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TRF2: TRansForming the view of general transcription factors

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Abbreviations: BRE^{d}, downstream TFIIB recognition element; BRE^{u}, upstream TFIIB recognition element; ChIP, Chromatin immunoprecipitation; DPE, downstream core promoter element; Inr, initiator; MTE, motif 10 element; PIC, preinitiation complex; RNAP II, RNA polymerase II; TAF, TBP-associated factor; TBP, TATA-box binding protein; TFIIA, (transcription factor, RNA polymerase II, A); TFIIB, (transcription factor, RNA polymerase II, B); TFIID, (transcription factor, RNA polymerase II, D); TRF, TATA-box-binding protein-related factor; TSS, transcription start site

Transcriptional regulation is pivotal for development and differentiation of organisms. Transcription of eukaryotic protein-coding genes by RNA polymerase II (RNAP II) initiates at the core promoter. Core promoters, which encompass the transcription start site, may contain functional core promoter elements, such as the TATA box, initiator, TCT and downstream core promoter element. TRF2 (TATA-box-binding protein-related factor 2) does not bind TATA box-containing promoters. Rather, it is recruited to core promoters via sequences other than the TATA box. We review the recent findings implicating TRF2 as a basal transcription factor in the regulation of diverse biological processes and specialized transcriptional programs.

Introduction

Transcriptional regulation is pivotal for the proper function of multiple cellular processes and signaling pathways. In eukaryotes, transcription of protein-coding genes by RNAP II initiates by formation of the preinitiation complex (PIC) at the core promoter (for a review see ref. 1). The PIC is a multisubunit complex composed of RNAP II and several basal transcription factors, also termed general transcription factors (or GTFs), which ensure accurate initiation of transcription. But how general are the general transcription factors? Several studies published in the last few years suggest that genes with specific core promoter composition recruit a specialized basal transcription factor, demonstrating the diversity of transcriptional regulation. This is the story of TRF2, TATA-box-binding protein-related factor 2, which was shown to be essential for transcription of genes having a unique role in multiple biological processes, including early embryonic development and differentiation.

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Transcription initiation can occur in a focused manner (at a single nucleotide or within a narrow region of several nucleotides), a dispersed manner (at multiple weak start sites over a broad region of about 50 to 100 nucleotides) or in a manner that combines both focused and dispersed transcription initiation. Focused core promoters encompass the RNA start site and are typically 80 nucleotides in length (−40 to +40 relative to the +1 transcription start site).[2-5] Core promoters may contain one or more functional DNA sequence elements, termed core promoter elements or motifs, such as the TATA box, TFIIB recognition elements (BRE^{u} and BRE^{d}), initiator (Inr), TCT motif, motif 10 element (MTE), and downstream core promoter element (DPE), which confer specific properties to the core promoter (for a review see refs. 3, 4, 6). There is no universal core promoter composition. Notably, dispersed promoters generally lack TATA, BRE, MTE and DPE motifs.[5,7,8] From this point onwards, this review will mainly relate to studies performed with focused core promoters.

The TATA box is the first eukaryotic promoter element discovered.[9] Its consensus sequence is TATAWAAR, where the upstream T is located about −31/−30 relative to the A_{+1} of the transcription start site (TSS). The TATA box is conserved from archaebacteria to humans.[10] Although the TATA box is well-known and extensively studied, it is only present in 10%-15% of mammalian core promoters, and in about 20% of *Drosophila* genes.[7,11-15] The BRE motifs function together with the TATA box. The BRE^{u} is located immediately upstream of the TATA box (with a SSRCGCC consensus sequence), and the BRE^{d} is located immediately downstream of the TATA box (with a RTDKKKK consensus sequence).[16-18] The initiator (Inr) is the most commonly occurring motif among core promoter elements.[12-15,19] The Inr encompasses the TSS [20] and its consensus

