The multifunctional TFIIH complex and transcriptional control

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RNA polymerase II (Pol II) requires seven general transcription factors (GTFs) and ATP for transcription initiation. Transcription factor IIH (TFIIH) has emerged as the sole GTF with enzymatic activity. In addition to its essential role in transcription initiation, recent studies have demonstrated a direct involvement of TFIIH in DNA excision repair processes. The enzymatic properties and functional duality of TFIIH make it a prime target for regulation by viral and cellular factors.

CELLULAR RESPONSES to development and environmental cues are typically mediated by a multitude of signal cascades and networks that often invoke *de novo* protein synthesis as well as modification of existing proteins. These changes are the hallmark of the physiological response.

Many of these responses involve intricate and timely communications between kinases and phosphatases, ultimately resulting in the fine tuning of gene expression. As such, it is probable that the function of many transcriptional regulators is governed directly by phosphorylation. The means by which phosphorylation of transcription factors affects regulation of gene expression are many and varied. Cellular compartmentalization of factors, alteration of DNA-binding activity and critical contact interfaces are all susceptible to modification by phosphorylation[1]. Modification of transcription factors involved in signal transduction cascades may affect the activity of the basal transcription apparatus and ultimately the response to diverse stimuli.

There has been considerable effort devoted to elucidating how transcription is regulated by phosphorylation. Interestingly, most of the emphasis has focused on the specific transcription factors[1], while relatively little is known about whether the basal transcription machinery is subject to phosphorylation and how this modification might affect its activity.

The general transcription machinery

It is now well established that the specificity of RNA polymerase II (Pol II) is dictated by seven activities known as the basal or general transcription factors (GTFs); they include transcription factors (TFs) IIA, IIB, IID, IIE, IIF, IIH and IIJ. The complementary DNAs for all the GTFs have been isolated with the exception of those for TFIIJ and some subunits of TFIIH. The prevailing model for GTF assembly on the promoter of protein-coding genes involves a highly ordered, stepwise loading of GTFs and Pol II onto the DNA, resulting in formation of a transcription-competent complex (reviewed in Ref. 2). A more recent model has emerged postulating the existence of preformed Pol II complexes that may facilitate preinitiation-complex formation[3] or stimulation by activator proteins[4]. The early studies that fueled the stepwise addition model used conditions designed to isolate and define the different GTFs. These studies provided a framework for understanding the important interactions that constitute a viable transcription complex. However, the stringency of these conditions precluded the isolation of large GTF–Pol II complexes. Subsequent experiments have defined numerous interactions between the various GTFs and Pol II (Refs 5–8). Hence, in retrospect, the existence of preformed complexes is not entirely surprising, and these complexes most probably eluded isolation as a consequence of extensive purification. Importantly, the observation that these holoenzymes do not contain all the GTFs still supports the notion that complex formation involves a multistep process that is susceptible to regulation at many stages. Notwithstanding the possibility that both pathways contribute to complex formation, Pol II can engage the template strand in the presence of ribonucleotide triphosphates and begin RNA synthesis at a specific start site.

The CTD and TFIIH

The first clue that the Pol II transcription complex may be subject to regulation by phosphorylation came from the observation that the carboxy-terminal domain (CTD) of the largest subunit of Pol II is composed of multiple, tandemly repeated copies of the heptapeptide Tyr-Ser-Pro-Thr-Ser-Pro-Ser. This heptapeptide is evolutionarily conserved from yeast to humans and is essential for viability (reviewed in Ref. 9). The mammalian Pol II enzyme contains 52 copies of the heptapeptide, while the *Drosophila* and yeast polymerases contain 43 and 26, respectively. The fact that five of the seven residues in the heptapeptide are serine (3), threonine (1) and tyrosine (1) suggests that the CTD is a strong candidate for phosphorylation. Indeed, *in vivo* labeling experiments established that the serine residues, and to a lesser extent the threonine, present in the CTD are sites for phosphorylation (reviewed in Ref. 10 and citations therein). Recently, it was shown that the CTD is also subject to tyrosine phosphorylation by the c-Abl oncoprotein[10]. As a result, the CTD is found in either an unphosphorylated or a hyperphosphorylated form *in vivo*[10]. The precise role of the CTD in transcription remains elusive, yet its phosphorylation has enabled investigators to decipher part of its role during the transcription cycle. Specifically, the unphosphorylated form has been shown to enter the preinitiation complex[10] and function in promoter-proximal transcription[11], while the form that catalyses elongation is highly phosphorylated[10,12]. Moreover, studies aimed at determining whether the unmodified CTD of Pol II makes contacts with components of the preinitiation complex revealed a direct and specific interaction with the TATA-box-binding protein

