Yeast transcription factors

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Studies of yeast transcription factors have contributed greatly to understanding basic molecular mechanisms of eukaryotic gene regulation, largely due to powerful genetic approaches that are unavailable in other organisms. The broad outlines of these mechanisms are fairly well understood, and there is an increasing number of examples where detailed information is available.

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Introduction

Transcriptional regulatory mechanisms are fundamentally similar in eukaryotic organisms from yeasts to humans (for reviews of yeast transcription, see [1,2]). Components of the chromatin template and the basic RNA polymerase II machinery [e.g. enzyme subunits, TATA-binding protein (TBP), TFIIA, TFIIB and carboxyl-terminal domain (CTD) kinase] are highly conserved and, in some cases, functionally interchangeable. Promoter-specific transcription factors with similar structures and DNA-binding specificities are found throughout the eukaryotic kingdom. Acidic activation domains stimulate the basic transcription machinery across a wide range of species. The DNA-binding and/or transcriptional activities of these proteins can be regulated by differential synthesis/degradation, phosphorylation, nuclear transport, and interactions with other proteins.

Complex promoters with multiple protein-binding sites are typical in all eukaryotic organisms, even those that appear to be simple superficially. Efficient transcription generally requires the combinatorial and synergistic action of activator proteins bound at multiple sites in the promoter; a single bound activator is usually inefficient. Activator proteins function bidirectionally at long and variable distances upstream or downstream from the mRNA initiation site, presumably because the intervening DNA can be looped out. Finally, many eukaryotic promoters contain negative regulatory sites that bind repressors competing with activators for target sites, sterically interfere with the function of bound activators, or directly inhibit the transcription machinery.

Given these extensive similarities, why write a review specifically focused on yeast transcription factors? The main reason is that studies in yeast have primarily utilized powerful genetic approaches that are not available in other eukaryotic organisms. In contrast, biochemical approaches, particularly transcription *in vitro*, are more highly developed and utilized in mammalian cells. As a consequence of these different experimental approaches, information about transcriptional mechanisms in yeast and higher cells is often complementary. Yeast is particularly amenable for identifying individual proteins involved in various transcriptional regulatory functions and for determining their physiological roles. This review of yeast transcription factors will not be comprehensive, but instead will emphasize aspects that provide unique insights into mechanisms of eukaryotic transcriptional regulation.

Basic transcription factors

Most yeast promoters contain a TATA element upstream of the mRNA start site that interacts with the TBP. TBP binding is the first step in the stepwise assembly of the transcription complex, and it potentiates the promoter for transcription in the context of chromatin. The CTD (180 residues) of yeast TBP very strongly resembles other eukaryotic TBPs, and it is necessary and sufficient for cell growth; the amino-terminal 60 residues are functionally dispensable and evolutionarily divergent.

The CTD contains two 40% identical repeats of 66–67 amino acids separated by a highly basic region. Both repeats are important for DNA binding. Dominant-negative mutations in either repeat eliminate DNA binding while maintaining aspects of normal structure and function [3]. Mutations in the second repeat alter DNA-binding specificity for TATA elements, suggesting that the affected residues directly interact with the DNA [4]. These observations suggest that the two repeats form an intramolecular dimer that interacts similarly, though not identically, with 'half-sites' of the TATA element. Consistent with these genetic observations, the crystal structure of TBP reveals a symmetric α/β saddle-like structure in which the concave DNA-binding surface is a curved, antiparallel β-sheet [5]. When bound to DNA, the convex surface of

Abbreviations

CTD—carboxyl-terminal domain; **TBP**—TATA-binding protein; **TF**—transcription factor.

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the TBP saddle would be available to interact with other transcription factors.

In cell-free extracts, yeast TBP is found predominantly as a 27 kDa monomer, whereas mammalian TBP associates with multiple proteins in a large macromolecular complex termed TFIID. Mammalian TBP-associated factors play an important role in transcription because TBP and TFIID are functionally distinct *in vitro*, particularly with regard to their ability to respond to activator proteins. Although a yeast TFIID-like complex has not yet been described biochemically, TBP-associated factors do exist. SPT3 co-immunoprecipitates with TBP, and mutations of either protein that eliminate this interaction affect transcription of particular promoters. Moreover, compensatory mutations in *SPT3* and *TBP* restore both the biochemically detected interaction and normal transcription patterns [6]. These compensatory mutations probably define the protein interaction surfaces, which in the case of TBP maps to an α-helix on the convex surface [5].

Another TBP-interacting protein, SRB2, physically associates with the initiation complex and plays an important role in basal and activated transcription *in vitro* [7]. Genetic analysis reveals a functional interaction between SRB2 and the CTD of the largest RNA polymerase II subunit. Thus, the SRB2–TBP association might enhance or compete with the interaction of TBP and the non-phosphorylated CTD [8].