is YYANWYY in humans and TCAKTY in *Drosophila*. Focused transcription generally starts at the A nucleotide of the Inr consensus that is referred to as "+1" of the TSS (whether transcription starts at this nucleotide or nearby). The TCT motif is a polypyrimidine initiator located from −2 to +6 relative to the TSS, which has been identified in genes encoding ribosomal proteins as well as other proteins involved in translation.[21] Both the MTE and DPE motifs are located at a specific position relative to the Inr (with strict spacing requirements from the A_{+1} of the Inr) and their function depends on the Inr. The MTE is located from +18 to +27 relative to the A_{+1} of the Inr, and its consensus sequence is CSARCSSAAC.[19,22] It is conserved from *Drosophila* to humans and functions cooperatively with the Inr.[22,23] The DPE, which has been identified in *Drosophila* as a TFIID-bound downstream core promoter element in promoters lacking a TATA box, is precisely located from +28 to +33 relative to the A_{+1} nucleotide of the Inr and has a functional range set of DSWYVY.[24-26] The DPE is conserved from *Drosophila* to humans.[25] The DPE has been shown to be prevalent among developmentally regulated genes, such as the Hox gene network and Dorsal target genes,[15,27] suggesting that the composition of the core promoter is a major contributor to transcriptional regulation.

RNAP II is a 12-subunit molecular machine that catalyzes the synthesis of RNA from the template DNA. It is, however, unable to discriminate between the core promoter region and other DNA regions. RNAP II is recruited to the core promoter by the basal transcription machinery (TFIIA, TFIIB, TFIID, TFIIE, TFIIF and TFIIH; for a review see ref. 1). TFIID, a protein complex composed of the TBP (TATA-box binding protein) and TBP-associated factors (TAFs), is the first protein complex that recognizes the core promoter: TBP binds the TATA-box motif, TAF1 and TAF2 bind the Inr motif and TAF6 and TAF9 bind the DPE and MTE motifs.[23,25,28-31] Several tissue-specific variants of TAFs have been discovered: TAF4 variants are important for ovarian development and spermatogenesis in mice, while *Drosophila* and human TAF5 and TAF7 paralogs are implicated in male gametogenesis, thus providing the TFIID with unique functions in a tissue-specific transcription environment.[32-37] Following the binding of TFIID, TFIIA binds and stabilizes the association of TFIID with the TATA-box. The formation of the TFIID-TFIIA-DNA complex is followed by the sequential binding of TFIIB, RNAP II/TFIIF, TFIIE and TFIIH, resulting in the assembly of the PIC. The hierarchical recruitment of the basal transcription factors to the core promoter was discovered using the TATA box-containing adenovirus major late promoter. Remarkably, these basal transcription factors, which are necessary for TATA box-dependent transcription, are insufficient to transcribe DPE-dependent promoters.[38,39] Moreover, whereas TBP binds and activates TATA-dependent transcription, it down regulates DPE-dependent transcription.[40] NC2 and MOT1, which are positive regulators of DPE-dependent transcription, counteract TBP and relieve its inhibition of DPE transcription.[40-42] Hence, the known basal transcription factors are not "general" and additional basal transcription factors that support DPE-dependent transcription exist.

TBP-related factors

The C-terminal core domain of TBP contains 2 structural repeats that fold into a saddle-like structure that is essential for the interaction with the TATA box.[29-31] Using low-stringency hybridization, 2 distinct TBPs were identified in *Arabidopsis thaliana* and then in maize.[43,44] Since then, 3 TBP-related factors (TRFs; TRF1, TRF2 and TRF3) have been discovered in the animal kingdom based on their homology to the C-terminal core domain of TBP (for a review see refs. 45-49). The existence of the variety of TRFs is another manifestation of the diversity and complexity of transcriptional regulation.

TFR1 exists in *Drosophila* and Anopheles, but not in yeast or humans.[50,51] TRF1 has 63% identity to the C-terminal core domain repeats of TBP. *In vitro* experiments showed that TRF1 can bind to TATA-box together with TFIIA and TFIIB, and can efficiently replace TBP in transcription of TATA-dependent promoters. In addition, whole genome ChIP analysis demonstrated that TRF1 mainly activates transcription through RNAP III, and a minor group of genes transcribed by RNAP II. *Drosophila* TRF1 associates with Brf1, a TFIIB-related RNAP III transcription factor to form a 300 kDa complex.[51]

TRF3 (also known as TBP2 (TATA-binding protein 2) and TBPL2 (TBP-like protein 2)), which is the TRF that is most closely related to TBP, is unique to vertebrates.[52-55] Similarly to TBP and TRF1, TRF3 can associate with TFIIA and TFIIB.[52,54] TRF3 binds TATA-box containing promoters and activates them. TRF3 has been shown to be important for initiation of hematopoiesis during zebrafish embryogenesis.[53,56] TRF3 has also been shown to form a complex with TAF3 and play a role in the *ex-vivo* differentiation of mouse myoblast to myotubes.[57,58] As skeletal muscle differentiation is unaffected in TRF3 knockout mice,[59] the involvement of TRF3 in terminal differentiation in different species awaits further investigation. Importantly, TRF3 of *Xenopus* and zebrafish is mainly expressed in oocytes and is essential for embryogenesis.[52,54] Mouse TRF3, which is exclusively expressed in oocytes, is essential for the differentiation of female germ cells but not for embryonic development.[59]

