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REVIEW

Recent advances in understanding the structure and function of general transcription factor TFIID

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Abstract The general transcription factor TFIID is a macromolecular complex comprising the TATA-binding protein (TBP) and a set of 13–14 TBP associated factors (TAFs). This review discusses biochemical, genetic and electron microscopic data acquired over the past years that provide a model for the composition, organisation and assembly of TFIID. We also revisit ideas on how TFIID is recruited to the promoters of active and possibly repressed genes. Recent observations show that recognition of acetylated and methylated histone residues by structural domains in several TAFs plays an important role. Finally, we highlight several genetic studies suggesting that TFIID is required for initiation of transcription, but not for maintaining transcription once a promoter is in an active state.

Keywords *Drosophila* · Yeast · Electron microscopy · Chromatin · Acetylation · Methylation

Introduction

Regulated initiation of transcription by RNA polymerase II requires the formation of a macromolecular preinitiation complex (PIC) that assembles over the transcription start site. In addition to RNA polymerase II (pol II), the PIC comprises a set of general transcription factors TFIIA, B, D, E, F and H. In yeast, the mediator (Med) and NC2 complexes are also found at the promoters of most active genes [1, 2]. TFIID is itself a macromolecular complex composed of the TATA-binding protein (TBP) and a set of 13–14 TBP-associated factors (TAFs). TFIID has been the subject of intense study over the last 20 years, and many review articles have illustrated how our understanding of its function has progressed during this time (see, for example, [3–7]). A subset of TAFs is also present in the Spt-Ada-Gcn5-acetyltransferase (SAGA)-type transcriptional regulatory complexes, and several recent reviews describe the important roles of these complexes in transcription regulation [7–10].

In this review, we will discuss results concerning the organisation and assembly of the TFIID complex and how it is recruited to active promoters, not only through interactions with DNA or activators, but also as a reader of covalent histone modifications. Lastly, we will address the question of when the function of TFIID is actually required. Several studies provide genetic data that should modify our view of TFIID's role in transcription.

TFIID comprises core and peripheral modules

TFIID was first characterised in *Drosophila* and in mammals where immunoprecipitation with antibodies against the TBP subunit revealed the presence of a set of tightly associated TAF proteins [11–13]. TFIID was subsequently biochemically characterised in the yeast *Saccharomyces cerevisiae* (hereafter yeast) [14–16]. The genes encoding the TAFs were isolated in each of these organisms, allowing the identification of structural and functional domains that are conserved from yeast to humans. While initial results suggested that there may be differences in the composition of TFIID in each species, an extensive series of biochemical and genetic studies rather showed that the

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core composition is well conserved between yeast and mammals [5, 17]. This conservation has allowed the adoption of a unified nomenclature, TAF1-TAF14, that clearly designates TAF orthologues in different species [18]. Yeast, TFIID comprises 14 TAFs, and with the exception of TAF14 the orthologues of each of these proteins have been identified as *bone fide* TFIID subunits in *Drosophila* and mammals.

Biochemical, structural and genetic techniques have all been used to address the molecular organisation of TFIID. An initial analysis of the amino acid sequences of TAF6, 9 and 12 revealed a striking similarity to the core H4, H3 and H2B histones, suggesting the existence of a histone octamer structure within TFIID [19]. Further studies showed however that 9 of the 13 TAFs contained a histone fold domain (HFD) specifying the formation of five distinct TAF heterodimers within TFIID [5, 17]. These heterodimers were also found in the context of native TFIID, thus underlining that the HFD is a fundamental building block of TFIID [20].

Genetic, biochemical and electron microscopy (EM) experiments clearly identified two classes of subunits based on their stoichiometries [20–22]. TAF1, TAF2, TAF7 and TBP are present as a single copy, whereas almost all of the others are present in at least two copies. Therefore, the total number of heterodimers and their distribution within TFIID (see below) show that the overall organisation is more complex than a simple octamer-like core.

Despite the importance of TFIID in transcription initiation, there is a remarkable paucity of structural data on TFIID subunits, and little is known of the mechanisms directing its supramolecular assembly. Structural information at the atomic level is currently only available for a few TAF subdomains (see, for example, [23–25]). EM has however provided detailed information on the overall shape of native TFIID and the localisation of TAF subunits. Single molecule analysis and image reconstruction show that yeast (y)TFIID and human (h)TFIID have a similar overall organisation comprising three major lobes linked by connecting regions to form a 'horseshoe'-shaped molecular clamp [20, 26, 27]. To date these studies are limited to low resolution, 32Å for hTFIID [28] and 23Å for yTFIID (see Fig. 1a; [29]), which are not sufficient to allow docking with the known crystal structures. Structural heterogeneity, in particular variable TAF2 content, and dynamic rearrangements of the complex are limitations to improved resolution.

EM coupled to immunolabelling of complete TFIID or of subpopulations have allowed the localisation of individual TAFs within this structure defining the composition of the lobes, each of which comprises a unique TAF combination [20, 22, 29] (see Fig. 1c). TAFs present as a single copy are found mainly in lobes A and C. The

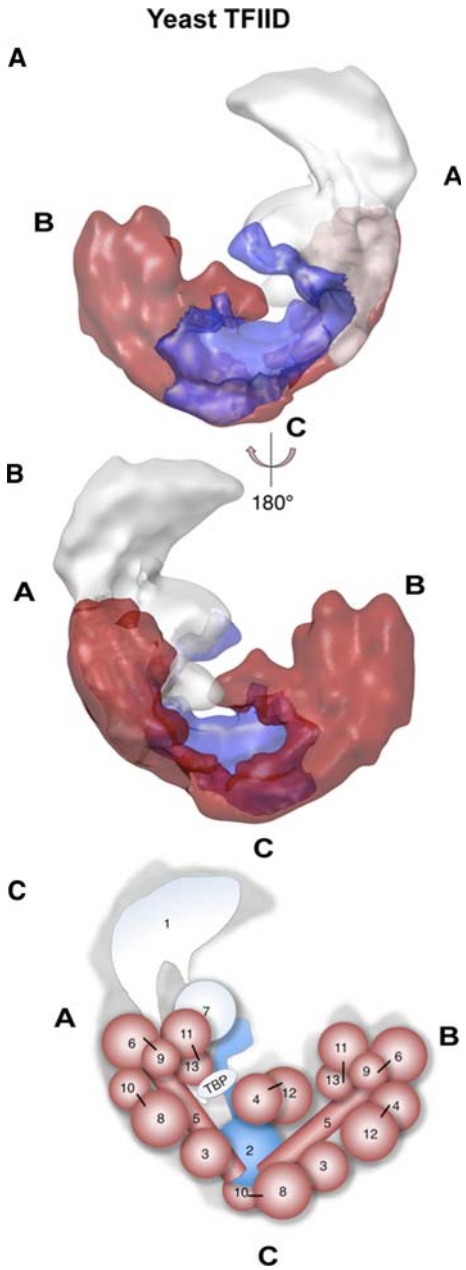

Fig. 1 Structural organisation of yeast TFIID; (**a**, **b**) two opposite views of the TFIID complex showing the location of TAF1, TAF7 and TBP (*white*), TAF2 (*blue*) and a quasi symmetric core module (*red*). **c** Schematic representation of the TAF localisation within TFIID. The approximate positions of the subunits are derived from antibody-labelling experiments. The size of the spheres is proportional to the molecular mass of the proteins. *Black lines* represent documented protein–protein interactions of histone fold domain containing TAFs

C-terminus of TAF1 and TAF7 localise on the top of lobe A, while the N-terminus of TAF1 and TBP localise at the interface of lobes A and C. TAF2 is also located in the interface between lobes A and C with its N-terminus close to the C-lobe and its C-terminus close to the A-lobe where

it could interact with TAF1. TAFs that are documented to be present in at least two copies are located in the bottom part of lobe A and in lobes B and C. The localisation of the HFD-containing TAFs in native yTFIID is consistent with the previous genetic, biochemical and structural data on the formation of specific TAF heterodimers. An exception is the TAF3/TAF10 heterodimer. In EM immunolabelling, TAF3 can be observed in lobe B, but no associated TAF10 can be seen, while in lobe A it is not possible to discriminate between the TAF3/TAF10 and the TAF8/TAF10 heterodimers.

Interestingly, when the potential protein densities of TAF1, TAF2, TAF7 and TBP are removed from the 23Å yTFIID model (blue and white in Fig. 1a, b), the shape of the remaining structure is reminiscent of that of a stable in vitro reconstituted complex composed of TAF5 and the three HFD-TAF heterodimers TAF4/12, TAF6/9 TAF8/10 [22] and presents an almost symmetric crescent-shaped structure (red in Fig. 1a). Residual asymmetry could result from the binding of the remaining HFD-containing TAFs. Altogether, the higher resolution structure and the labelling studies strongly suggest that the 3D architecture of TFIID is composed of two subcomplexes: (1) a core complex containing TAF5 and most of the HFD-containing TAF heterodimers (TAF6/9, TAF4/12, TAF8/10, TAF11/13) that adopts a crescent-shaped twofold symmetric structure; (2) a subcomplex containing TAF1, TAF7, TAF2 and TBP that is recruited to the core complex to form full TFIID (Fig. 2). The TAFs shared between TFIID and SAGA are all found in the core complex. In SAGA, the TAF8/TAF10 and TAF4/TAF12 heterodimers are replaced by the SPT7/TAF10 and ADA1/TAF12 heterodimers. This core domain is therefore pivotal in the assembly of both of these complexes. Perhaps competition between the SAGA and TFIID-specific heterodimerisation partners regulates the relative abundance of each of these complexes in the cell.

TBP is located in the linker region that lies within the major cavity of the clamp and is flanked by TAF1, TAF2, TFIIA and TFIIB, suggesting that this is the principal DNA binding site [27]. The structure of TFIID complexed with DNA has not yet been determined, but would be extremely informative and help to put in perspective the multiple TAF-DNA-chromatin interactions that have been described (see below).

TFIID structure may not be static, but rather appears to be dynamic as distinct ‘open’ and ‘closed’ conformations have been observed. Cryo-electron microscopy identifies two distinct conformations where the relative positions of the three lobes change in a coordinated and reproducible fashion resulting in an opening or closing of the central cavity [28]. The significance of these distinct states in terms of function or PIC formation has not been elucidated.

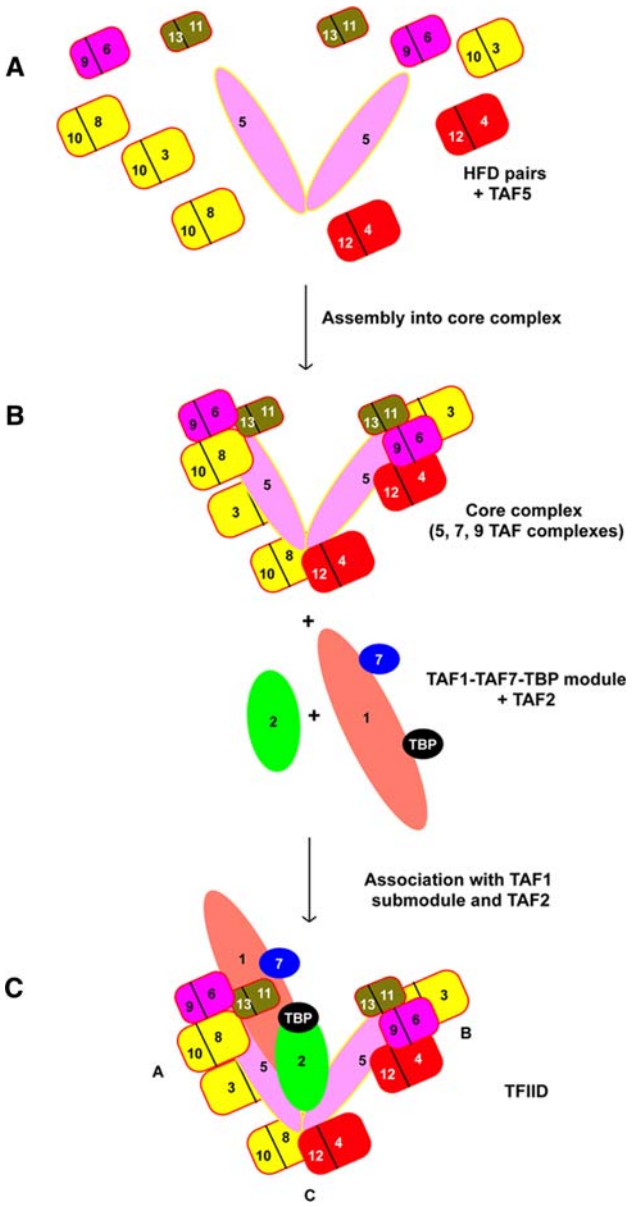

Fig. 2 Schematic model for TFIID assembly. **a** The histone fold containing TAFs form heterodimers and associates with TAF5 to form the core complex. The ability of TAF5 to homodimerise is still open to question, and it is as yet unclear whether the histone-like heterodimers associate to form higher order ‘lobe’ structures in the absence of TAF5. **b** TAF5 and the histone-like heterodimers associate to form the core complex. Variants of this complex in the form of 5 TAF (*Drosophila* S2 cells), 7 TAF (baculovirus reconstitution in vitro) or 9 TAF (yeast in vivo) complexes have been described and are discussed in the text. **c** The core complex interacts with the TAF1-TAF7-TBP sub-module to form TFIID. TAF2 may associate independently with TFIID through interaction with TAF1, but may not be always present in TFIID

Also it is not yet clear whether these distinct states result from an inherent flexibility in the structure or whether they represent TFIID with different subunit compositions or TAFs bearing post-translational modifications.

Evidence that TAF-composition may influence TFIID topology comes from comparison of the EM structure of distinct TFIIDs containing either two molecules of TAF4 or TAF4 along with its paralogue TAF4b. TAF4 and TAF4b are encoded by related genes and share a central conserved region I, called the TAFH domain, as well as the larger conserved C-terminal region II containing an atypical HFD. TAF4 and TAF4b both heterodimerise with TAF12 and interact with TFIIA [24, 30–33]. A comparison of the EM structures of TFIID from Hela cells containing predominantly TAF4 with that purified from Daudi cells containing TAF4 and TAF4b shows that the complexes containing TAF4b adopt a more open conformation [34]. This difference is achieved by changes in the relative positions of lobes A and B. TAF4b localises to lobes B and C, and TFIIA spans the lobe A–C chanel. Consequently, it has been proposed that incorporation of TAF4b into TFIID leads to an 'open' conformation of lobe A, facilitating TAF4b interaction with TFIIA and various transcriptional activators. These observations thus provide evidence that differences in subunit composition affect TFIID conformation.

The status of TAF2 as a bona fide subunit of TFIID has been under debate since it was either missing or present at a reduced molar ratio in hTFIID preparations [35]. A more recent study [29] shows that the presence or absence of TAF2 also affects TFIID structure. Analysis of immunopurified yTFIID preparations that are heterogeneous in TAF2 content revealed complex conformational changes of the TFIID structure where at least four distinct states could be observed. The presence of TAF2 selectively stabilises one of these conformations, whereas in the absence of TAF2 significant domain reorganizations were observed, especially in the central lobe, as was noted for hTFIID. The TAF2-TFIID interaction is therefore labile, and while TAF2 can be dissociated without compromising TFIID integrity, its presence or absence can have a major influence on TFIID conformation. How these differences in subunit composition and in conformational state influence TFIID recognition and recruitment to promoters with different core sequences remains to be fully understood. The possibility that the structure of TFIID can be adapted to allow for the recognition of a large variety of promoters, each with distinct activator binding site distributions, is particularly attractive.

Several TAFs are critical for assembly and stability of TFIID

Although we now have a better understanding of TFIID subunit composition and organisation, the mechanism of assembly is much less well understood. An initial series of in vitro reconstitution studies put forward the idea that TAF1 formed a scaffold for TFIID assembly through its interactions with TBP and several other TAFs [36]. However, these studies were performed before the full subunit composition of TFIID was determined, and several TAF subunits were not included in these assays. More recent results reveal a more complex mechanism.

Genetic and biochemical studies in yeast have addressed the role of TAF1 in TFIID assembly. Biochemical analysis of a series of pseudodiploid yeast strains harbouring deletion mutants in a tagged allele of TAF1 shows that deletion of the N-terminal domain of TAF1 leads to diminished association with TBP, but not with the TAFs [37]. In contrast, deletion of the region between amino acids 200–303 leads to a loss of interaction with all of the TAFs except TAF7, but does not affect interaction with TBP. These data are consistent with the observation that the N-terminus of TAF1 (the TAND domain) interacts with TBP [38], while TAF7 interacts directly with several regions in the C-terminal portion of TAF1 [39, 40].

Two hybrid assays further show that the TAF1 200–303 region interacts with TAF4 and TAF6, and biochemical analysis shows that expression of this region alone is sufficient to nucleate the formation of a partial TFIID complex. Temperature-sensitive (TS) TAF1 mutants with amino acid substitutions in this region were also isolated and shown to affect interaction of the TAF1/TBP/TA7 module with the other TAFs. However, immunoprecipitation of TAF4 from the mutant strain shows that although interaction with TAF1 is lost, TAF4 is associated with other TAFs in a stable complex.

TFIID stability has also been investigated in *Drosophila* Schneider 2 (S2) cells where expression of TAF subunits was disrupted by siRNA. In this approach, the effect of siRNA knock-down of individual TAF subunits on TFIID integrity and an associated proteolytic degradation of the other TAFs was evaluated [41]. Knock-down of TAF1 did not destabilise the other tested TAFs, and in its absence a stable complex comprising TAF4, TAF5, TAF6, TAF9 and TAF12 was observed. In contrast, siRNA knock-down of TAF4 or its heterodimerisation partner TAF12 leads to degradation of TAF1 and most other TAFs, with the exception of TAF2. This observation shows that TAF4 is critical for TFIID assembly consistent with the fact that it is present in two of the globular lobes. Similar observations were made upon knock-down of TAF5 and TAF6 that also led to degradation of TAF1, suggesting that TFIID integrity is compromised. Moreover, expression of the conserved HFDs of TAF4 and TAF6 is sufficient to complement the loss of the corresponding native proteins for assembly and stability of the TFIID complex.

The idea that TAF4 is critical for TFIID assembly/stability is relevant to several functional observations. For

example, in *C. elegans*, siRNA of TAF4 had the most potent effect on transcription compared to other TAFs [42]. More recently it has been shown that TAF4 is a target of the *C. elegans* oocyte maturation (OMA)-1 and OMA-2, zinc finger proteins of the CCCH class that bind to RNA and are important for oocyte maturation and early embryonic development [43]. In early embryos, the OMA proteins bind to TAF4 by mimicking the HFD domain interaction with TAF12 and sequestering TAF4 in the cytoplasm, thus silencing transcription at these early stages. Similarly, it has been proposed that sequestration of TAF4 by variants of the Huntington protein carrying expanded polyglutamine domains interferes with transcription and contributes to neurodegenerative disease [44, 45]. Given the important role of TAF4 in TFIID assembly, its sequestration would therefore provide a mechanism to control the overall function of TFIID through targeting of a single subunit.

Further insight into TFIID assembly comes from reconstitution of TAF complexes by baculovirus coinfections. In these studies, a stable and homogenous seven-subunit complex comprising TAF5 and the TAF4/12 TAF6/9 and TAF8/10 HFD heterodimers could be isolated [22]. In the absence of TAF5, the stability of this complex is compromised. EM images of this sub-complex show a trilobed structure that is reminiscient of the TFIID core domain. These observations suggest that TAF5 may dimerise through its N-terminal domain, while its C-terminal domain containing the beta-transducin (WD40) repeats interacts with the HFD TAFs to form the globular lobes. The dimerisation of TAF5 is still under discussion as conflicting results have been obtained [25, 46].

Do the HFD-TAF heterodimers assemble by themselves into higher order 'lobe' structures or does TAF5 play an active role in this process? TS mutations in the WD40 repeats of yTAF5 were found to cause broad transcription defects showing that these motifs are critical in maintaining the integrity of both the TFIID and SAGA complexes [47]. However, in S2 cells, TAF5 knock-down leads to degradation of TAF1, but not other TAFs. Thus, either some type of higher order complexes form in the absence of TAF5, or perhaps heterodimer formation ensures their stability even without their assembly in 'lobe' structures. The full set of interactions required for the formation of the core TAF subcomplex therefore remains to be determined.

To further complicate matters, genetic experiments in mammalian cells revealed that TAF10 is critical for TFIID integrity. Somatic inactivation of TAF10 by Cre-mediated deletion in F9 embryonic carcinoma cells, in early embryos and in adult liver have shown that loss of TAF10 leads to disassemby of TFIID [48–50]. In contrast, inactivation of TAF4 in cells that express TAF4b facilitates integration of TAF4b into TFIID without affecting its stability [51].

Taken altogether, the studies in yeast, *Drosophila* and in vitro all suggest a similar modular model of TFIID organisation and assembly. In each approach, a stable HFD-containing TAF subcomplex can be formed lacking TAF1, TAF2, TAF7 and TBP (see Fig. 2a, b). In yeast, this complex comprises most other TAFs and corresponds to the pseudo-symmetric core complex described by EM. In *Drosophila*, a subcomplex containing only five TAFs was described, but the presence of several others was not assayed and so could also be present in this complex. There is compelling evidence that TAF4, TAF5 and TAF10 all play primary roles in the assembly and stability of the core complex and hence of TFIID. The core subcomplex associates via TAF4 and TAF6 with a second submodule comprising TAF1-TBP-TAF7 to assemble the TFIID complex (see Fig. 2c).

These observations can be better understood in the context of the known EM structure. TAF4 and TAF10 are both present in at least two distinct lobes. Their loss presumably destabilises these lobes, leading to release of the TAF1-TBP-TAF7 module, which in S2 cells is unstable and degraded. TAF5 seems to link lobes A and B together and may be required to assemble the HFD-heterodimers into stable lobe structures. In contrast, TAF1, TAF7 and TBP are located on top of the pseudo-symmetric TFIID core, and this module may be unstable in the absence of the other TAFs forming the core structure.

TAF2 is not essential for TFIID assembly, but probably associates with TFIID via interactions with TAF1. Moreover, TAF1 and TAF2 have been shown to form a subcomplex with TBP that specifically binds to promoter DNA in vitro [52]. Although the existence of such a subcomplex has yet to be demonstrated in vivo, the *P. falciparum* genome encodes orthologues of TAF1, TAF2 and TBP, but not of other TAFs (with the possible exception of TAF10), further highlighting the idea of a functional TAF1-TAF2-TBP subcomplex [83].

The precise roles of TAF3, TAF7, TAF11 and TAF13 in the stability and assembly of TFIID remain to be investigated. As mentioned above, TAF7 is known to interact with TAF1 and to negatively regulate its HAT activity [39]. TAF7 also interacts with TFIIH and Positive Transcription Elongation Factor b (pTEFb) to inhibit their ability to phosphorylate the carboxy-terminal domain of the largest subunit of RNA polymerase II, but is released upon entry of the polymerase into the preinitiation complex [53]. TAF7 may therefore function as a check-point regulator suppressing premature transcription initiation [54]. These observations are consistent with the above model of TFIID organisation where TAF7 can dissociate from the complex without loss of integrity.

In conclusion, the above results show that TFIID stability depends on a complex set of interactions in which not

one, but several TAFs that form the core structure play a critical role.

Functional TAF subcomplexes in male germ cells

While TFIID has been purified and studied from cell extracts, the question arises whether the five or seven TAF subcomplexes of the core structure naturally exist in cells and whether they have any specific functions or serve simply as assembly intermediates. Evidence that such subcomplexes exist and may have specific functions comes from studies of transcription in male germ cells.

In addition to the core TAFs described above, the *Drosophila* genome encodes five additional testits (t)TAF paralogues that are specifically expressed in a coordinated manner in spermatocytes. *No hitter (nht)* (TAF4L), *cannonball (can)* (TAF5L), *meiosis I arrest (mia)* (TAF6L), *spermatocyte arrest (sa)*(TAF8L) and *ryan express (rye)* (TAF12L) are paralogues of TAF4, TAF5, TAF6, TAF8 and TAF12, respectively [55, 56]. These paralogues share the same structural domains as the corresponding core TAFs and therefore may form stable 5 or 7-TAF complexes. Such an organisation would require additional partners (TAF9 and TAF10a or TAF10b) or as yet unidentified components as heterodimerisation partners for the HFDs of dTAF6L and dTAF8L.

A biochemical analysis of their function shows that most of the tTAF protein localises to the nucleolus where they are required for a nucleolar relocalisation of the polycomb (Pc), polyhomeotic (Ph) and dRING (really interesting new gene) subunits of the *Drosophila* PRC1 repressor complex that takes place in spermatocytes [57]. Sequestration of PRC1 facilitates activation of a series of genes required for germ cell differentiation.

The mechanism described above is not conserved in mammals. However, the mouse genome encodes two TAF paralogues involved in spermatogenesis. TAF7L is a protein with high sequence similarity to somatically expressed TAF7 that is expressed in spermatogonia and in early primary spermatocytes, where it is localised in the cytoplasm [40, 58]. During spermatocyte development, TAF7L is imported into the nucleus and accumulates strongly in post-meiotic round spermatids where it is associated with TBP.

The import of TAF7L into the nucleus is coordinated with both a loss of TAF7 expression and a potent upregulation of TBP. In addition, the expression of TAF4 and TAF10 are strongly downregulated in round spermatids. As a consequence, haploid round spermatids strongly express TAF7L and TBP, but little or no TAF4 and TAF10, suggesting that they do not contain high levels of intact TFIID. In agreement with this, TAF6 is not associated with TBP in these cells. Therefore, in contrast to what has been discussed above, in haploid spermatids a stable and functional TAF7L-TAF1-TBP complex may exist.