Although initially defined as a basal factor for transcription by RNA polymerase II, TBP is required for transcription by all three nuclear RNA polymerases [9,10]. The TATA-binding activity of TBP is critical for transcription from conventional RNA polymerase II promoters, but not from RNA polymerase I and III promoters [10]. TBP carries out its multiple functions by associating with other proteins into distinct complexes (SL1, TFIID and TFIIIB) that are specific for the three RNA polymerase machineries. A component of the TFIIIB complex, TDS4/PCF4/BRF1, contains a domain related to TFIIB [11–13]; this conserved domain might interact with TBP whereas non-conserved regions of these proteins might interact with components specific for RNA polymerase II and III machineries. TBP is also required for RNA polymerase II transcription from promoters that lack conventional TATA elements and from promoters whose TATA elements differentially respond to acidic activator proteins [9]. Multiple TFIID-like complexes, distinguished by their associated proteins, are likely to account for transcription from promoters with functionally distinct (or no apparent) TATA elements.

The basal factor TFIIA associates with TBP and alters its interaction with the TATA element. Yeast TFIIA is composed of two subunits both of which are essential for cell viability [14]. However, it is unclear if the essential role of TFIIA reflects its requirement for transcription from all or only a subset of RNA polymerase II promoters. TFIIA interacts with the highly basic region of TBP. Some mutations in the TBP basic region disrupt the TFIIA association without affecting TATA-element binding [15] and the DNA-binding defects caused by other mutations in this region overcome by TFIIA [16]. The TFIIA interaction appears to induce a conformational change in TBP that overcomes the inhibitory effect of the dispensable and evolutionarily divergent amino-terminal region [16].

TFIIB is recruited to the promoter after the binding of TBP (with or without TFIIA), and it appears to bridge the region between the TATA element and the mRNA initiation site. Consistent with this view, TFIIB is important for selecting the correct initiation site [17]. Mutations in yeast TFIIB can reduce initiation from the normal site while increasing initiation from more downstream sites. Yeast and human TFIIB are 35 % identical in sequence, but the proteins are not functionally interchangeable. Functional differences between TFIIBs may explain why the distance between the TATA element and mRNA initiation is longer and more variable in yeast than in most eukaryotic organisms. At least one other gene, *SHI*, plays an important role in selecting initiation sites [18]. Initiation in the *sbi* mutant strain is shifted to more upstream sites, the opposite effect of the *TFIIB* mutant strain phenotypes. *SHI* might influence TFIIB activity or it might encode (or affect) another basal transcription factor or RNA polymerase II subunit.

It is clear that TBP plays a central role in transcription. It is associated with distinct complexes that are specific for the various RNA polymerase machineries, and it interacts with the basic factors IIA and IIB as well as the CTD of the largest RNA polymerase II subunit. Many of these interactions are evolutionarily conserved as shown by the interchangeable nature of TBPs for TATA-dependent transcription *in vitro* and the ability of human TBP to respond to yeast activator proteins [4,19]. However, human TBP replaces yeast TBP for cell growth [20,21], probably because it is unable to support transcription by RNA polymerases I and III.

DNA-binding, transcriptional regulators

In yeast, numerous sequence-specific DNA-binding activities have been identified, and the genes encoding many of them have been cloned. In most cases, a single gene is responsible for the DNA-binding activity and the DNA-binding domain is localized to a small (100 residues) region of the protein. Typical eukaryotic DNA-binding motifs (e.g. homeodomain, zinc finger, bZIP, bHLH and MADS) have been observed, and many yeast proteins have trendy counterparts in higher organisms (e.g. oncogenes, developmental regulators and targets of signal transduction pathways). There are families of structurally related proteins that recognize similar sequences: the AP-1 proteins, GCN4, YAP1, YAP2; the ATF/CREB proteins, ACR1 and an uncloned activator(s); SWI5 and ACE2 [22].

Because yeast is less complex than multicellular organisms, it is often, but incorrectly, assumed that yeast promoters are simple (containing one or few protein-binding sites upstream of the TATA element) and that yeast regulatory proteins play discrete physiological roles. Part of this mistaken belief stems from the bias imposed

by the classical genetic methods that identified the first transcriptional regulatory proteins. As these methods depend on selecting mutant strains with very specific phenotypes, it has been difficult to identify transcription factors that are functionally redundant, essential for cell growth, or that perform multiple physiological roles. Upon the increased use of molecular and biochemical approaches employed to study mammalian transcription factors, it has become clear that individual yeast promoter regions interact with multiple nuclear proteins. Further, individual transcription factors often bind to multiple genes whose biological functions are apparently unrelated.