TRF2 is the TRF protein with the least similarity to TBP.[60-65] In 1999-2000, when different research groups have cloned TRF2 from multiple species, different names were coined. The name TRF2 was used for *Drosophila*[64] and humans,[65] as it followed the discovery of TRF1 in *Drosophila*. It was also named TLP (TATA-like protein; identified in mouse and humans),[62,63] TLF (TBP-like factor; identified in *C. elegans*),[60,66] TRP (TBP-related protein; identified in humans)[61] and TBPL1 (TBP-like 1; L is used by the Human Gene Nomenclature Committee to denote paralogs of named genes), based on its homology to TBP and perhaps, taking into account that there is no vertebrate TRF1. TRF2 is involved in RNAP II transcription.[65] Similarly to TRF1 and TRF3, TRF2 can directly interact with TFIIA[61,65,67] and TFIIB.[61] Interestingly, *Drosophila trf2* encodes 2 protein products - a short (632 aa) protein, and a protein of 1715 aa (which will henceforth be referred to as long TRF2), in which the same short amino acid sequence is preceded by an N-terminal domain composed of coil-coiled motifs.[68] Translation of the short isoform probably results from an internal translation initiation by

an IRES mechanism.[68] Both proteins show similarity to the C-terminal core domain of TBP. The long TRF2 has only been identified in *Drosophila*. The short TRF2, which is highly conserved in evolution,[45,55,61,64,69,70] has been extensively studied and will henceforth be referred to as TRF2. The TRF2 core domain shows 40% identity and 60% similarity to the TBP core domain.[64] Despite the homology between the TRF2 and TBP core domains, the TATA-interacting Phe residues of TBP are not conserved in TRF2, and indeed TRF2 cannot bind the TATA-box.[61,64,70] Hence, the variety of TBP-related factors adds another level of complexity to the regulation of transcription. As discussed below, recent evidence suggests that TRF2 can direct RNAP II to subsets of TATA-less promoters and mediate diverse biological processes and transcriptional programs (**Fig. 1**).

TRF2 is involved in transcription of specific pathways

In *Drosophila*, TRF2 was shown to bind polytene chromosomes at sites distinct from those of TBP, suggesting that TRF2 regulates a subset of genes that differ from TBP-regulated genes.[64,71] Specifically, TRF2 has been shown to regulate the TATA-less Histone H1 gene, whereas TBP regulates the core histone genes.[71] Recent single cell imaging analysis of the endogenous histone gene cluster in *Drosophila* cells, showed differential transcription kinetics of TRF2-directed histone H1 gene expression (transcribed throughout S phase) vs. TBP-directed core histones gene expression (only transcribed in a short pulse during early S phase).[72]

Furthermore, ChIP-chip analysis revealed that *Drosophila* TRF2, but not TBP, is associated with a large group of TATA-less core promoters, including core promoters of ribosomal protein genes.[71] The core promoters of most ribosomal protein genes in *Drosophila* and humans contain a functional TCT motif, which is not recognized by the TBP/TFIID complex.[21] Remarkably, TRF2, but not TBP, has recently been shown to mediate the transcription of ribosomal protein genes that lack a TATA box and have functional TCT motifs.[73] *In vitro* transcription analysis using *Drosophila* TRF2-depleted embryonic nuclear extracts demonstrated that transcription of 4 TCT-dependent ribosomal genes (*RpL30*, *RpLP1*, *RpS12* and *RpS15*) was reduced, while no effect on transcription of TATA-dependent genes was observed.[73] Moreover, the addition of recombinant TRF2 to the TRF2-depleted extracts restored the transcriptional activity, further supporting the hypothesis that TRF2 regulates transcription of specific pathways.

ChIP-seq analysis of TRF2 on early (2 to 4 h) *Drosophila* embryos showed a peak of TRF2 in the TSS region.[73] Interestingly, MEME analysis performed on the top TRF2-bound genes revealed enrichment of the DPE motif, while no enriched motif was identified in the least TRF2-bound genes.[74] *Drosophila* short TRF2 was recently identified by a biochemical complementation analysis as an enriched factor in fractions that support DPE-dependent transcription.[74] Microarray analysis of *Drosophila* S2R+ cells that overexpress inducible short TRF2 identified multiple DPE-dependent targets. *In vitro* transcription followed

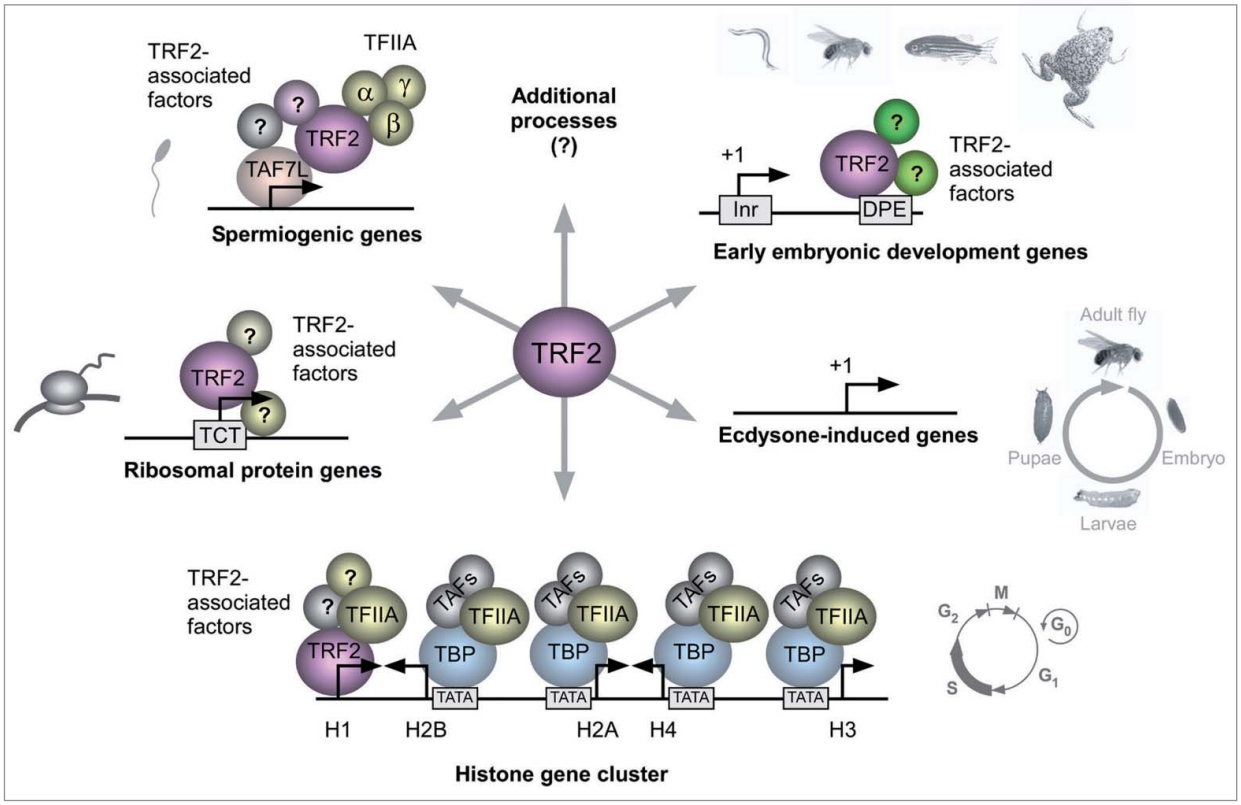

Figure 1. Schematic model depicting the regulation of diverse biological processes and transcriptional programs by TRF2.

by primer extension analysis of 4 TRF2 target genes (*pvf2*, *sodh-2*, *bgm* and *inx3*) indicated that their transcription was highly dependent on an intact DPE motif.[74] Furthermore, using microfluidics affinity analysis, protein extracts from S2R+ cells that over-express inducible TRF2, were shown to bind these DPE-containing promoters in a sequence-specific manner. Taken together, these findings suggest the existence of specialized transcriptional systems that do not involve TBP and regulate diverse biological pathways.

