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Roles of CTCF in conformation and functions of chromosome

Fangming Liu, Duojiao Wu*, Xiangdong Wang*

Zhongshan Hospital Institute of Clinical Science, Fudan University Medical School, Shanghai Institute of Clinical Bioinformatics Shanghai, China

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ABSTRACT

CCCTC-binding factor (CTCF) plays indispensable roles in transcriptional inhibition/activation, insulation, gene imprinting, and regulation of 3Dchromatin structure. CTCF contributes to formation of genome multi-dimensions, regulation of dimensional changes, or control of central signals to transcriptional networks. A large number of factors affect CTCF binding, methylation/demethylation, base mutation, or poly(adp-ribosyl)ation. CTCF is one of the most important elements in the regulation of chromatin folding by combining with CBSs in TADs in a positive-reverse or reverse-positive orders. CTCF acts as a versatile nuclear factor, a transcriptional activator or repressor, an insulator binding factor, or a regulator of genomic imprinting as required for various biological procedures. Although molecular regulatory mechanisms of CTCF in cell differentiation and disease development remains unclear, roles of CTCF in carcinogenesis have been intensively explored. There is little understanding about regulatory roles of CTCF in inflammation-associated transcriptional signaling, cell injury, organ dysfunction, and systemic responses. It is also highly expected that further in-depth studies of CTCF control mechanisms can provide better understanding of disease development and potential disease-specific biomarkers and therapeutic targets.

Contents

1. Introduction

The chromosomes are assembled into three-dimensional architecture (3D) to play an important role on the regulation of gene transcriptional function. There is a growing consensus that genome functions are associated with two-dimensional base sequence of chromatin and with the higher-grade space position of genomes [1,2]. The 3D package of nuclear chromosome is uncovered, and the chromatin bends and folds into about 10, 000 loops [3]. Though not so large in number, almost every folding domain can trigger the gene switch. Most of the high-level architectures are related to CCCTC-binding-factor (CTCF), a versatile transcription regulator that plays a key role in development and differentiation of cells.

The main component of CTCF consists of 11 zin. fingers, of which each is a dactylitic motif with about 30 amino acids and a zinc ion [4]. The Zinc finger folds in an α-helix and two antiparallel β strands. The zinc ion is bound with a pair of cysteines and a pair of

* Corresponding authors.
E-mail addresses: wuduojiao@126.com (D. Wu), Xiangdong.wang@clintransmed.org (X. Wang).

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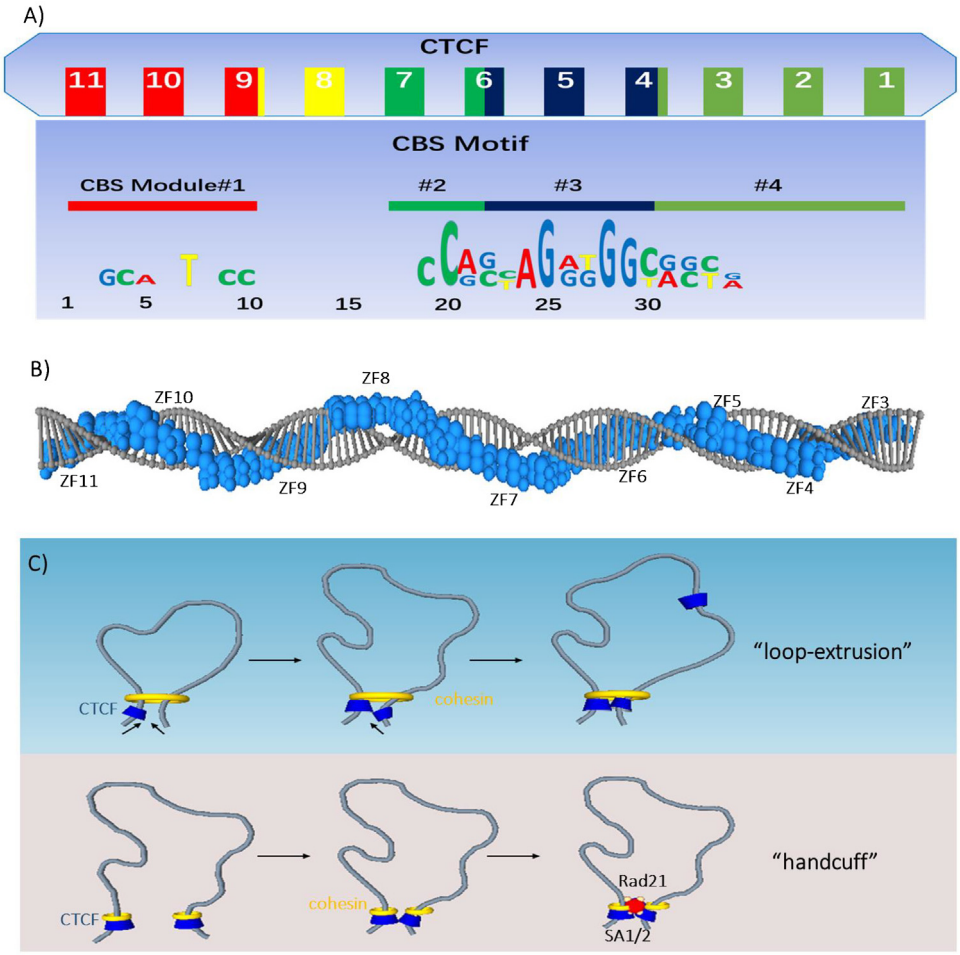