In general, yeast transcription factors are present at low intracellular concentrations and their target sites are present in relatively few promoters. However, some DNA-binding proteins such as RAP1, ABF1 and REB1 are abundant, essential for cell growth, and interact with many unrelated promoters. Although these proteins often function as transcriptional activators, they also play important roles at DNA replication origins, telomeres and the mating type silencer [23–25]. These proteins might not be true transcription factors, but instead might carry out their diverse roles by affecting chromatin. In this regard, a REB1-binding site can position nucleosomes and affect transcription in a highly distance-dependent manner [26,27].

Some target sites are recognized by heteromeric complexes. The CCAAT activator is composed of three subunits, HAP2–4, all of which are necessary for DNA binding [28]. BUF, a repressor that binds to the *URS1* site in many yeast promoters, contains two subunits [29]. SWI4 and SWI6 form a complex that binds the *HO* promoter and activates transcription at the start of the cell cycle [30]. SWI6 also appears to interact with a 120 kDa protein to form a distinct complex that binds to a different cell cycle control element [31,32]. Although SWI6 is present in both complexes, SWI4 and the 120 kDa protein appear to be more directly involved in DNA binding.

Heteromeric complexes play a critical role in the control of cell type. The **a**1 and α2 homeodomain proteins form a heterodimer that mediates repression of haploid-specific genes [33]. The α2 protein also interacts with MCM1, a homologue of the mammalian serum response factor, to bind the complex operators that mediate repression of **a**-specific genes. Both α2 and MCM1 can independently bind to distinct parts of the operator, but a cooperative interaction between the proteins is necessary for high-affinity binding to the intact operator. This cooperative interaction is mediated by a short, disordered region of α2 and the core of MCM1 [34], and it sets the spacing and orientation of the α2 homeodomains [35]. The core of MCM1 also cooperates with α1 to form a complex necessary for DNA binding and transcriptional activation of α-specific genes [36]. An additional feature of MCM1 is its conformational change upon binding to **a**-specific, but not α-specific, promoters [37].

Transcriptional activation domains

Transcriptional activation by proteins bound to upstream promoter sequences requires an activation region that is functionally distinct, and usually physically separate, from the DNA-binding domain. It is believed that the DNA-binding domain serves merely to bring the protein to the DNA target, whereupon the activation region stimulates the basic transcription machinery. Activation domains are often defined by short acidic regions that function autonomously when fused to heterologous DNA-binding domains. Many different acidic sequences can serve as transcriptional activation regions and negative charge is clearly important, but the level of transcriptional stimulation is also influenced by other structural, but ill-defined, features. Some activation regions become acidic upon phosphorylation [38,39]. Acidic regions function across a diverse range of eukaryotic species, indicating that they affect some part(s) of the basic transcription machinery that is functionally conserved.

Because activation domains are defined operationally, whether they stimulate the basic transcription machinery directly or indirectly has become a critical issue. A large number of experiments have been devoted to this question and evidence has been gathered in support of TFIID, the carboxyl-terminal tail of the largest subunit of RNA polymerase II, intermediary proteins (termed adaptors, mediators and co-activators) and histones. It is becoming increasingly clear, however, that activation domains stimulate transcription by distinct molecular mechanisms. Not all yeast activators contain regions that are acidic or are likely to be highly phosphorylated. The glutamine-rich and proline-rich activation regions found in some mammalian proteins do not function in yeast cells. Even acidic activation domains appear to be functionally distinct. Acidic activators can differ in their ability to activate transcription from certain TATA sequences [40], and they are selectively affected by mutations in the *ADA2* [41] and *GCN5* [42] genes. At present, it is unclear whether these apparently distinct domains all converge upon a universal activation mechanism or whether they are fundamentally different; the latter seems more likely.

Although transcriptional activation and DNA-binding functions are usually physically separate, some DNA-binding domains play additional roles in transcription beyond bringing the protein to the promoter. Positive control mutations in the *HAP1* [43] and *ADR1* [44] DNA-binding domains interfere with transcriptional activation while not affecting DNA binding. Moreover, one class of positive control mutants eliminates activation by HAP1 bound at the CYC7 but not the UAS1 target site. DNA-binding domains also may be involved in the transcriptional synergy of multiple activator proteins bound to the promoter [45]. In these cases, the DNA-binding domain might recruit protein co-factors (presumably using a different protein surface than that involved in recognizing DNA) and/or alter chromatin structure. Multifunctional DNA-binding domains are likely to be more prevalent than is currently appreciated. In particular, the crude deletions typically employed to dissect

transcription factors is highly biased towards identifying activation regions that are physically separate from, rather than interdigitated with, their DNA-binding domains.