TRF2 is involved in embryonic development, differentiation and morphogenesis

TRF2 has been shown to be essential for embryonic development of *C. elegans*, *Drosophila*, zebrafish and *Xenopus*.[60,66,68,75,76] Interestingly, *Xenopus* TRF2 was shown to play a role in the expression of catabolic genes during embryonic development.[77] Recent analysis of *Drosophila* genes with high TRF2 occupancy revealed a strong relationship between TRF2 and processes such as cell differentiation and development.[70,73] An evolutionary conservation analysis indicated that TRF2 evolved by duplication of the TBP gene.[70] TRF2 is highly conserved in evolution and is present in all bilaterian organisms containing 3 germ layers: endoderm, mesoderm and ectoderm. TRF2 was not found in any of the non-bilaterian genomes that are currently available.[70] As more ancient animals only contain 2 germ layers (endoderm and ectoderm) and the emergence of the bilateria was at the same evolutionary point as that of *trf2*, one can speculate that TRF2 is important for mesoderm formation. Notably, analysis of core promoter composition of *Drosophila* genes involved in embryonic development and differentiation reveals the prevalence of the DPE motif.[15,78] Moreover, *Drosophila* embryos with reduced TRF2 have previously shown homeotic and segmentation defects, as well as dorsal-ventral abnormalities.[68] Unlike TRF2 in *Drosophila*, zebrafish and *Xenopus*, mouse TRF2 is not required for embryonic development.[79,80]

TRF2 is widely expressed in the adult animal.[61-63,65] Mouse TRF2 is essential for spermiogenesis.[79-81] It was recently demonstrated that TRF2 works in concert with the tissue-specific TAF7L, which is associated with testis-specific promoters, to regulate a subset of postmeiotic genes directing spermiogenesis.[82] Notably, *Drosophila* TRF2 has been shown to be involved in differentiation of germ cells of both male and female.[68] Interestingly, it was recently demonstrated that Taspase1-mediated proteolytic cleavage of the TFIIAα-β precursor (into the α and β subunits of TFIIA) is necessary for the activation TRF2-specified transcriptional spermiogenic program in the juvenile and adult mouse testes.[83] Hence, TRF2 may form tissue-specific preinitiation complexes that regulate transcription of specific subsets of genes necessary for germ cell differentiation.

Drosophila trf2 has been shown to be required for transcriptional and developmental responses to ecdysone during *Drosophila* metamorphosis.[84] Hypomorphic *trf2* mutations display defects in major ecdysone-triggered biological responses, including puparium formation, anterior spiracle eversion, gas bubble translocation, adult head eversion, and larval salivary gland cell death. *Drosophila trf2* appears to be required for the proper timing and levels of ecdysone-regulated gene expression required for entry into metamorphosis.[84] Additional support for the involvement of TRF2 in *Drosophila* metamorphosis comes from RNAi depletion of TRF2 in larval salivary glands that results in a significant reduction in the sizes of the cells and the glands.[71] Although these mutant embryos develop to the third instar larval stage, a majority of them fail to pupate or die during pupal stages. Hence, even though a detailed mechanism has not been demonstrated, TRF2 is involved in the regulation of *Drosophila* metamorphosis.

Conclusions and future perspectives

Recent findings have highlighted the involvement of TRF2 in the regulation of diverse biological processes and specialized transcription programs (**Fig. 1**). It is possible that TRF2 regulates additional pathways and systems that remain to be discovered.

Historically, promoters have been classified as TATA box-containing or TATA-less. It is now clear that it takes much more than the presence of a TATA box to define the characteristics of a core promoter. Likewise, it is clear that there is no universal transcription machinery and the term general transcription machinery should be replaced by basal transcription machinery. Since its discovery, it has been known that TRF2 does not bind TATA-containing DNA. In fact, based on multiple studies in the last 15 years implying that TRF2 regulates specialized transcription systems, the name TBP-related factor 2, rather than TBP-like factor (TLF) or TBP-like protein (TLP), seems more appropriate. Hence, based on functionality, rather than homology to TBP, we suggest adopting the TRF terminology for the TBP family of proteins.

It remains to be determined whether TRF2 binds sequence-specific DNA directly. The Kadonaga Lab did not observe sequence-specific DNA binding under an extensive range of conditions with many different template DNAs and methodologies in the absence or presence of different combinations of purified TFIIA and TFIIB.[73] ChIP-seq data indicated that TRF2 binds in the vicinity of the TSS.[73] Microfluidic affinity analysis has demonstrated DNA binding of TRF2-containing complexes to DPE-containing promoters.[74] It is likely that there are TRF2-associated factors (like TBP-associated factors), which assist TRF2 in binding to its target promoters. Such TRF2-associated factors remain to be discovered.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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