Furthermore, a critical role for TAF1 in spermatogenesis is suggested by the observation that in old world monkeys, apes and humans, there is a retrotransposed copy of TAF1 encoding TAF1L that has been selected to evade meiotic sex chromosome inactivation of the ancestral TAF1 gene present on the X chromosome [59]. The study of male germ cells therefore reveals potential functions for both the HFD-containing TAFs and the TAF1-TAF7-TBP submodules.

Multiple interactions with DNA, activators and covalent histone modifications are involved in promoter recruitment of TFIID

While TBP binding to canonical TATA elements has been well studied both biochemically and structurally [60], the vast majority of promoters do not contain a recognisable TATA element. A number of observations indicate that TFIID recognises promoters through additional interactions of TAFs with other DNA promoter elements and also through interaction of TAFs with acetylated and methylated histone lysine residues.

Genetic evidence showing that TAFs contribute to promoter recognition was first obtained studying the effect of TS TAF mutations in yeast. A TS mutation in TAF1 affects the expression of only a limited number of promoters, for example those of cyclin (CLN)2 or ribosomal protein (RP)S5 [61]. The dependence of these promoters on functional TAF1 was shown to reside in the core promoter sequence and not in the upstream activating sequence (UAS) element where the gene regulatory factors interact. The region conferring TAF1 dependence was mapped to a region around the TATA element, but a precise sequence element could not be determined.

Using biochemical approaches, multiple TAF-promoter DNA contacts due to ‘wrapping’ of DNA around TFIID [62] have been described along with several more specific TAF-promoter interactions. Cross-linking and electrophoretic mobility shift assay-mediated binding site selection has been used to show that the recombinant TAF1–TAF2 complex has specificity for interaction with DNA containing the Initiator (Inr) sequence, a loosely defined sequence with a 5′-YC/TANT/AYY-3′ consensus [35, 52]. In vitro reconstitution and transcription studies also indicate a role for TAF2 in transcription from Inr containing promoters. On the other hand, cross-linking has been used to show that the TAF6-TAF9 heterodimer may contact the downstream promoter element (DPE), an element found downstream of the transcription start site that has been well

characterised in a subset of *Drosophila* promoters and is likely also present in mammalian promoters (for review see [63, 64]). The presence of a DPE is often associated with that of an Inr, and both elements functionally cooperate. Most of the TAFs involved in the interaction with promoter elements are located at the base of lobe A (Fig. 1c) and are therefore likely to define the major DNA binding interface within TFIID.

Promoters containing combinations of TATA, Inr or DPE or other well-defined and -characterised promoter elements generally belong to the 'sharp' class characterised by a single transcription start site [65–67]. The majority of promoters, however, fall into the 'broad' class characterised by multiple start sites, the lack of identifiable promoter elements and the presence of a CpG island. How does TFIID get recruited and stabilised at such promoters? Several lines of evidence suggest that protein-protein interactions may play a critical role.

A large body of evidence indicates that transcription activator proteins can interact with TAFs and recruit TFIID to the promoter. Well-characterised examples are the interactions between SP1 or CREB (cyclic AMP response element binding) and TAF4 [68–70]. More importantly it has been shown that activators can interact with TAFs in the context of native TFIID and recruit it to promoters [71, 72].

In addition to the above, interactions between TAFs and covalently modified histone lysines have been identified that probably also play an important role in TFIID promoter recognition. A large body of evidence has clearly established that transcriptionally active promoters are characterised by the presence of specific covalent modifications of histone residues (for recent reviews, see [73, 74]). Several marks are tightly associated with active promoters, such as the trimethylation of lysine 4 on histone H3 (H3K4me3) and acetylation of lysine 9 on histone H3 (H3K9ac). These and other covalent modifications are recognised by structural domains present in proteins that interact with chromatin (for an extensive review, see [73]). Amongst these domains, three are present in the TAFs, a double bromodomain in TAF1, a plant homeodomain (PHD) in TAF3 and a WD40 repeat domain in TAF5.

The first TAF domain to be characterised as interacting with modified histones was the double bromodomain in TAF1. Structural and biochemical studies showed that the TAF1 bromodomains did not bind the unacetylated H4 tail, but recognised with low affinity the H4 tail acetylated on K16, and with a much higher affinity H4 tails doubly acetylated at positions K5/K12 or K8/K16 [75]. These marks are characteristic of actively transcribed euchromatin, suggesting that TFIID may be recruited and/or stabilised at active promoters through interaction of TAF1 with nucleosomes bearing these modifications. As TAF1 has also been reported to be a histone acetyl transferase [76], it may be both a reader and writer of histone modifications.

Metazoan TAF3 comprises a C-terminal PHD domain. Stable isotope labelling with amino acids in cell culture (SILAC) proteomics experiments identified TAF3 and other TFIID subunits interacting specifically with histone tails carrying the H3K4me3 modification via this PHD domain [77]. Previously it had been reported that the PHD domains of subunits of a transcriptional repressor complex (inhibitor of growth, ING2) and the chromatin remodelling complex (bromodomain PHD finger transcription factor, BPTF) also interacted specifically with this mark (see [73] and references therein). However, the affinity of TAF3 for H3K4me3 is 10–20-fold higher than for ING2 and BPTF [77, 78]. In addition, the combination of H3K4me3 with K9 and K14 acetylation strongly increases the interaction with TFIID, presumably through recognition of the acetylated residues by the TAF1 double bromodomains. The affinity of the TAF3 PHD domain with the H3K4me3 mark is significantly higher than the bromodomains for the acetylated resides, suggesting that the PHD-mediated interaction is dominant, while the bromodomain interactions further stabilise the histone-TFIID complex. In contrast, binding of TAF3 is reduced when the H3K4me3 modification is coupled with asymmetric dimethylation of the adjacent arginine (R)2 residue, a mark that anti-correlates with transcriptional activity.