Fig. 1. CTCF is engaged in the formation of higher-grade architecture of chromosome. A) the main component of CTCF consists of 11 zin. fingers. CBS consists of four modules defined as module 1-4. CTCF recognizes CBS through different combination of these 11 zin. fingers. B) CTCF is inserted into the main channel of DNA duplex through combination of zinc fingers with CBSs. The combination is carried out through hydrogen bond, base pair contacts, and electrostatic effect. C) Patterns of CTCF mediated chromatin folding. In "loop-extrusion" hypothesis, chromatin actively goes through circular cohesin. When come across with the CTCF embedded in CBS loci, cohesin stop extrusion. When the chromatin on both sides stops at the junction of CTCF, the local chromosome loops are formed. In "handcuff" mode, cohesin works in pairs rather than alone, each cohesin binds a strand of DNA. The cohesin complex is grouped together by Rad21, SA1 and SA2.

histidines, which are separated by 12 amino acids. The hydrophobic core of zinc finger exists as a conservative and stable motif. More than 3% of human genome express zinc finger proteins [5]. CTCF recognizes CTCF binding sites (CBSs) as short sequences within DNA duplex, through different combination of those 11 zin. fingers with the target sequence about 50bp [4]. The mechanism by which CTCF regulates gene expression in 3D architecture is that two or more regulatory elements far away from each other in the linear genome approach and interact through the recognition of CTCF and CBSs.

The chromosome was divided into discrete megabase-scale regions termed topologically associated domain (TAD) [6], of which regulatory elements such as enhancers and promoters interact actively. CBSs are located nearby or within enhancers, promoters or silencers. The combination of CTCF with CBS complies with a single direction [5,7], as a critical step for the formation of 3D genomic architecture. The present review aims to overview biological function of CTCF, patterns of CTCF-mediated chromatin folding, and various roles of CTCF as nuclear factor, transcriptional activator or repressor, insulator binding factor, or a regulator of genomic imprinting. We specially discuss about potential mechanisms by which CTFC contributes to the development of carcinogenesis through alterations of genome organization and dynamics.

2. Patterns of CTCF mediated chromatin folding

CTCF binding patterns are basically unchanged in diverse cell types [8,9]. Yin et al. [5] took the protocadherin 2 alpha a 15 (PCDH) gene as an example to explain the directional combination of CTCF and CBS with four modules defined as module 1–4, as shown in Fig. 1A [5,10]. CBSs in TADs are arranged in a positive-reverse order, while adjacent TAD CBSs in a reverse-positive order [11]. For example, CBSs in PCDH promoters are organized in a convergence positive direction of modules from 1 to 4, whereas CBSs in enhancers in a divergent opposite direction of modules from 4 to 1. In PCDH gene enhancers and promoters, CTCF is inserted to the process of Zinc finger (ZF)3, ZF4-7 and ZF9-11 into the main channel of CBS modules 4, 3 and 2, 1, respectively. As a space element, ZF8 controls the distance between modules 1 and 2. The combination is carried out through hydrogen bond, base pair contacts, and electrostatic effect [5] (Fig. 1B).

About 93% of amino acids in CTCF are the same between avian and mammals, whereas amino acids of 11 zin. fingers are identical [3]. CTCF is highly conservative between different types of cells and different species, of which binding sites with high affinity are highly conservative, while binding sites with low affinity are tissue specific [12]. The tolerance of CTCF for diverse CBS sequences

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play an important role in the transcriptional regulation [5]. For example, the base 21 of CBS in the promoter or enhancer of PCDH gene is guanine or adenine, respectively. Those CBS sites are recognized by ZFs6-7. Both G21 and A21 can combine with Arg448 by two hydrogen bonds, indicating that CTCF fails to show base-specific recognition when G21 is changed to A21. The A26-G27 of CBS is changed to G26-T27 by modeling, and G26 formed hydrogen bonds with lys393 of ZF5, similar to the combination between A26 and ZF5. The G27 similar to A26 react without CTCF. The replaced nucleotides (e.g. T27 or other nucleotides) have no effect on CTCF identification. Changes of CTCF binding sites to a certain extent are independent of CTCF-CBS combination. CTCF tolerates the diversity of bases, as a mechanism to explain why CTCF is conservative in the in vivo system and recognize different CBS sites between cell types and species.

Interactions between CTCF and DNA duplex rely on the assistance of other proteins, among which the cohesin is vital for most CTCF binding locus. Cohesin is enriched at proper CTCF binding sites and plays a role in the anchoring [13]. Dolgin [14] proposed the process of CTCF mediated ring formation of chromatin actively through circular cohesin as "loop-extrusion factor". CTCF is combined with the SA subunit of cohesin through the C terminal region [8]. Local chromosome loops are formed, when the chromatin on both sides stops at the junction of CTCF (Fig. 1C). CTCF acts as the termination signal of loop extrusion and is recognized by cohesin when CBSs are in the positive-reverse direction within TAD. The formation of TAD requires the location and orientation of CBSs, which is not an arbitrary process that two random remote CTCFs are combined together, to ensure the well-ordered higher-grade architecture of genome. The cohesin binds to CTCF and a strand of DNA to form the chromosome ring and work in pairs. The cohesin complex is grouped together by SA1 and SA2, two Scc3 orthologues, as well as Rad21, forming a "handcuff" mode [15]. Two cohesins are connected in a reverse parallel way and have the important role in the location and orientation of CBSs, as shown in Fig. 1C [3,11].

3. Various effects of CTCF on genetic function

CTCF acts as a versatile nuclear factor, transcriptional activator or repressor, insulator binding factor, or regulator of genomic imprinting for various biological procedures. CTCF plays a necessary role in the development and differentiation of cells and the maintenance of discontinuous structural domains on the chromosome, ensure its normal functions. CTCF could effectively isolate functional domains between homeobox A5 (HOXA5) and HOXA6 during the differentiation of embryonic stem cells into motor neurons [16,17]. The deletion of CTCF up-regulated the expression level of HOXA7 rather than HOXA1-6, while expression of HOXA10-13 was completely inhibited. CTCF can regulate the expression of HOX gene cluster in space and time, similar to other genes [18,19].

3.1. CTCF as a transcriptional activator

CTCF facilitates the transcription as a transcriptional activator (Fig. 2A), e.g. in promoter of the amyloid β-protein precursor (APP) gene [20]. There is a nuclear factor binding site APBβ located between positions 93 and 82 in the promoter to carry out an in-vitro transcriptional link between CTCF and APP promoter transcriptional activity through the CTCF in nucleus. The competitive binding site between APBβ-80WT and myc-80 can affect transcription activity of APP promoter, rather than binding with APBβ-80Mβ2 which cannot combine with CTCF. This indicates that the combination of CTCF and APP promoter is an important condition to ensure the transcriptional activity. The structure domain of 107 amino acids in the n-terminal area of CTCF plays a role of transcriptional activation and chromatin de-condensation [21]. This segment of the structure exhibits mild transcriptional activation as it approaches the promoter location. When SUMO is combined with the activation domain, sumoylation will limit the ability of transcriptional activation and de-condensation in the domain.

3.2. CTCF as a transcriptional repressor

CTCF has the potential to achieve transcriptional inhibition probably by combining promoter and upstream silencer together, as explained in Fig. 2A. CTCF was identified as a transcriptional repressor of chicken c-myc gene [22,23]. A negative T3 response element was found between the first exon nucleotide +237 and +268, adjacent to the binding site of CTCF. Binding of CTCF and thyroid hormone receptor to the isogenous locus could form a repressor complex to reduce the expression of c-myc [24]. CTCF has several repression domains, of which 11-zinc-finger could form different combinations to identify multiple DNA sequences. The process of CTCF transcription inhibition needs the involvement of various factors. The zinc-finger cluster was capable of binding to co-repressor SIN3 transcription regulator family member A at the PAH3 domain and C-terminal region, respectively. The transcription repression mediated by CTCF may be achieved by recruiting histone deacetylase and deacetylation of CTCF via binding of SIN3 transcription regulator family member A [25].

3.3. CTCF participates in gene imprinting

CTCF promotes the formation of gene imprinting, e.g. regulation of H19/Igf2 locus. The area between the H19 and Igf2 genes is called the imprinting control area (ICR), of which the methylation degree varies. ICR of the parent unmethylated and band with CTCF can block the effect of shared enhancers near H19 gene on Igf2 gene (Fig. 2B) and activate H19 gene. On the contrary, the ICR region methylated in the paternal allele leads to inability of CTCF to be combined, after which enhancers stimulate the transcription of Igf2 gene [12,26].

3.4. CTCF as an insulation element

CTCF acts as an insulator bounding factor by blocking the interaction between promoter, enhancer, and silencer. CTCF plays a role of insulator under the condition that the CBS is located between regulatory elements, and enhancers or promoters fail to work [4]. Bell et al. found an insulator sequence with a length of 42bp could inhibit promoter activity of β-globulin, be the binding site of CTCF, and play an equally important role in human body [27]. The insulation effect on enhancers disappeared after mutation of 3′tail sequence. In addition, the binding of drugs with multiple DNA fragments has an insulating effect, rather than a sequence with mutations. The proteins extracted from the complex were found to be the same as CTCF which acts as transcription insulation and limits its estrogen-regulated function of a gene [28]. Putative insulators were in Trefoil factor (TFF) locus, where ERα was in TFF1 promoter and E2 activated TFF1 and TFF2 by CTCF binding, but not adjacent genes TMPRSS3 and TFF3 (Fig. 2C).

3.5. X chromosome inactivation

During development of certain kinds of mammals, paternal X chromosome experiences a process of inactivation, which relies on the transcription of inactive x-specific transcript (Xist) and is blocked by the antisense gene Tsix. CTCF plays the important role in the process of X chromosome inactivation [29]. The choice/imprinting center of X chromosome contains a series of CTCF binding sites, with methylation-sensitive enhancer blocking

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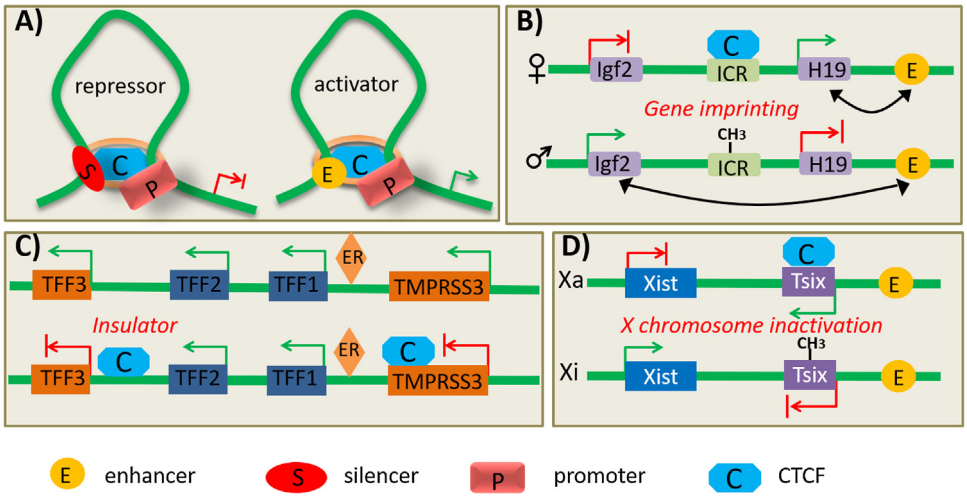

Fig. 2. Various effect of CTCF on genetic function. A) CTCF acts as transcriptional repressor and activator. B) CTCF participates in gene imprinting of H19/Igf2 locus. C) CTCF acts as an insulator bounding factor. D) CTCF in X chromosome inactivation.

activity. Tsix regulates the epigenetic switch of X chromosome inactivation together with CTCF. CTCF combines with unmethylated Xa chromosome to stimulate Tsix transcription or prevent Xist from contacting with shared enhancer (Fig. 2D). Transcription of Tsix blocks accumulation of Xist RNA. The gene transcription is up-regulated to lead to the inactivation of Xi chromosome, since CTCF cannot combine with Tsix on the X chromosome Xi due to the methylation of CTCF binding sites in Tsix.

4. CTCF and cancer

Interruption of combination between CTCF and CBS or cohesin may damage TAD boundary, leading to interactions among regulatory elements. For example, an enhancer in a certain TAD domain activates a promoter located in another TAD. A number of factors can cause CTCF deregulations, associated with the development of genetic diseases or cancers [6].

4.1. Methylation

Some CBSs consist of CpG islands of which the methylation status influences combination of CTCF. For example, isocitrate dehydrogenase (IDH) mutant gliomas is highly methylated at cohesin and CTCF-binding sites, to affect CTCF binding, confuse TADs boundaries, and lead to abnormal gene activation [30]. Aberrant activation of a constitutive enhancer on receptor tyrosine kinase gene platelet derived growth factor receptor alpha (PDGFRA), which is an important glioma oncogene, further causes carcinogenesis. The demethylation of IDH mutant gliomas partially recovers the insulation function of CTCF and down-regulate the expression of PDHFRA (Fig. 3A). This indicates that the methylation affect the isolation of CTCF on the edge of topological domain, to avoid the abnormality of gene expression. Such methylation process can be influenced or interrupted as the therapeutic target for the development of new drugs and tumor therapy.

HOXA10 is a suppressor of breast cancer through activation of p53. Abnormal CTCF enrichment on HOAX10 promoter region could

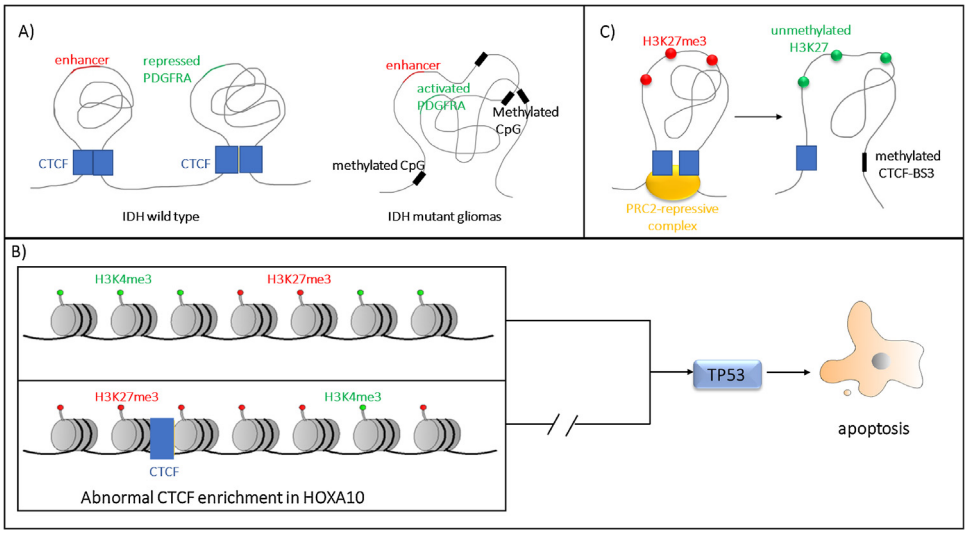

Fig. 3. Carcinogenesis related to CTCF. A) methylation of CTCF-binding sites in IDH mutant gliomas leads to aberrant activation of PDGFRA through interaction with a constitutive enhancer, which further causes carcinogenesis. B) Abnormal CTCF enrichment on HOAX10 promoter could lead to inactivation of HOXA10 expression and repression of H3K27me3, so that contributes to the tumorigenesis in breast cancer. C) CTCF combines with GAD1 gene through a binding site CTCF-BS3, in order to recruitment the PRC2-repressive complex. CpG methylation of CTCF-BS3 blocks CTCF recognition and hinders methylation of H3K27, up-regulating the expression of GAD1 gene and protein in cancer cells.

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contribute to the tumorigenesis in breast cancer by inactivating HOXA10 expression and repressing H3K27me3 [31,32]. In addition, down-regulation of CTCF results in promotion of apoptosis by up-regulating proapoptotic protein, Bax [33] (Fig. 3B). The enrichment of CTCF changes aberrant methylation status [31]. miR-125b1 is associated with tumor suppression in breast cancer and other cancers, where increased methylation of miR-125b1 down-regulated the expression of miR-125b1.

Dysfunction of CTCF is associated with chaotic DNA methylation and incorporation of histone repressive marks such as H3K27me3 [34]. CTCF plays a role in cancer repression by combining with the third intron of glutamic acid decarboxylase 1 (GAD1) with a binding site CTCF-BS3, in order to recruitment the PRC2-repressive complex. CpG methylation of CTCF-BS3 blocks CTCF recognition and hinders methylation of H3K27, up-regulating the expression of GAD1 gene and protein in colon and liver cancer cells [35] (Fig. 3C). CTCF could influence methylation status, evidenced by the deletion of CTCF could verify the molecular origins of DNA methylation in cancer [36]. CTCF haploinsufficiency led to a higher risk of cancer in diverse tissues due to deregulated methylation.

4.2. Other mutation patterns associated with CTCF

CBSs had frequent mutations in different types of cancers where mutations of A-T base pairs play a major role [37]. Docquire et al. defined the presence of both 180-kDa and 130-kDa of CTCF in breast cancer, whereas only 180-kDa CTCF in normal breast tissues [38]. Transition from CTCF-180-kDa to CTCF-130-kDa is related to the loss of CTCF poly(ADP-ribosyl)ation, resulting in the development of breast tumor [38]. CTCF regulate expression of Rb2/p130 gene in normal lung fibroblast depending on high-order chromatin organization, while down-regulate expression of Rb2/p130 gene through the binding of the Brother of Regulator of Imprinted Sites in lung cancer [39]. Although CTCF-130-kDa or Rb2/p130 have the biomarker potential for the progress of cancer, it is questioned whether CTCF-130-kDa has the characteristics of disease biomarkers and the specificities of disease duration, phase, severity, and response to therapy [40–47]. With development and innovation of new methodologies to monitor dynamic alterations of multi-dimensional genome [48–50], we will understand more how CTCF regulates changes of 3D genome organization and disorganization in the pathogenesis of disease, whether CTCF-controlled multi-dimensional loops of genome can signal transomic profiles within cell or organ, and whether CTCF-regulated 3D genome structure can influence the profiling of immune repertoire or change transcriptomic characterization of the gene [51–54].

5. Conclusion

CTCF plays indispensable roles in transcriptional inhibition/activation, insulation, gene imprinting, and regulation of 3Dchromatin structure. CTCF contributes to formation of genome multi-dimensions, regulation of dimensional changes, or control of central signals to transcriptional networks. A large number of factors affect CTCF binding, methylation/demethylation, base mutation, or poly(adp-ribosyl)ation. CTCF is one of the most important elements in the regulation of chromatin folding by combining with CBSs in TADs in a positive-reverse or reverse-positive orders. CTCF acts as a versatile nuclear factor, a transcriptional activator or repressor, an insulator binding factor, or a regulator of genomic imprinting as required for various biological procedures. Although molecular regulatory mechanisms of CTCF in cell differentiation and disease development remains unclear, roles of CTCF in carcinogenesis have been intensively explored. There is little understanding about regulatory roles of CTCF in inflammation-associated transcriptional signaling, cell injury, organ dysfunction, and systemic responses. It is also highly expected that further in-depth studies of CTCF control mechanisms can provide better understanding of disease development and potential disease-specific biomarkers and therapeutic targets.

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