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(TBP) component of TFIID, and with TFIIE[6,7]. Together, these observations point to phosphorylation of the CTD as being critical for the disengagement of the polymerase from the promoter during the transition from initiation to elongation. Phosphorylation of the CTD presumably induces a conformational change within the preinitiation complex that disrupts certain protein–protein interactions, thereby triggering clearance of the polymerase from the promoter (Fig. 1).

The above model implies a cycling of Pol II from an unphosphorylated state capable of forming initiation complexes to a highly phosphorylated form that catalyses RNA chain elongation. Attempts to isolate a kinase capable of phosphorylating the CTD have resulted in the identification of a number of activities, including the cell cycle regulator cdc2, casein kinase II and the DNA-dependent protein kinase, among others[10]. When the GTFs were analysed for kinase activity, several groups discovered that TFIIH copurifies with a kinase specific for the CTD of Pol II (Refs 13–15). The significance of the TFIIH-associated CTD kinase activity is underscored by the fact that it is conserved among the yeast, rat and human TFIIH homologs. Conditions that favor CTD phosphorylation by TFIIH have been defined by various groups and have resulted in some controversy. Certain studies have suggested that TFIIH can phosphorylate a CTD peptide or Pol II efficiently in solution, and argue that this activity is independent of DNA and GTFs[16,17]. Others have observed that the TFIIH phosphorylation reaction is maximally stimulated when the polymerase is in the context of a complete preinitiation complex and promoter DNA; under those conditions phosphorylation of Pol II or a CTD peptide by TFIIH was inefficient in solution[15,17]. The latter results are perhaps more relevant since it is the unphosphorylated form of Pol II that is loaded onto the promoter, and its conversion to a hyperphosphorylated form occurs within the preinitiation complex.

The TFIIH complex and its unique polypeptide composition

TFIIH, like TFIID, is a multisubunit complex consisting of approximately eight polypeptides ranging in size from 34 to 89 kDa (Fig. 2; Refs 14, 17–21). TFIIH is unique in its complexity. It is the only GTF that exhibits enzymatic activity; it copurifies with a

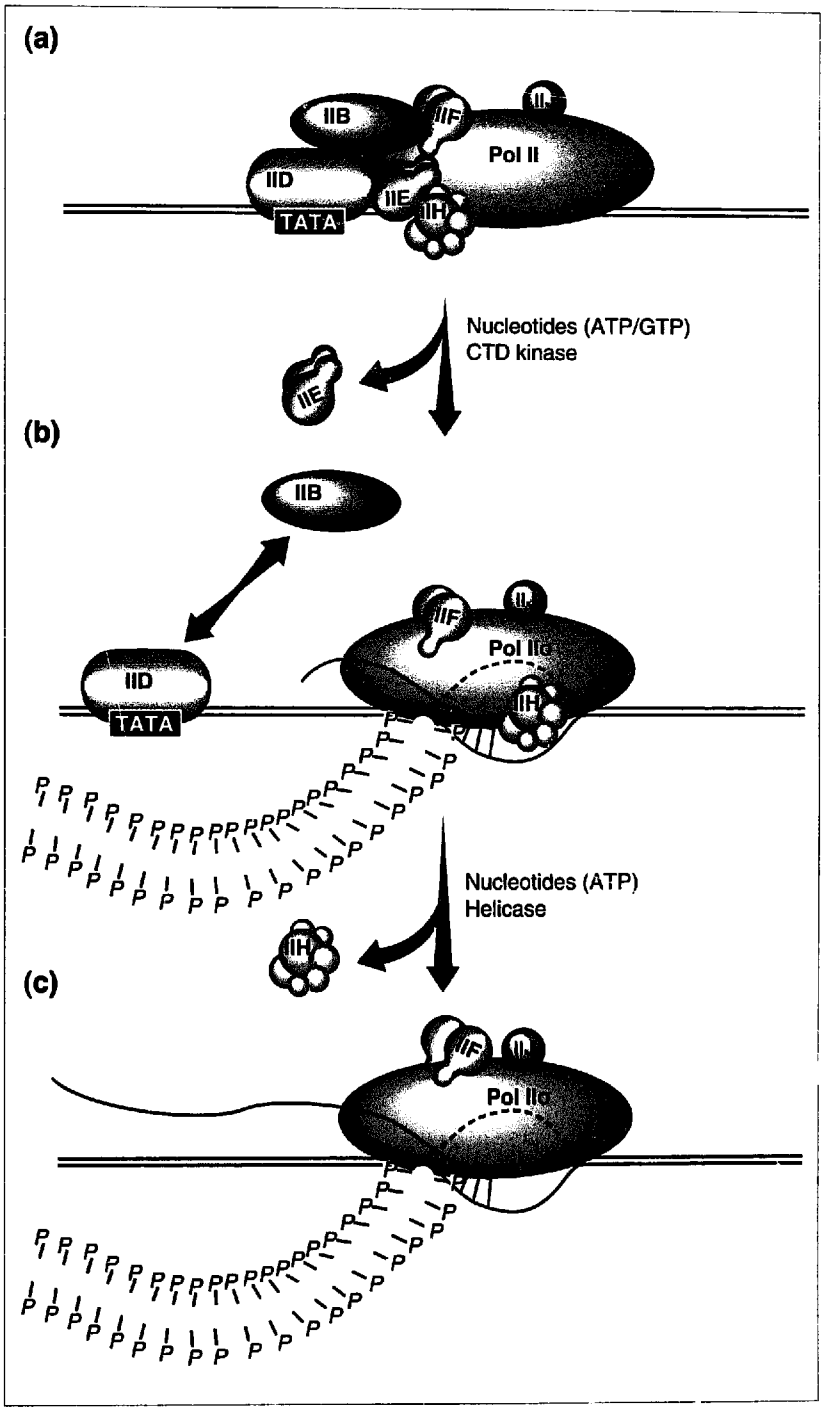
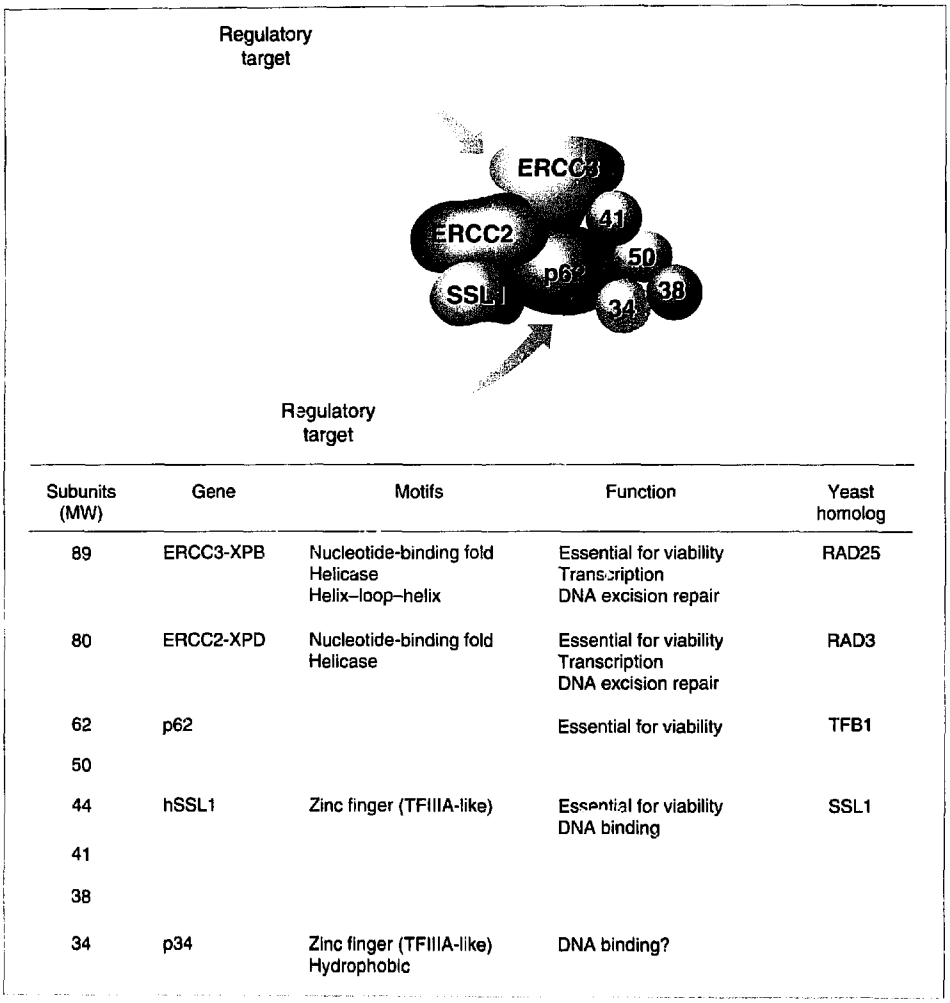


Figure 1

Transcription initiation model. **(a)** The assembly of the preinitiation complex is nucleated by the binding of the transcription factor (TF) TFIID to the TATA motif. The general transcription factors (GTFs) and RNA polymerase II (Pol II) make specific protein–protein contacts that help position the polymerase over the transcription start site. The carboxy-terminal domain (CTD) of Pol II is depicted as a string of yellow spheres making contact with the TATA-box-binding protein (TBP) component of TFIID. **(b)** In the presence of nucleotide triphosphates, the TFIIH kinase, assisted by TFIIE, catalyses phosphorylation of the CTD. This phosphorylation event causes a conformational change within the complex, which results in the departure of TFIIE and disruption of the CTD–TBP interaction. TFIIB also leaves but rapidly reassociates with the TFIID complex still bound at the promoter. Once TFIIE leaves the complex, the TFIIH helicase enables the polymerase to clear the promoter in an ATP-dependent fashion. **(c)** Promoter clearance signals entry into the elongation phase of transcription and the recycling of the TFIIH complex. The nascent transcript is shown in red.



Subunits (MW)	Gene	Motifs	Function	Yeast homolog
89	ERCC3-XPB	Nucleotide-binding fold Helicase Helix–loop–helix	Essential for viability Transcription DNA excision repair	RAD25
80	ERCC2-XPD	Nucleotide-binding fold Helicase	Essential for viability Transcription DNA excision repair	RAD3
62	p62		Essential for viability	TFB1
50				
44	hSSL1	Zinc finger (TFIIIA-like)	Essential for viability DNA binding	SSL1
41				
38				
34	p34	Zinc finger (TFIIIA-like) Hydrophobic	DNA binding?	

Figure 2

The TFIIH transcription–repair factor. TFIIH is a multisubunit complex involved in transcription and DNA excision repair. Being the only enzymatic GTF, TFIIH represents a prime target for viral and cellular regulatory proteins.

DNA-dependent ATPase[22,23], an ATP-dependent DNA helicase[24,25] and a kinase specific for the CTD of the largest subunit of Pol II (Refs 13–15). In addition to being the sole GTF with catalytic properties, the subunit composition of TFIIH has proved to be intriguing and exciting. Five of the eight putative polypeptides of TFIIH have been cloned (Fig. 2). The 62 kDa subunit was the first to be cloned[26], but it lacked any motifs that suggest an enzymatic function. None the less, mutations in the yeast p62 counterpart reveal hypersensitivity to UV irradiation, implicating p62 in DNA repair processes (S. Buratowski, pers. commun.). TFIIH entered the limelight when its largest subunit (p89) was identified as the DNA excision repair protein ERCC3 (excision repair cross complement)[24]. Mutations in the *ERCC3* gene are responsible for the DNA repair defects in patients with xeroderma pigmentosum (XP) group B and Cockayne's syndrome (reviewed in Refs 27, 28). ERCC3 contains the signature helicase motifs that enable it to locally unwind RNA and DNA templates in an ATP-dependent manner. Interestingly, the DNA repair gene *ERCC2*, which corrects the repair defect in patients with XP group D[27,28], is also a component of TFIIH[20,21,29]. Like ERCC3, ERCC2 can unwind RNA and DNA substrates in a reaction that is dependent on ATP. Both proteins are required for DNA excision repair and are essential for viability in yeast. The essential nature of these proteins is linked to their obligatory role in Pol II-mediated transcription[30–33]. Genetic and biochemical analyses of ERCC2 and ERCC3 in yeast have defined the transcriptional role of the ATPase/helicase domains of these proteins. Mutations in the nucleotide-binding pocket of ERCC2 cripple its DNA repair function but are not lethal, and leave the transcription activity of TFIIH intact[29,34]. Similar mutations in ERCC3, however, are lethal. Thus, although both proteins are absolutely required for transcription, the ERCC2 ATPase/helicase is dispensable for this process, while that of ERCC3 is essential. Clearly, the essential role of ERCC2 resides in other regions of the protein. Bardwell *et al.*[35] have demonstrated that the yeast homolog of ERCC2 (RAD3) can interact with ERCC3 (RAD25) and SSL1, a subunit of yeast TFIIH that was initially isolated as a suppressor of stem–loop mutations in the leader region of *HIS4* mRNA[36]. These interactions suggest that ERCC2 perhaps fulfils a structural, rather than enzymatic, role within the TFIIH complex during transcription initiation. Interestingly, SSL1 is also essential for viability. Sequence analysis of the gene encoding the 44 kDa subunit of human TFIIH indicates that it is the human counterpart of SSL1 (Ref. 37). Surprisingly, the 34 kDa subunit also has homology with domains of SSL1, suggesting that it corresponds to an as yet unidentified DNA repair protein. All three proteins contain TFIIIA-like zinc-finger motifs, which facilitate interaction with DNA (Ref. 37; Fig. 2). The presence of zinc-finger domains in p44 and p34 alludes to the possibility that the TFIIH complex may be anchored to the promoter region by DNA contacts as well as protein–protein interactions. Such contacts could help stabilize TFIIH in the preinitiation complex.

One of the most striking aspects of the composition of TFIIH is that none of the cloned subunits contain consensus kinase motifs. Though surprising, it is possible that the activity does not reside in an integral subunit of TFIIH, but rather copurifies with the complex as an associated factor present in substoichiometric amounts, thereby eluding identification. Another possibility is

that one of the remaining uncloned subunits (p38, p41 or p50; Fig. 2) contains the CTD kinase, and a third alternative is that the kinase comprises two or more subunits. Distinction between these scenarios will require isolation and cloning of the remaining polypeptides of TFIIH. None the less, the fact that TFIIH in diverse species, from yeast to humans, fractionates with a CTD kinase activity is reassuring, especially when one considers that the TFIIH homologs were purified from different sources using different purification schemes.

The role of TFIIH in DNA excision repair

The five TFIIH subunits whose genes have been cloned all appear to play some role in nucleotide excision repair. This indicates that the entire TFIIH complex may participate in DNA repair. Indeed, analysis of DNA excision-repair mutants under transcription-independent conditions demonstrated that TFIIH participates directly in nucleotide excision repair[20,38,39]. The dual function of TFIIH may be regulated by factors that tether or escort TFIIH to DNA lesions or promoters of protein-coding genes. These include: TFIIE, which can interact directly with TFIIH and influence its enzymatic activities[7,15–17,20]; XPC, which can also interact with TFIIH[20,40] and is thought to be involved in overall genome repair[41]; and ERCC6, the putative transcription–repair coupling factor presumed to recognize a Pol II complex stalled at DNA lesions and recruit components of the repair machinery[27,42]. TFIIE is of paramount interest because it is not only required for the stable association of TFIIH with the preinitiation complex but also regulates its enzymatic activities. TFIIE is a heterodimer of 34 and 56 kDa subunits[43]. Studies in the human system have demonstrated that recombinant TFIIE can quantitatively stimulate the CTD kinase of TFIIH[15,17]. Recently, Serizawa *et al.*[16] reported that an oligomeric form of recombinant p56 can enhance phosphorylation of the CTD by TFIIH. The significance of the oligomeric form of p56 is unclear, yet it suggests that certain GTF subunits may exist in forms different from those isolated based on transcription activity. Recombinant TFIIE also stimulates the ATPase activity of TFIIH[17], and under certain conditions either stimulates or inhibits the helicase activity of TFIIH[16,20]. The functional interplay between TFIIE and TFIIH is underscored by studies that demonstrated that TFIIE from *Saccharomyces cerevisiae* could not substitute for the *Schizosaccharomyces pombe* TFIIE in an *S. pombe* system unless the *S. cerevisiae* TFIIE and TFIIH were swapped together[44].

It would be predicted, based on its intimate connection with TFIIH, that TFIIE is also required for DNA excision repair. This prediciton may prove to be true, as recent studies demonstrated a direct interaction between TFIIE and the DNA excision repair protein XPA (C-H. Park, D. Reinberg and A. Sancar, unpublished). XPA has been shown to interact specifically with damaged DNA[45]. Recognition of DNA lesions by XPA may serve as the nucleation step for the other components of the DNA repair machinery. Parallels could be drawn between this process and the binding of TFIID to the TATA element, ultimately resulting in the recruitment of the other GTFs and Pol II. Recruitment of TFIIE by XPA may facilitate entry of TFIIH to the repair complex in much the same way that TFIIE mediates loading of TFIIH onto promoters of protein-coding genes. The consequences of these interactions may influence transcription-coupled DNA repair. Specifically, the putative transcription repair coupling factor, ERCC6, can interact with XPA and TFIIH (C. P. Selby, D. Reinberg and A. Sancar, unpublished). Recruitment of XPA, and consequently TFIIE and TFIIH, by ERCC6 may facilitate the coupling of active genes to the repair machinery at DNA lesions. Hence, TFIIE and TFIIH are a dynamic duo that play pivotal roles in transcription and DNA excision repair.

The role of TFIIH in transcription

The precise role of TFIIH during initiation of transcription has been a topic of intense investigation. Pol II is unique among the three mammalian RNA polymerase systems in that it requires a hydrolysable source of ATP for transcription initiation[46,47]. The energy-dependent step and the factor that catalyses this step have been elusive. Since TFIIH functions within the limits of the Pol II system, the observation that it contains a kinase activity suggested a link between the requirement for ATP hydrolysis by Pol II and the CTD kinase. However, the CTD kinase of TFIIH does not discriminate between ATP and GTP as phosphate donors[14,15]. Moreover, forms of the polymerase that lack the CTD still require a hydrolysable form of ATP for initiation[10]. In fact, biochemical analyses using CTD kinase inhibitors indicate that basal transcription can occur in the absence of CTD phosphorylation[23,48]. Importantly, under the conditions discussed, TFIIH remains an obligatory component for transcription initiation. Together these results argue against the CTD kinase as the obligatory energy-dependent step in Pol II transcription.

The observation that the TFIIH complex contains two ATPases/helicases involved in DNA excision repair has fueled speculation that the TFIIH helicase may be the critical energy-dependent activity unique to Pol II. Chemical footprinting had previously demonstrated that the β–γ bond of ATP was required for open complex formation[49]. The obvious extension of this observation is that the ATP-dependent helicase activity of TFIIH is catalysing this reaction. However, recent evaluation of these results indicated that open complex formation is not strictly dependent on ATP; any nucleotide can apparently provide the β–γ energy bond to melt the template (Y. Jiang and J. Gralla, pers. commun.; reviewed in Ref. 33). The observation that the helicase activity of TFIIH is ATP specific[24] and that abortive transcription can occur in the absence of TFIIH[50] argues against the simple model that TFIIH mediates open-complex formation.

Yeast genetic and biochemical analysis have clearly demonstrated that the ERCC3 helicase activity of TFIIH is essential for viability owing to its role in Pol II transcription[31,32]. The physical (P. Kumar and D. Reinberg, unpublished) and functional[50] absence of TFIIH from the elongating Pol II ternary complex excludes the involvement of TFIIH, and thus ERCC3 and ERCC2, in elongation. Collectively, these observations define a kinetic window in which the TFIIH helicase must act to fulfil its vital function, namely before elongation but subsequent to open-complex formation. In the absence of TFIIH, the polymerase stalls immediately downstream of the transcription start site (Ref. 50; P. Kumar and D. Reinberg, unpublished). These observations conjure up the notion that, shortly after open-complex formation, the polymerase encounters a block that prevents it from entering the elongation phase of RNA synthesis. This phase appears to be the point at which the TFIIH helicase, and perhaps the kinase, acts to mediate promoter clearance. Verification of this model will require a correlation

between the nucleotide requirements for initiation and the corresponding factor requirements.

TFIIH as a regulatory target

Since the identification of TFIIH a few years ago, a wealth of information has emerged regarding its role in transcription, and more recently in DNA repair. Clearly, the enzymatic activities of TFIIH play a role in regulating gene expression. A prediction that stems from such analysis is that this factor could be a prime regulatory target for a host of cellular and viral proteins. Modulation of TFIIH enzymatic activity could have dramatic impact on transcription initiation and presumably DNA repair pathways as well. Indeed, this prediction has been validated by recent studies with the herpes simplex virus transcriptional activator VP16. Previous studies established that the targeting of the TBP component of TFIID and TFIIB is a critical step in the VP16 activation process[51,52]. Now it appears that VP16 can also interact specifically with TFIIH[53] and facilitate the promoter clearance stage of transcription (P. Kumar and D. Reinberg, unpublished). This interaction does not appear to be unique to VP16, as the Epstein–Barr nuclear antigen 2 (EBNA2) transactivator can also interact specifically with TFIIH *in vitro* and *in vivo*. Mutations in EBNA2 that inactivate its transcription activity are also incapable of interacting with TFIIH (D. Reinberg and E. Kieff, unpublished).

TFIIH can also be targeted by cellular proteins. The tumor suppressor p53 is a multifunctional factor that is involved in transcription, replication, apoptosis and cell-cycle control (reviewed in Ref. 54). Transcriptional control by p53 seems to be mediated by a direct interaction with TBP[54]. Interestingly, its involvement in cell-cycle progression becomes evident when cells are stressed by damage-inducing agents. Levels of endogenous p53 rise dramatically in response to DNA damage[54]. Now evidence exists that p53 interacts with TFIIH[53]. This interaction may play a role in facilitating DNA repair before entry into S phase; it may have consequences in transcription; or perhaps it implicates TFIIH in the cascade of events leading to apoptosis.

Outlook

TFIIH has emerged as a complex factor with enzymatic activity and unexpected functional duality. Its pivotal roles in transcription and DNA excision repair highlight the cell's ability to co-regulate important cellular processes by delegating multiple functions to one factor. Development of more convenient purification schemes for TFIIH, such as epitope-tagged cell lines, may prove helpful in identifying and cloning the remaining TFIIH subunits. The isolation of the elusive TFIIH CTD kinase is anxiously awaited and will undoubtedly reveal intricate regulatory pathways that will keep researchers busy for years to come.

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