Intermediary transcription factors

Intermediary transcription factors are nuclear proteins that do not bind promoter DNA sequences nor are components of the basic machinery. With the exception of one factor defined by its requirement for activated, but not basal, TATA-dependent transcription *in vitro* [46], most intermediary proteins have been identified by mutations. Such proteins have been called co-activators, adaptors and mediators, but these terms are mechanistically loaded and poorly defined.

In principle, intermediary proteins could act in different ways. An intermediary protein carrying an acidic (or other) activation domain could stimulate transcription upon association with a DNA-bound protein. Mechanistically, this situation would resemble transcriptional enhancement by a simple (or heteromeric) DNA-bound activator. Alternatively, an intermediary protein might be necessary to transduce the signal from the activation domain to a component of the basic machinery. Although heuristically simple, this mechanism ignores the critical issue of what defines an activation domain; semantics is hopeless at out current state of knowledge. Finally, intermediary proteins might not directly affect the basic machinery, but instead increase transcription by altering chromatin structure. By the definition used here, intermediary proteins do not include those that modify (e.g. by phosphorylation or by proteolysis) or alter the level/expression pattern of transcription factors. The distinction between intermediary transcription factors and modifiers/regulators of transcription factors is not always easy.

ADA2 is important for the function of certain transcriptional activation domains [41]. Mutations relieve the toxicity associated with the VP16 activation domain, and they reduce activation by the GCN4 and VP16 acidic domains. However, ADA2 does not appear to be involved in activation by the HAP4 acidic region or in basal TATA-dependent transcription *in vitro*.

GAL11 is important for transcriptional activation by GAL4, RAP1, PPR1, and probably other proteins [47,48]. GAL11 mediates its effect through the GAL4 DNA-binding domain, and it contains a transcriptional activation region. GAL4 or RAP1 activation does not require GAL11 in promoters where the protein-binding sites are moved closer to the TATA element. These observations suggest GAL11 associates with certain DNA-bound activators and, through its activation domain, increases transcription from promoters where the protein-binding sites are not close to the TATA element.

GCN5 is required for full activation by GCN4 and by the HAP2–4 heterotrimer, but is unimportant for activation mediated by the *DED1* upstream promoter element [42]. The GCN5 requirement is greater for promoters with weaker GCN4-binding sites, suggesting that GCN5 might not directly affect the activation domain, but instead might stabilize weakly bound activators to the promoter. GCN5 contains a 'bromodomain' motif found in a variety of eukaryotic proteins including yeast intermediary activator proteins SNF2/SWI2 and SPT7 (see below).

The SNF2/SWI2, SNF5, SNF6, SWI1 and SWI3 proteins are important for transcriptional enhancement by a variety of yeast and mammalian DNA-bound activators including GAL4, Bicoid and steroid receptors. The relative importance of these proteins depends on the activator and the promoter. Several lines of evidence suggest that these proteins function together, possibly as a large complex. Mutations in any one of these genes often result in common, though not identical, phenotypes [49,50]. When fused to a heterologous DNA-binding domain, SNF2/SWI2 and SNF5 activate transcription, but only in the presence of the other SNF and SWI proteins. SNF6 may act more directly as its activation domain has only a modest requirement for the other SNF and SWI proteins [51]. SNF2 and SNF5 also affect chromatin structure independently of the transcriptional status of the promoter [52]. SWI3 co-immunoprecipitates with the steroid receptor in a manner that requires SWI1 and SWI2/SNF2 function; SWI1 also may be present in the co-precipitates [53]. SWI3 antibody inhibits transcriptional activation by steroid receptor in *Drosophila* extracts, but only if added before the formation of the pre-initiation complex. A speculative model incorporating these observations is that the SNF/SWI complex associates with DNA-bound activators and stimulates transcription.

SPT3, SPT7 and SPT8 are required for normal transcription of the Ty retrotransposon. Mutations in these genes have very similar phenotypes to certain mutations in the TATA-binding protein that affect interactions with the TATA element. As discussed above, SPT3 interacts with TBP [6]; perhaps, SPT7 and SPT8 do as well.

SUG1 was identified by mutations that relieve the requirement for the activation domain located at the carboxyl terminus of GAL4. Unlike GAL11 and the SWI/SNF proteins, SUG1 mediates its effects through internal GAL4 sequences that are distinct from this activation region and from the DNA-binding domain [54]. The protein resembles two human proteins that affect expression mediated by the HIV TAT protein.

Repression

Transcription is repressed by a variety of distinct mechanisms (reviewed in [2]). The most general repression, which affects all genes, involves nucleosome coating of the DNA, which severely restricts access of transcriptional regulatory proteins to promoters. Disruption of the normal nucleosome structure by histone loss, histone mutations or poly(dA)·poly(dT) sequences results in increased transcription. The simplest forms of gene-specific repression involve blocking the function of activator proteins. Repressor proteins can compete with activators by

binding to coincident or overlapping sites that can not be occupied simultaneously. