (Poxvirus and Zinc finger)-domain [27], KRAB (Kruppel-associated box)-domain [28], and SCAN-domain as well [29, 30]. These domains – either separately or in combinations (for instance, KRAB A and SCAN) – comprise more than a half the characterized ZF-proteins. Presence of these domains allows division of ZF-containing transcription factors into functional groups with differing implication in gene expression regulation. Both the proteins containing tandem ZFs and the proteins containing not only ZFs, but also the other mentioned domains will be considered below.

CLASSIFICATION OF C2H2-ZF-PROTEINS

Given localization and number of zinc fingers, all C2H2-ZF-proteins, which are present in genomes of vertebrates, in particular humans, can be divided into three major groups [31].

The first group consolidates the proteins containing one cluster of three close ZFs. Many various transcription factors, such as the KLF (Kruppel-like factors) family [32] and related family of SP-factors (SP1-like transcription factors) [33, 34] belong to this group. All transcription factors belonging to the KLF family (17 KLF factors are found in the human genome) are characterized by the presence of a conserved DNA-binding domain composed of three ZFs located in the *C*-terminal part of the polypeptide chain. The *N*-terminal part of the polypeptide chain of different KLF factors can contain domains that directly influence assembly of the transcription preinitiation complex or bind coactivators and, sometimes, corepressors, so that biological functions of KLF members are very diverse [32].

The second ZF-protein group contains proteins containing one pair or more of ZFs; in the latter case individual ZF pairs are located far from each other. This

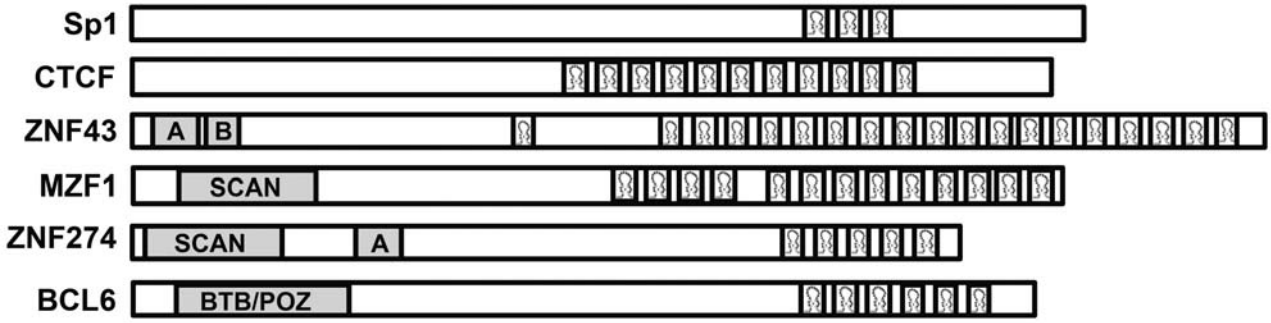

Fig. 2. Schematic representation of domain structure of several C2H2-ZF-proteins. Proteins are specified on the left. Gray rectangles denote domains KRAB A (A), KRAB B (B), SCAN, and BTB/POZ; light rectangles denote the C2H2-type zinc finger motif.

is the smallest group that includes several transcription factors, such as tramtrack (TTK) (one ZF pair), PRDII-BF1 [35] (two ZF pairs), and basonuclin [36, 37] (three ZF pairs).

The third (and the most abundant) group of ZF-proteins is characterized by presence of clusters composed of four or more ZFs. One protein can contain one or several domains containing several closely spaced ZFs. The most talked-about member of this group is the multifunctional transcription factor CTCF containing 11 ZFs arranged in one cluster [38-41]. Other examples of ZF-proteins containing numerous ZFs are MZF1 [21], Nizp1 [42], ZNF394 [43], and many other functionally important C2H2-ZF-proteins.

Division of ZF-proteins into the above three groups is not completely definite. Some proteins (for example, ZNF305 and PEG3) contain both paired ZFs and clusters composed of more than four ZFs.

Other classifications of ZF-proteins take into account the presence of additional, ZF-unrelated, conserved domains (Fig. 2). The most widespread of them, the KRAB-domain, is found in 45% of the annotated human C2H2-ZF-proteins [28]. The KRAB-domain is composed of two subdomains, KRAB A (about 38 a.a.) and KRAB B (about 32 a.a.). The KRAB B-domain may either be absent or replaced by a KRAB b (about 32 a.a.) or KRAB C (about 21 a.a.) domain [44-46]. KRAB A is a repressor domain that recruits KAP1 protein, an element of the repressor complex containing SETDB1 histone methylase that trimethylates histone H3 at lysine 9 [47], which, in turn, recruits heterochromatin protein 1 (HP1) and stimulates formation of heterochromatin domain [48].

Seven percent annotated human C2H2-ZF-proteins contain a leucine-rich conserved domain of about 84 a.a. called SCAN [29, 30]. This name is composed of the first letters of names of four C2H2-ZF-proteins (SRE-ZBP, CTfin51, AW-1 (ZNF174), and Number 18 cDNA), which analysis has led to identification of this domain. It has been demonstrated using the yeast two-hybrid system and some other experimental approaches that SCAN-domains of various proteins can form homo- and heterodimers [49-51]. The role of homo- and heterodimerization of C2H2-ZF-proteins containing the SCAN-domain is just beginning to be explored. In particular, the SCAN-domain was demonstrated to be essential for localization of MZF1 (a C2H2-ZF-transcription factor that plays an important role in differentiation of myeloid cells) in PML-bodies of the cell nucleus, in which it very likely forms heterodimers with ZNF34, another C2H2-ZF-SCAN-protein [52]. Despite highly conserved sequences of SCAN-domains, stability of their homo- and heterodimers differs significantly [51, 53]. Some SCAN-domains cannot form homodimers. The most thoroughly studied SCAN-domain of the protein ZNF174 only forms heterodimers with a few of the tested SCAN-domains of other proteins [54].

Some annotated C2H2-ZF-proteins (2.5% of annotated human C2H2-ZF-proteins) contain both KRAB- and SCAN-domains [28]. There is no data on the interaction between SCAN-domains and other protein motifs. At the same time, SCAN-domains were also found in proteins that do not contain zinc fingers [51]. So, the spectrum of C2H2-ZF-SCAN-protein partners can be quite broad.

Besides the above-mentioned domains, C2H2-ZF-proteins often contain the BTB-domain or POZ-domain (5.7% of annotated human C2H2-ZF-proteins) [26, 27]. One can find in the literature either name or the combined name BTB/POZ. This domain is rather long (~120 a.a.) and can form dimers and oligomers and interact with other proteins, including some not having a BTB/POZ-domain [55]. The BTB/POZ-domain also demonstrates repressor features mediated by recruitment of corepressors [56-58]. BTB/POZ-C2H2-ZF-proteins also concentrate in a small number of nuclear compartments, which is attributed to BTB/POZ-domain oligomerization [59-61]. Although the BTB/POZ-C2H2-ZF-protein family is relatively small, it contains many functionally important transcription factors, such as PLZF (promyelocytic leukemia zinc finger), Bcl-6 (B cell lymphoma 6), HIC-1 (hypermethylated in cancer 1), Kaiso

(protein recognizing methylated CpG-dinucleotides with its zinc fingers), and FAZF (Fanconi anemia zinc finger) associated with cell differentiation and malignization [62].

FUNCTIONS OF C2H2-ZF-PROTEINS

The functional roles of a majority of annotated C2H2-ZF-proteins are poorly understood. There are several experimental approaches to solve this problem, including analysis of genomic targets the studied C2H2-ZF-proteins bind with, search for protein partners, study of their influence on DNA transcription in nuclear extracts of *Xenopus* oocytes and other systems, and analysis of consequences of knockout or temporary switching-off of transcription of a particular C2H2-ZF-protein. All these approaches are labor-intensive, so that a systematic examination of all annotated C2H2-ZF-proteins has not been done. Studies have been primarily focused on functions of C2H2-ZF-proteins whose altered expression correlates with development of some particular disease [62] and on functional properties of conserved domains comprising C2H2-ZF-proteins as well. The most of functionally important C2H2-ZF-proteins in some way influence transcription of individual genes or gene groups.

Before analyzing mechanisms of transcription control by C2H2-ZF-proteins, it is worth noting that in eukaryotes transcription is regulated at several levels, including the level of assembly of a preinitiation complex on a promotor and at the level of gene folding into various types of chromatin domains [63]. Among C2H2-ZF-proteins, some are transcription activators and some are suppressors. Most of the known C2H2-ZF-activators of transcription act at the level of individual promoters, facilitating assembly of a stable transcription preinitiation complex. Examples include a large KLF family of transcription factors [32] and related family of SP1-like factors [34]. SP1 is necessary for recruitment of TATA-binding protein (TBP) to promoters that do not contain the TATA-box. Other transcription activators belonging to the KLF/SP-groups also contain domains directly influencing the transcription preinitiation complex assembly. Some transcription repressors also bind to gene promoters, directly hampering assembly of the preinitiation complex. An example is NZFP factor belonging to the C2H2-ZF-protein group with multiple zinc fingers. NZFP directly interacts with TBP, thus counteracting its interaction with general transcription factors TFIIA and TFIIB [64].

Most of the studied C2H2-ZF-proteins are transcription repressors. However, the repression is commonly realized via creation of an inactive chromatin domain rather than via direct influence on preinitiation complex assembly. This can be achieved in different ways, such as histone deacetylation (an easily reversible modification), histone methylation, recruitment of HP1 protein, and formation of a sufficiently stable repressed domain (heterochromatin). C2H2-ZF-proteins themselves do not possess enzymatic activities. Due to the presence of a DNA-recognizing domain and some other domains capable of binding other proteins, they act as "conductors" recruiting various enzymatic complexes to distinct genome sites. Existence of various domains, particularly conserved domains KRAB, SCAN, and BTB/POZ, which can interact with other proteins, is essential for integration of C2H2-ZF-proteins into various multienzyme complexes executing histone modifications and chromatin remodeling.

The best studied are KRAB-C2H2-ZF-repressors. These proteins recruit a protein complex initiating formation of facultative heterochromatin to their genome targets [47, 48, 65]. The process is mediated by recruitment of the corepressor KAP1 [66] that directly binds to the KRAB-domain. In turn, KAP1 attracts the multifunctional complex NURD (a complex causing chromatin remodeling and histone deacetylation) and histone methylase SETDB1 that initiates heterochromatin formation by trimethylation of histone H3 at K9 [67, 68]. The human genome encodes several hundred KRAB-C2H2-ZF-repressors [69]. So, an important question is: what genes are the targets of these repressors? Recent studies [70, 71] have shown that such targets are endogenous retroviruses. A hypothesis that endogenous retroviruses are key targets of KRAB-C2H2-ZF-repressors is also confirmed by the data of bioinformatic analysis indicating tight correlation between the number of genes encoding KRAB-C2H2-ZF-proteins and the number of LTR-containing endogenous retroelements in vertebrate genomes [72]. The list of genes inactivated by KRAB-C2H2-ZF/KAP1 is not restricted to retroelements. KAP1 is located on 3′-ends of many genes encoding C2H2-ZF-proteins [73, 74]. This suggests that KRAB-C2H2-ZF-proteins regulate transcription of their own genes in feedback manner. Full-genome analysis of KAP1-binding sites using the ChIP-on-Chip technique has revealed many other genes inactivated with the involvement of KAP1 [74].

Many of BTB/POZ-C2H2-ZF-proteins also play a role of transcription repressors. Like KRAB-C2H2-ZF-proteins, they repress by recruitment of histone modifying complexes. However, unlike KAP1, corepressors recruited by BTB/POZ-proteins do not stimulate formation of facultative heterochromatin. In most cases, suppression of transcription occurs via histone deacetylation. A typical example is the oncoprotein LAZ3 (BCL6). This protein recruits a repressor complex containing SMRT, mSIN3A, and histone deacetylase HDAC-1; the latter interacts directly with the LAZ3 (BCL6) BTB/POZ-domain. The LAZ3 (BCL6) repressor activity is significantly suppressed by inhibitors of histone deacetylases, which directly indicates the crucial

role of these enzymes in transcription repression caused by LAZ3 (BCL6) [57, 58]. Another BTB/POZ-transcription factor, PLZF (promyelocytic leukemia zinc finger), which is often damaged in various leukemias, also recruits histone deacetylase comprising the SMRT-mSin3-HDAC complex [75-77]. Both BCL6 and PLZF can also recruit class II histone deacetylases, particularly HDAC-4, HDAC-5, and HDAC-7 [78, 79]. Other BTB/POZ-C2H2-ZF-proteins also suppress transcription via recruitment of histone deacetylases. The BTB/POZ-C2H2-ZF-repressor Kaiso, which binds methylated CpG-dinucleotides [80], represses by recruitment of the N-CoR corepressor [81], which is tightly associated with HDAC-3 [82] and other histone deacetylases as well [83, 84].

These data suggest the following conclusion: repression mechanisms of KRAB- and BTB/POZ-C2H2-ZF-proteins differ significantly. The KRAB-C2H2-ZF-proteins recruit corepressors, which stimulate formation of facultative heterochromatin. This kind of repression is a long-term and can be sustained over cell generations. In contrast, the BTB/POZ-proteins recruit corepressors deacetylating histones. This repression is easily reversible.

The SCAN-domain has no pronounced activating or repressor activity. Nevertheless, one should take in account that many ZF-proteins contain both a SCAN-domain and one or more KRAB-domains. Dimerization of such proteins via association of SCAN-domains can influence the ability of the KRAB-domain to bind to KAP1 [85]. In some cases, the SCAN-domain determines the protein localization in subnuclear compartments [52, 86].

About half of the annotated C2H2-ZF-proteins do not contain SCAN-, KRAB-, and BTB/POZ-domains. Nonetheless, many of them are repressors recruiting various corepressor complexes. The notable examples are Ikaros and related proteins (Aiolos, Helios, Eos, and Pegasus) playing a crucial role in control of lymphoid cell differentiation [87-89]. The Ikaros molecule contains two ZF groups: an *N*-terminal group essential for DNA recognition and a *C*-terminal group essential for dimerization and interaction with other proteins. With its *C*-terminal ZFs, Ikaros recruits different corepressor complexes containing histone deacetylases, such as mSin3, NURD, and CtBP [90-93]. The C2H2-ZF-protein Myt1 (myelin transcription factor 1) controlling differentiation of central nervous system cells recruits histone deacetylases via complex formation with Sin3B [94]. The list of C2H2-ZF-repressors recruiting histone deacetylases is rather large [95-97]. In many cases, histone demethylase BHC110/LSD1 removing the active chromatin label (H3K4 trimethylation) is recruited together with histone deacetylases [98]. It was also shown that, besides the above enzymes and enzyme complexes, the C2H2-ZF-protein ZNF217 recruits histone methylases methylating histone H3 at K9 and K27. The enzyme methylating H3K9 is histone methylase G9a [99]. The only known enzyme methylating H3K27 is the methylase EZH2 comprising one of the Polycomb complexes. Thus, there is a reason to believe that ZNF217 also recruits this repressor complex [99].

As mentioned above, most known C2H2-ZF-proteins activating transcription are functioning at the level of transcription preinitiation complex assembly. Nonetheless, in some cases, C2H2-ZF-proteins recruit activating complexes to distinct chromatin domains. Histone deacetylases, in particular p300, play the role of coactivators [100, 101].

THE MOST BIOLOGICALLY IMPORTANT MEMBERS OF THE C2H2-ZF-PROTEIN FAMILY

C2H2-ZF-Proteins Lacking Additional Conserved Domains

SP1 is a universal transcription factor that is necessary for transcription preinitiation complex assembly on a wide range of eukaryotic RNA-polymerase II promoters lacking an expressed TATA box. The DNA-binding domain is composed of three ZFs recognizing GC-rich motifs (GC/GT boxes). About 12,000 SP1-binding sites are known in the human genome [102]. Initially, SP1 was supposed to preferably activate housekeeping genes associated with CpG-islands, but it became obvious recently that this factor is also implicated in expression regulation of many tissue-specific and inducible genes, including those controlling the cell cycle and apoptosis [33, 103-107]. Some factors exist related to SP1 protein, including SP3, recognizing the same motifs of nucleotide sequence. Competition between these factors for binding sites contributes to regulation of genes controlled by SP1 [107]. Although the main mechanism of transcription activation/inhibition by SP1 and SP3 is the direct influence on preinitiation complex assembly, these transcription factors can also recruit various coactivators and corepressors, such as chromatin remodeling complexes [108, 109], histone deacetylases (complex Sin3A) [110, 111], and histone acetylases [107, 112].

The KLF transcription factor family. This transcription factor family closely resembles the SP transcription factor family. Sometimes the two families are fused together. The KLF transcription factors play an important role in control of hematopoiesis [113, 114] and a number of other differentiation pathways [32]. Like SP members, the KLF factors can recruit various coactivators and corepressors [32].

Ikaros and related proteins (Aiolos, Helios, Eos, and Pegasus). This group of transcription factors plays a crucial role in differentiation of lymphoid and myeloid cells [87-89]. Dysfunction of proteins of this group is often observed in various leukemias [115-117].

CTCF. Initially, CTCF was described as a factor regulating the transcription of the *c-myc* gene [118, 119]. This protein is now better known for its implication in function of enhancer-blocking elements [120, 121]. At the same time, CTCF is a communicating protein maintaining the 3D structure of the eukaryotic genome [122-125]. Functional tests have demonstrated that cooperation between CTCF and cohesin is essential for maintenance of 3D organization of the genome [126, 127]. One of the subunits of cohesin (SA2) interacts directly with a distinct area of the CTCF *C*-terminal domain [128].

BORIS (brother of the regulator of imprinted sites, CTCFL). It is a CTCF paralog that is only expressed in cells that do not express CTCF, namely, in spermatocytes [129]. BORIS contains the same 11 ZFs as CTCF, but it differs from the latter in its *C*- and *N*-terminal sequences [129].

WT1 (Wilms' tumor gene). The tumor suppressor WT1 discovered in the 1990s [130, 131] plays an important role in urogenital development, and in the mature organism it is expressed in gonads and mesothelial tissues. Mutations of WT1 are found in 10-15% of Wilms' tumors (nephroblastoma), as well as in acute myeloid leukemia and Denys–Drash and Frasier syndromes [132-136]. Apart from four C2H2-type zinc fingers, WT1 also contains a Q/P-rich transregulatory domain and a domain responsible for dimerization [137]. In gene expression regulation WT1 can be either a transcription activator [138] or coactivator [139] or repressor [140].

YY1 (Yin Yang 1) is a multifunctional ZF-protein containing four C2H2-type zinc fingers that can either activate or suppress transcription of multiple cellular and viral genes [141]. Interestingly, under certain conditions YY1 can functionally substitute for the TATA-binding protein (TBP). It was shown that YY1 taken together with TFIIB and RNA-polymerase II can correctly initiate transcription *in vitro* [142]. It is also known that YY1 can be associated with mRNP in *Xenopus* oocytes [143]. Overexpression of YY1 is observed in development of some cancers [144].

BTB/POZ-C2H2-ZF-Proteins

HIC1 (hypermethylated in cancer 1). This protein is an anti-oncogene that often undergoes inactivation in tumors via methylation of its promotor [145]. The HIC1 DNA-binding domain is made up of five tandem zinc fingers. Expression of HIC1 is controlled by the tumor suppressor p53 [145, 146]. Knockout of both HIC1 alleles is lethal (death occurs in embryogenesis) [147]. Heterozygous mice with one HIC1 knocked-out allele (*Hic1*+/–) demonstrate a broad spectrum of malignant neoplasias [148].

PLZF (promyelocytic leukemia zinc finger). The human *PLZF* gene initially attracted attention because of the chromosomal rearrangement t(11;17)(q23;q21) resulting in formation of a chimeric gene *PLZF-RAR-α* (retinoic acid receptor α) and development of acute promyelocytic leukemia [149, 150]. The normal retinoic acid receptor binds with a series of corepressors, such as NCoR, HDAC-1, SMRT, and mSin3A, which are released following the interaction of the receptor with retinoic acid [84]. The chimeric receptor (PLZF-RAR-α) also binds these corepressors, but their complete release following the interaction with retinoic acid does not occur, so the chimeric protein acts as a dominant inhibitor of the normal receptor [151, 152]. As a result, expression of a series of genes controlling apoptosis, cell cycle, and DNA repair is dysregulated. The wild-type PLZF can also be directly implicated in control of cell proliferation via suppression of *c-myc* gene expression [153]. Consequences of murine PLZF knockout have shown an important role of this gene in control of skeleton (particularly limb) formation [154]. Elimination of both PLZF alleles led to dysregulated expression of *Hox*-genes. This is most likely because PLZF recruits the Polycomb complex to regulatory elements of a number of *Hox*-genes [155].

LAZ3/BCL-6 (B cell lymphoma 6). The gene *LAZ3/BCL6* originally attracted attention because its rearrangements are often observed in some B cell lymphomas. It is now considered to be an oncogene [156]. At the same time, BCL-6 is a key regulator of B- and T-lymphocyte differentiation [62, 157]. As a transcription repressor, BCL6 counteracts expression of genes required for final stages of B- and T-cell differentiation. In addition, BCL6 directly controls transcription of a number of genes essential for DNA repair, cell cycle arrest, and the function of various signaling pathways, such as the cytokine-, toll-like receptor-, TGFβ-, and WNT-signaling pathways [157]. Mice with both knocked-out BCL6 alleles are viable, but they demonstrate germinal hypoplasia and attenuated inflammatory response [158].

C2H2-ZF-proteins comprise the second largest gene family in the human genome. Distinct functions of the majority of these proteins remain unknown. However, many of them are transcription repressors. Mechanisms of repression can vary, but they are commonly associated with recruitment of various groups of corepressors. About half the annotated human C2H2-ZF-proteins contain so-called KRAB-domain and are capable of initiating formation of facultative heterochromatin via recruitment of H3K9 histone methylases and heterochromatin protein HP1. It seems that these proteins are essential for establishment and maintenance of differentiated cell status during development. Many characterized C2H2-ZF-proteins are integrated into various multienzyme complexes, in which they can play the role of DNA-binding subunit recruiting these complexes to distinct genomic sites.

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REFERENCES

1. Klug, A., and Schwabe, J. W. (1995) *FASEB J.*, **9**, 597-604.
2. Messina, D. N., Glasscock, J., Gish, W., and Lovett, M. (2004) *Genome Res.*, **14**, 2041-2047.
3. Emerson, R. O., and Thomas, J. H. (2009) *PLoS Genet.*, **5**, e1000325.
4. Fulton, D. L., Sundararajan, S., Badis, G., Hughes, T. R., Wasserman, W. W., Roach, J. C., and Sladek, R. (2009) *Genome Biol.*, **10**, R29.
5. Wolfe, S. A., Nekludova, L., and Pabo, C. O. (2000) *Annu. Rev. Biophys. Biomol. Struct.*, **29**, 183-212.
6. Choo, Y., and Klug, A. (1994) *Proc. Natl. Acad. Sci. USA*, **91**, 11168-11172.
7. Isalan, M., Choo, Y., and Klug, A. (1997) *Proc. Natl. Acad. Sci. USA*, **94**, 5617-5621.
8. Lam, K. N., van Bakel, H., Cote, A. G., van der Ven, A., and Hughes, T. R. (2011) *Nucleic Acids Res.*, **39**, 4680-4690.
9. Ramirez, C. L., Foley, J. E., Wright, D. A., Muller-Lerch, F., Rahman, S. H., Cornu, T. I., Winfrey, R. J., Sander, J. D., Fu, F., Townsend, J. A., Cathomen, T., Voytas, D. F., and Joung, J. K. (2008) *Nat. Methods*, **5**, 374-375.
10. Molparia, B., Goyal, K., Sarkar, A., Kumar, S., and Sundar, D. (2010) *Genom. Proteom. Bioinform.*, **8**, 122-126.
11. Klug, A. (2010) *Annu. Rev. Biochem.*, **79**, 213-231.
12. Santiago, Y., Chan, E., Liu, P. Q., Orlando, S., Zhang, L., Urnov, F. D., Holmes, M. C., Guschin, D., Waite, A., Miller, J. C., Rebar, E. J., Gregory, P. D., Klug, A., and Collingwood, T. N. (2008) *Proc. Natl. Acad. Sci. USA*, **105**, 5809-5814.
13. Bae, K. H., Kwon, Y. D., Shin, H. C., Hwang, M. S., Ryu, E. H., Park, K. S., Yang, H. Y., Lee, D. K., Lee, Y., Park, J., Kwon, H. S., Kim, H. W., Yeh, B. I., Lee, H. W., Sohn, S. H., Yoon, J., Seol, W., and Kim, J. S. (2003) *Nat. Biotechnol.*, **21**, 275-280.
14. Young, J. J., Cherone, J. M., Doyon, Y., Ankoudinova, I., Faraji, F. M., Lee, A. H., Ngo, C., Guschin, D. Y., Paschon, D. E., Miller, J. C., Zhang, L., Rebar, E. J., Gregory, P. D., Urnov, F. D., Harland, R. M., and Zeitler, B. (2011) *Proc. Natl. Acad. Sci. USA*, **108**, 7052-7057.
15. Letovsky, J., and Dynan, W. S. (1989) *Nucleic Acids Res.*, **17**, 2639-2653.
16. Frietze, S., Lan, X., Jin, V. X., and Farnham, P. J. (2010) *J. Biol. Chem.*, **285**, 1393-1403.
17. Jothi, R., Cuddapah, S., Barski, A., Cui, K., and Zhao, K. (2008) *Nucleic Acids Res.*, **36**, 5221-5231.
18. Gu, H., Li, D., Sung, C. K., Yim, H., Troke, P., and Benjamin, T. (2011) *Biochim. Biophys. Acta*, **1809**, 276-283.
19. Tsai, R. Y., and Reed, R. R. (1998) *Mol. Cell. Biol.*, **18**, 6447-6456.
20. Morris, J. F., Rauscher, F. J., III, Davis, B., Klemsz, M., Xu, D., Tenen, D., and Hromas, R. (1995) *Blood*, **86**, 3640-3647.
21. Morris, J. F., Hromas, R., and Rauscher, F. J., III (1994) *Mol. Cell. Biol.*, **14**, 1786-1795.
22. Brayer, K. J., Kulshreshtha, S., and Segal, D. J. (2008) *Cell Biochem. Biophys.*, **51**, 9-19.
23. Brayer, K. J., and Segal, D. J. (2008) *Cell. Biochem. Biophys.*, **50**, 111-131.
24. Cass, D., Hotchko, R., Barber, P., Jones, K., Gates, D. P., and Berglund, J. A. (2011) *BMC Mol. Biol.*, **12**, 20.
25. Brown, R. S. (2005) *Curr. Opin. Struct. Biol.*, **15**, 94-98.
26. Albagli, O., Dhordain, P., Deweindt, C., Lecocq, G., and Leprince, D. (1995) *Cell Growth Differ.*, **6**, 1193-1198.
27. Bardwell, V. J., and Treisman, R. (1994) *Genes Dev.*, **8**, 1664-1677.
28. Tadepally, H. D., Burger, G., and Aubry, M. (2008) *BMC Evol. Biol.*, **8**, 176.
29. Stone, J. R., Maki, J. L., Blacklow, S. C., and Collins, T. (2002) *J. Biol. Chem.*, **277**, 5448-5452.
30. Sander, T. L., Stringer, K. F., Maki, J. L., Szauter, P., Stone, J. R., and Collins, T. (2003) *Gene*, **310**, 29-38.
31. Iuchi, S. (2001) *Cell Mol. Life Sci.*, **58**, 625-635.
32. Swamynathan, S. K. (2010) *Hum. Genomics*, **4**, 263-270.
33. Suske, G. (1999) *Gene*, **238**, 291-300.
34. Kaczynski, J., Cook, T., and Urrutia, R. (2003) *Genome Biol.*, **4**, 206.
35. Fan, C. M., and Maniatis, T. (1990) *Genes Dev.*, **4**, 29-42.
36. Tseng, H., and Green, H. (1992) *Proc. Natl. Acad. Sci. USA*, **89**, 10311-10315.
37. Teumer, J., Tseng, H., and Green, H. (1997) *Gene*, **188**, 1-7.
38. Dunn, K. L., and Davie, J. R. (2003) *Biochem. Cell. Biol.*, **81**, 161-167.
39. Filippova, G. N., Fagerlie, S., Klenova, E. M., Myers, C., Dehner, Y., Goodwin, G., Neiman, P. E., Collins, S. J., and Lobanenkov, V. V. (1996) *Mol. Cell. Biol.*, **16**, 2802-2813.
40. Ohlsson, R., Renkawitz, R., and Lobanenkov, V. (2001) *Trends Genet.*, **17**, 520-527.
41. Ohlsson, R., Bartkuhn, M., and Renkawitz, R. (2010) *Chromosoma*, **119**, 351-360.
42. Nielsen, A. L., Jorgensen, P., Lerouge, T., Cervino, M., Chambon, P., and Losson, R. (2004) *Mol. Cell. Biol.*, **24**, 5184-5196.
43. Huang, C., Wang, Y., Li, D., Li, Y., Luo, J., Yuan, W., Ou, Y., Zhu, C., Zhang, Y., Wang, Z., Liu, M., and Wu, X. (2004) *Biochem. Biophys. Res. Commun.*, **320**, 1298-1305.
44. Urrutia, R. (2003) *Genome Biol.*, **4**, 231.
45. Looman, C., Hellman, L., and Abrink, M. (2004) *Mamm. Genome*, **15**, 35-40.
46. Witzgall, R., O'Leary, E., Leaf, A., Onaldi, D., and Bonventre, J. V. (1994) *Proc. Natl. Acad. Sci. USA*, **91**, 4514-4518.
47. Sripathy, S. P., Stevens, J., and Schultz, D. C. (2006) *Mol. Cell. Biol.*, **26**, 8623-8638.
48. Groner, A. C., Meylan, S., Ciuffi, A., Zangger, N., Ambrosini, G., Denervaud, N., Bucher, P., and Trono, D. (2010) *PLoS Genet.*, **6**, e1000869.
49. Williams, A. J., Blacklow, S. C., and Collins, T. (1999) *Mol. Cell. Biol.*, **19**, 8526-8535.
50. Sander, T. L., Haas, A. L., Peterson, M. J., and Morris, J. F. (2000) *J. Biol. Chem.*, **275**, 12857-12867.
51. Schumacher, C., Wang, H., Honer, C., Ding, W., Koehn, J., Lawrence, Q., Coulis, C. M., Wang, L. L., Ballinger, D., Bowen, B. R., and Wagner, S. (2000) *J. Biol. Chem.*, **275**, 17173-17179.
52. Noll, L., Peterson, F. C., Hayes, P. L., Volkman, B. F., and Sander, T. (2008) *Leuk. Res.*, **32**, 1582-1592.

53. Wu, Y., Yu, L., Bi, G., Luo, K., Zhou, G., and Zhao, S. (2003) *Gene*, **310**, 193-201.
54. Edelstein, L. C., and Collins, T. (2005) *Gene*, **359**, 1-17.
55. Dhordain, P., Albagli, O., Ansieau, S., Koken, M. H., Deweindt, C., Quief, S., Lantoine, D., Leutz, A., Kerckaert, J. P., and Leprince, D. (1995) *Oncogene*, **11**, 2689-2697.
56. Melnick, A., Carlile, G., Ahmad, K. F., Kiang, C. L., Corcoran, C., Bardwell, V., Prive, G. G., and Licht, J. D. (2002) *Mol. Cell. Biol.*, **22**, 1804-1818.
57. Dhordain, P., Albagli, O., Lin, R. J., Ansieau, S., Quief, S., Leutz, A., Kerckaert, J. P., Evans, R. M., and Leprince, D. (1997) *Proc. Natl. Acad. Sci. USA*, **94**, 10762-10767.
58. Dhordain, P., Lin, R. J., Quief, S., Lantoine, D., Kerckaert, J. P., Evans, R. M., and Albagli, O. (1998) *Nucleic Acids Res.*, **26**, 4645-4651.
59. Nakayama, K., Nakayama, N., Davidson, B., Sheu, J. J., Jinawath, N., Santillan, A., Salani, R., Bristow, R. E., Morin, P. J., Kurman, R. J., Wang, T. L., and Shih, I. M. (2006) *Proc. Natl. Acad. Sci. USA*, **103**, 18739-18744.
60. Valenta, T., Lukas, J., Doubravska, L., Fafilek, B., and Korinek, V. (2006) *EMBO J.*, **25**, 2326-2337.
61. Dai, M. S., Chevallier, N., Stone, S., Heinrich, M. C., McConnell, M., Reuter, T., Broxmeyer, H. E., Licht, J. D., Lu, L., and Hoatlin, M. E. (2002) *J. Biol. Chem.*, **277**, 26327-26334.
62. Kelly, K. F., and Daniel, J. M. (2006) *Trends Cell Biol.*, **16**, 578-587.
63. Razin, S. V., Iarovaia, O. V., Sjakste, N., Sjakste, T., Bagdoniene, L., Rynditch, A. V., Eivazova, E. R., Lipinski, M., and Vassetzky, Y. S. (2007) *J. Mol. Biol.*, **369**, 597-607.
64. Kim, M., Park, C. H., Lee, M. S., Carlson, B. A., Hatfield, D. L., and Lee, B. J. (2003) *Biochem. Biophys. Res. Commun.*, **306**, 231-238.
65. Ryan, R. F., Schultz, D. C., Ayyanathan, K., Singh, P. B., Friedman, J. R., Fredericks, W. J., and Rauscher, F. J., III (1999) *Mol. Cell. Biol.*, **19**, 4366-4378.
66. Friedman, J. R., Fredericks, W. J., Jensen, D. E., Speicher, D. W., Huang, X. P., Neilson, E. G., and Rauscher, F. J., III (1996) *Genes Dev.*, **10**, 2067-2078.
67. Schultz, D. C., Ayyanathan, K., Negorev, D., Maul, G. G., and Rauscher, F. J., III (2002) *Genes Dev.*, **16**, 919-932.
68. Iyengar, S., and Farnham, P. J. (2011) *J. Biol. Chem.*, **286**, 26267-26276.
69. Huntley, S., Baggott, D. M., Hamilton, A. T., Tran-Gyamfi, M., Yang, S., Kim, J., Gordon, L., Branscomb, E., and Stubbs, L. (2006) *Genome Res.*, **16**, 669-677.
70. Rowe, H. M., Jakobsson, J., Mesnard, D., Rougemont, J., Reynard, S., Aktas, T., Maillard, P. V., Layard-Liesching, H., Verp, S., Marquis, J., Spitz, F., Constam, D. B., and Trono, D. (2010) *Nature*, **463**, 237-240.
71. Matsui, T., Leung, D., Miyashita, H., Maksakova, I. A., Miyachi, H., Kimura, H., Tachibana, M., Lorincz, M. C., and Shinkai, Y. (2010) *Nature*, **464**, 927-931.
72. Thomas, J. H., and Schneider, S. (2011) *Genome Res.*, **21**, 1800-1812.
73. Frietze, S., O'Geen, H., Blahnik, K. R., Jin, V. X., and Farnham, P. J. (2010) *PLoS One*, **5**, e15082.
74. O'Geen, H., Squazzo, S. L., Iyengar, S., Blahnik, K., Rinn, J. L., Chang, H. Y., Green, R., and Farnham, P. J. (2007) *PLoS Genet.*, **3**, e89.
75. David, G., Alland, L., Hong, S. H., Wong, C. W., DePinho, R. A., and Dejean, A. (1998) *Oncogene*, **16**, 2549-2556.
76. Hong, S. H., David, G., Wong, C. W., Dejean, A., and Privalsky, M. L. (1997) *Proc. Natl. Acad. Sci. USA*, **94**, 9028-9033.
77. Wong, C. W., and Privalsky, M. L. (1998) *J. Biol. Chem.*, **273**, 27695-27702.
78. Chauchereau, A., Mathieu, M., de Saintignon, J., Ferreira, R., Pritchard, L. L., Mishal, Z., Dejean, A., and Harel-Bellan, A. (2004) *Oncogene*, **23**, 8777-8784.
79. Lemercier, C., Brocard, M. P., Puvion-Dutilleul, F., Kao, H. Y., Albagli, O., and Khochbin, S. (2002) *J. Biol. Chem.*, **277**, 22045-22052.
80. Sasai, N., Nakao, M., and Defossez, P. A. (2010) *Nucleic Acids Res.*, **38**, 5015-5022.
81. Yoon, H. G., Chan, D. W., Reynolds, A. B., Qin, J., and Wong, J. (2003) *Mol. Cell*, **12**, 723-734.
82. Li, J., Wang, J., Nawaz, Z., Liu, J. M., Qin, J., and Wong, J. (2000) *EMBO J.*, **19**, 4342-4350.
83. Fischle, W., Dequiedt, F., Hendzel, M. J., Guenther, M. G., Lazar, M. A., Voelter, W., and Verdin, E. (2002) *Mol. Cell*, **9**, 45-57.
84. Nagy, L., Kao, H. Y., Chakravarti, D., Lin, R. J., Hassig, C. A., Ayer, D. E., Schreiber, S. L., and Evans, R. M. (1997) *Cell*, **89**, 373-380.
85. Porsch-Ozcurumez, M., Langmann, T., Heimerl, S., Borsukova, H., Kaminski, W. E., Drobnik, W., Honer, C., Schumacher, C., and Schmitz, G. (2001) *J. Biol. Chem.*, **276**, 12427-12433.
86. Kahns, S., Losson, R., and Nielsen, A. L. (2010) *Biochim. Biophys. Acta*, **1799**, 539-545.
87. Rebollo, A., and Schmitt, C. (2003) *Immunol. Cell Biol.*, **81**, 171-175.
88. Schmitt, C., Tonnelle, C., Dalloul, A., Chabannon, C., Debre, P., and Rebollo, A. (2002) *Apoptosis*, **7**, 277-284.
89. John, L. B., and Ward, A. C. (2011) *Mol. Immunol.*, **48**, 1272-1278.
90. Koipally, J., Renold, A., Kim, J., and Georgopoulos, K. (1999) *EMBO J.*, **18**, 3090-3100.
91. Sridharan, R., and Smale, S. T. (2007) *J. Biol. Chem.*, **282**, 30227-30238.
92. Zhang, C. L., McKinsey, T. A., Lu, J. R., and Olson, E. N. (2001) *J. Biol. Chem.*, **276**, 35-39.
93. Koipally, J., and Georgopoulos, K. (2002) *J. Biol. Chem.*, **277**, 27697-27705.
94. Romm, E., Nielsen, J. A., Kim, J. G., and Hudson, L. D. (2005) *J. Neurochem.*, **93**, 1444-1453.
95. Wang, J., Lee, S., Teh, C. E., Bunting, K., Ma, L., and Shannon, M. F. (2009) *Int. Immunol.*, **21**, 227-235.
96. Kiefer, S. M., McDill, B. W., Yang, J., and Rauchman, M. (2002) *J. Biol. Chem.*, **277**, 14869-14876.
97. Wu, Y., Zhang, X., Salmon, M., and Zehner, Z. E. (2007) *Genes Cells*, **12**, 905-918.
98. Cowger, J. J., Zhao, Q., Isovic, M., and Torchia, J. (2007) *Oncogene*, **26**, 3378-3386.
99. Banck, M. S., Li, S., Nishio, H., Wang, C., Beutler, A. S., and Walsh, M. J. (2009) *Epigenetics*, **4**, 100-106.
100. Hoffmann, A., Barz, T., and Spengler, D. (2006) *Mol. Cell. Biol.*, **26**, 5544-5557.
101. Hoffmann, A., and Spengler, D. (2008) *Mol. Cell. Biol.*, **28**, 6078-6093.

102. Cawley, S., Bekiranov, S., Ng, H. H., Kapranov, P., Sekinger, E. A., Kampa, D., Piccolboni, A., Sementchenko, V., Cheng, J., Williams, A. J., Wheeler, R., Wong, B., Drenkow, J., Yamanaka, M., Patel, S., Brubaker, S., Tammana, H., Helt, G., Struhl, K., and Gingeras, T. R. (2004) *Cell*, **116**, 499-509.
103. Lu, S., and Archer, M. C. (2010) *Int. J. Cancer*, **126**, 416-425.
104. Sherr, C. J., and Roberts, J. M. (1999) *Genes Dev.*, **13**, 1501-1512.
105. Abdelrahim, M., Samudio, I., Smith, R., III, Burghardt, R., and Safe, S. (2002) *J. Biol. Chem.*, **277**, 28815-28822.
106. Olofsson, B. A., Kelly, C. M., Kim, J., Hornsby, S. M., and Azizkhan-Clifford, J. (2007) *Mol. Cancer Res.*, **5**, 1319-1330.
107. Li, L., and Davie, J. R. (2010) *Ann. Anat.*, **192**, 275-283.
108. Lu, F., Zhou, J., Wiedmer, A., Madden, K., Yuan, Y., and Lieberman, P. M. (2003) *J. Virol.*, **77**, 11425-11435.
109. Chen, H., Li, B., and Workman, J. L. (1994) *EMBO J.*, **13**, 380-390.
110. Clem, B. F., and Clark, B. J. (2006) *Mol. Endocrinol.*, **20**, 100-113.
111. Zhang, Y., and Dufau, M. L. (2003) *Mol. Cell. Biol.*, **23**, 6958-6972.
112. Nunes, M. J., Milagre, I., Schnekenburger, M., Gama, M. J., Diederich, M., and Rodrigues, E. (2010) *J. Neurochem.*, **113**, 418-431.
113. Nuez, B., Michalovich, D., Bygrave, A., Ploemacher, R., and Grosveld, F. (1995) *Nature*, **375**, 316-318.
114. Drissen, R., von Lindern, M., Kolbus, A., Driegen, S., Steinlein, P., Beug, H., Grosveld, F., and Philipsen, S. (2005) *Mol. Cell. Biol.*, **25**, 5205-5214.
115. Dovat, S. (2011) *World J. Biol. Chem.*, **2**, 105-107.
116. Mullighan, C., and Downing, J. (2008) *Leuk. Lymphoma*, **49**, 847-849.
117. Matulic, M., Paradzik, M., Cicin-Sain, L., Kapitanovic, S., Dubravcic, K., Batinic, D., and Antica, M. (2009) *Am. J. Hematol.*, **84**, 375-377.
118. Klenova, E. M., Nicolas, R. H., Paterson, H. F., Carne, A. F., Heath, C. M., Goodwin, G. H., Neiman, P. E., and Lobanenkov, V. V. (1993) *Mol. Cell. Biol.*, **13**, 7612-7624.
119. Lobanenkov, V. V., Nicolas, R. H., Adler, V. V., Paterson, H., Klenova, E. M., Polotskaja, A. V., and Goodwin, G. H. (1990) *Oncogene*, **5**, 1743-1753.
120. Bell, A. C., West, A. G., and Felsenfeld, G. (1999) *Cell*, **98**, 387-396.
121. Bell, A. C., and Felsenfeld, G. (2000) *Nature*, **405**, 482-485.
122. Bartkuhn, M., and Renkawitz, R. (2008) *Biochim. Biophys. Acta*, **1783**, 2161-2166.
123. Ling, J. Q., Li, T., Hu, J. F., Vu, T. H., Chen, H. L., Qiu, X. W., Cherry, A. M., and Hoffman, A. R. (2006) *Science*, **312**, 269-272.
124. Splinter, E., Heath, H., Kooren, J., Palstra, R. J., Klous, P., Grosveld, F., Galjart, N., and de Laat, W. (2006) *Genes Dev.*, **20**, 2349-2354.
125. Zlatanova, J., and Caiafa, P. (2009) *Cell. Mol. Life Sci.*, **66**, 1647-1660.
126. Kim, Y. J., Cecchini, K. R., and Kim, T. H. (2011) *Proc. Natl. Acad. Sci. USA*, **108**, 7391-7396.
127. Degner, S. C., Verma-Gaur, J., Wong, T. P., Bossen, C., Iverson, G. M., Torkamani, A., Vettermann, C., Lin, Y. C., Ju, Z., Schulz, D., Murre, C. S., Birshtein, B. K., Schork, N. J., Schlissel, M. S., Riblet, R., Murre, C., and Feeney, A. J. (2011) *Proc. Natl. Acad. Sci. USA*, **108**, 9566-9571.
128. Xiao, T., Wallace, J., and Felsenfeld, G. (2011) *Mol. Cell. Biol.*, **31**, 2174-2183.
129. Loukinov, D. I., Pugacheva, E., Vatolin, S., Pack, S. D., Moon, H., Chernukhin, I., Mannan, P., Larsson, E., Kanduri, C., Vostrov, A. A., Cui, H., Niemitz, E. L., Rasko, J. E., Docquier, F. M., Kistler, M., Breen, J. J., Zhuang, Z., Quitschke, W. W., Renkawitz, R., Klenova, E. M., Feinberg, A. P., Ohlsson, R., Morse, H. C., III, and Lobanenkov, V. V. (2002) *Proc. Natl. Acad. Sci. USA*, **99**, 6806-6811.
130. Call, K. M., Glaser, T., Ito, C. Y., Buckler, A. J., Pelletier, J., Haber, D. A., Rose, E. A., Kral, A., Yeger, H., Lewis, W. H., Jones, C., and Housman, D. E. (1990) *Cell*, **60**, 509-520.
131. Gessler, M., Poustka, A., Cavenee, W., Neve, R. L., Orkin, S. H., and Bruns, G. A. (1990) *Nature*, **343**, 774-778.
132. Lee, S. B., and Haber, D. A. (2001) *Exp. Cell Res.*, **264**, 74-99.
133. King-Underwood, L., and Pritchard-Jones, K. (1998) *Blood*, **91**, 2961-2968.
134. Scharnhorst, V., van der Eb, A. J., and Jochemsen, A. G. (2001) *Gene*, **273**, 141-161.
135. Menssen, H. D., Renkl, H. J., Rodeck, U., Maurer, J., Notter, M., Schwartz, S., Reinhardt, R., and Thiel, E. (1995) *Leukemia*, **9**, 1060-1067.
136. Miyagawa, K., Hayashi, Y., Fukuda, T., Mitani, K., Hirai, H., and Kamiya, K. (1999) *Genes Chromosomes Cancer*, **25**, 176-183.
137. Ladomery, M., and Dellaire, G. (2002) *Ann. Hum. Genet.*, **66**, 331-342.
138. Lee, S. B., Huang, K., Palmer, R., Truong, V. B., Herzlinger, D., Kolquist, K. A., Wong, J., Paulding, C., Yoon, S. K., Gerald, W., Oliner, J. D., and Haber, D. A. (1999) *Cell*, **98**, 663-673.
139. Nachtigal, M. W., Hirokawa, Y., Enyeart-VanHouten, D. L., Flanagan, J. N., Hammer, G. D., and Ingraham, H. A. (1998) *Cell*, **93**, 445-454.
140. Loeb, D. M., Korz, D., Katsnelson, M., Burwell, E. A., Friedman, A. D., and Sukumar, S. (2002) *J. Biol. Chem.*, **277**, 19627-19632.
141. Park, K., and Atchison, M. L. (1991) *Proc. Natl. Acad. Sci. USA*, **88**, 9804-9808.
142. Usheva, A., and Shenk, T. (1994) *Cell*, **76**, 1115-1121.
143. Ficzycz, A., Eskiw, C., Meyer, D., Marley, K. E., Hurt, M., and Ovsenek, N. (2001) *J. Biol. Chem.*, **276**, 22819-22825.
144. Castellano, G., Torrisi, E., Ligresti, G., Malaponte, G., Militello, L., Russo, A. E., McCubrey, J. A., Canevari, S., and Libra, M. (2009) *Cell Cycle*, **8**, 1367-1372.
145. Wales, M. M., Biel, M. A., el Deiry, W., Nelkin, B. D., Issa, J. P., Cavenee, W. K., Kuerbitz, S. J., and Baylin, S. B. (1995) *Nat. Med.*, **1**, 570-577.
146. Britschgi, C., Rizzi, M., Grob, T. J., Tschan, M. P., Hugli, B., Reddy, V. A., Andres, A. C., Torbett, B. E., Tobler, A., and Fey, M. F. (2006) *Oncogene*, **25**, 2030-2039.
147. Carter, M. G., Johns, M. A., Zeng, X., Zhou, L., Zink, M. C., Mankowski, J. L., Donovan, D. M., and Baylin, S. B. (2000) *Hum. Mol. Genet.*, **9**, 413-419.

148. Chen, W. Y., Zeng, X., Carter, M. G., Morrell, C. N., Chiu Yen, R. W., Esteller, M., Watkins, D. N., Herman, J. G., Mankowski, J. L., and Baylin, S. B. (2003) *Nat. Genet.*, **33**, 197-202.
149. Chen, S. J., Zelent, A., Tong, J. H., Yu, H. Q., Wang, Z. Y., Derre, J., Berger, R., Waxman, S., and Chen, Z. (1993) *J. Clin. Invest.*, **91**, 2260-2267.
150. Chen, Z., Guidez, F., Rousselot, P., Agadir, A., Chen, S. J., Wang, Z. Y., Degos, L., Zelent, A., Waxman, S., and Chomienne, C. (1994) *Proc. Natl. Acad. Sci. USA*, **91**, 1178-1182.
151. Lin, R. J., Nagy, L., Inoue, S., Shao, W., Miller, W. H., Jr., and Evans, R. M. (1998) *Nature*, **391**, 811-814.
152. Grignani, F., De Matteis, S., Nervi, C., Tomassoni, L., Gelmetti, V., Cioce, M., Fanelli, M., Ruthardt, M., Ferrara, F. F., Zamir, I., Seiser, C., Lazar, M. A., Minucci, S., and Pelicci, P. G. (1998) *Nature*, **391**, 815-818.
153. McConnell, M. J., Chevallier, N., Berkofsky-Fessler, W., Giltnane, J. M., Malani, R. B., Staudt, L. M., and Licht, J. D. (2003) *Mol. Cell. Biol.*, **23**, 9375-9388.
154. Barna, M., Hawe, N., Niswander, L., and Pandolfi, P. P. (2000) *Nat. Genet.*, **25**, 166-172.
155. Barna, M., Merghoub, T., Costoya, J. A., Ruggero, D., Branford, M., Bergia, A., Samori, B., and Pandolfi, P. P. (2002) *Dev Cell*, **3**, 499-510.
156. Basso, K., and Dalla-Favera, R. (2010) *Adv. Immunol.*, **105**, 193-210.
157. Crotty, S., Johnston, R. J., and Schoenberger, S. P. (2010) *Nat. Immunol.*, **11**, 114-120.
158. Niu, H. (2002) *Hematol. Oncol.*, **20**, 155-166.