Together these studies suggest a model where interactions with transcriptional activators and with appropriately modified histone tails act to recruit and stabilise TFIID at active promoters. These interactions can complement those of TBP and TAFs with promoter DNA elements or substitute for these interactions at CpG island-type promoters. Interestingly, although these histone modifications exist in yeast, yTAF1 and yTAF3 lack the bromo and PHD domains, respectively.

As a further complication to the above model, the TAF4 subunit has been shown to interact with heterochromatin protein (HP)1α and HP1γ, but not HP1β [79]. The HP1s interact with a variety of partner proteins through a conserved PXVXL motif (for recent reviews, see [80, 81]). Such a motif has been identified in the C-terminal domain of TAF4 and shown to be required for interaction with HP1. The HP1 proteins were first described as heterochromatin-associated proteins recruited through interactions with H3K9me3 and involved in gene silencing. More recent studies however have also shown that HP1s can be found in euchromatin and be involved in both activation and repression. It therefore remains to be determined whether the TAF4-HP1 interaction contributes to recruitment of TFIID to a subset of active promoters or is involved in TAF-dependent repression (see below).

Two further TAF domains may be involved in chromatin interactions. As mentioned above, the C-terminus of TAF5 comprises a WD40 repeat domain. WD40 domains form a beta-propellor type structure. The WD40 domain in the WDR5 subunit of the SET1 [*Drosophila* Su(var) 3-9, Enhancer of zeste (E(z)), and Trithorax (trx)] methylation complexes has been shown to interact with H3K4 in the di-, tri- and un-methylated states, with a preference for di-methylation and also with the H4 tail (for review, see [82]). It will be interesting to determine whether the TAF4 WD40 domain can also interact with modified histones and provide yet another surface for TFIID interaction with chromatin.

Lastly, the amino terminus of TAF2 comprises an enzymatically inactive amino-peptidase fold [83]. A similar fold exists in the suppressor of P-element transcription (SPT)16 subunit of the factor required for transcription elongation on chromatin templates (FACT) complex and has been shown to interact with the globular core and tails of H3 and H4 [84]. It remains to be determined whether TAF2 can also interact with histones.

Is TFIID required to maintain promoters in an active state?

Once recruited to active promoters, what is the function of TFIID? In the classical view TFIID nucleates PIC formation and promotes transcription initiation. In vitro studies also suggested that TFIID remains at the promoter once transcription has been initiated as part of the reinitiation scaffold [85]. Several recent observations suggest a rather different model.

Inactivation of TBP in early mouse embryos leads to arrest of proliferation at the 32 cell stage after depletion of the maternal TBP and subsequent apoptosis [86]. Nevertheless, the levels of pol II transcription in the arrested cells of the TBP knockout embryo were comparable to that seen in normal embryos at the same stage. These observations led to the idea that TBP/TFIID may be differentially required in proliferating and post-mitotic cells [87]. During cell division, active transcription complexes are dissociated and must be reformed in the daughter cells. TBP plays a central role in this process as it remains associated with a subset of promoters during mitosis [88]. Comprehensive chromatin immunoprecipitaion experiments show that TBP remains bound to many chromosomal sites during mitosis, thus 'bookmarking' promoters for re-expression in interphase [89]. TBP interacts with the protein phosphatase (PP)2A to locally inactivate condensin at these sites and inhibit their compaction. The results of the TBP knockout in post-mitotic cells suggest that once the active transcription complex has been established, TBP/TFIID may be dispensible for the reinitiation step and persistance of the active state, but that cells can no longer undergo mitosis.

This model is also supported by observations of genetic knockout of TAF subunits. For example, inactivation of TAF10 in proliferating F9 embryonal carcinoma cells leads to TFIID disassembly, cell cycle arrest and apoptosis, whereas non-dividing differentiated F9 cells survive [49]. Similarly, TAF10 is required in the proliferating inner cell mass of the early embryo, but not in post-mitotic trophoblast cells [48]. Again, these results suggest an essential function for TFIID in proliferating, but not post-mitotic cells.

Further evidence for this idea has been provided by the inactivation of TAF10 in mouse hepatocytes. Knockout of TAF10 in proliferating embryonic hepatoblasts affects their proliferation and differentiation and leads to subsequent defective liver organogenesis [50]. In contrast in the adult liver, loss of TAF10 does not lead to an immediate apoptosis of the non-dividing hepatocytes. Transcriptome analysis showed that the expression of only a small number of genes was affected corresponding to those that are specifically activated in the adult hepatocytes, while genes that were already active in embryonic hepatocytes were not affected upon TAF10 inactivation. A biochemical analysis confirmed that TFIID is disassembled in the absence of TAF10 and that neither TBP nor TAFs are present at the promoters of active genes and are not recruited at the appropriate time to the developmentally regulated promoters.

In contrast, several genes expressed in embryonic hepatocytes and normally silenced in adult cells are re-expressed in the absence of TAF10, suggesting that TFIID plays an active repressive role. This idea is supported by the fact that while pol II is lost from these promoters during the normal developmental silencing, TAFs remain associated with these promoters. Perhaps it is in this type of situation that the TAF4-HP1 interaction would be required to recruit or stabilise TFIID.

Together the above results suggest a model whereby intact TFIID is required to mediate gene activation either after mitosis or in a developmentally regulated fashion (Fig. 3). However, once a promoter is active and even although in normal circumstances TFIID remains associated with the promoter, its function is no longer required to maintain the promoter in an active state and to promote transcription reinitiation.

One set of observations that do not obviously fit this model comes from the inactivation of TAF10 in the basal keratinocytes of the epidermis [90]. Loss of TAF10 in adult keratinocytes has no obvious effect on skin homeostasis, hair cycle or wound healing. Presumably loss of TAF10 leads to TFIID disassembly in keratinocytes as in other cell

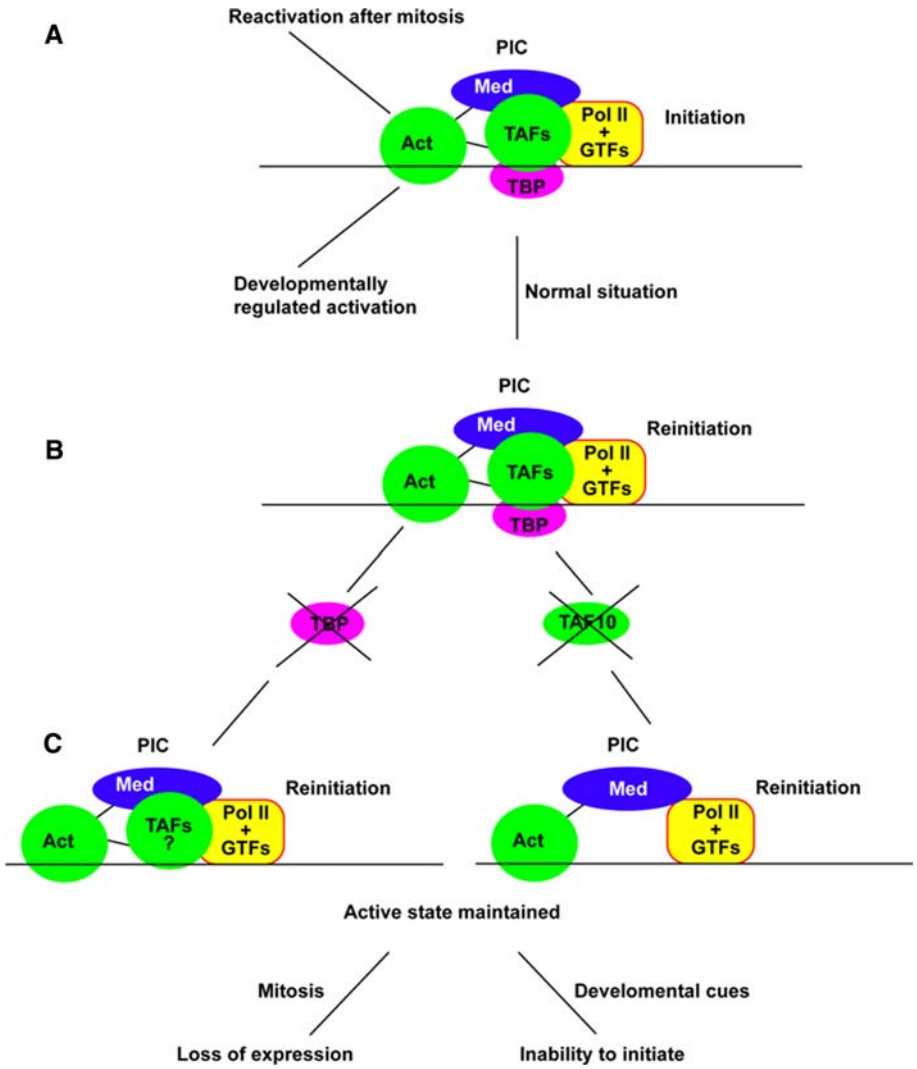

Fig. 3 Function of TFIID. **a** In wild-type cells TFIID is recruited along with pol II and the general transcription factors to facilitate PIC formation and promoter activation following mitosis or upon developmental cues. The transcriptional activators (*Act*), mediator complex *(Med)*, *TBP* and *TAFs*, *RNA pol II* and the other general transcription factors (*Pol II + GTFs*) are all schematically depicted. **b** In normal cells, TFIID remains associated with the active promoter during the reinitiation step. **c** Following genetic inactivation of TBP or TAF10, the promoter remains in an active state until mitosis when the PIC is disassembled upon chromatin condensation and is unable to reform at the next interphase. Post-mitotic cells are unable to activate new sets of genes upon developmental cues or in response to signalling pathways. While inactivation of TAF10 has been shown to lead to loss TBP and TAFs at active promoters, it is not yet known whether TAFs remain at promoters in the absence of TBP

types, yet this has no detrimental effect on the above processes all of which require extensive cell proliferation.

Much of our understanding of TFIID's role in transcription regulation has come from studies in cultured animal cells or in yeast, both of which are proliferating systems. The observations cited above concerning inactivation of TBP or TAF10 in vivo show that the lessons we have learned from cell culture or yeast cannot be simply extrapolated to more complex physiological situations. These considerations should modify our classical view of the role of TFIID in transcription regulation in post-mitotic cells.

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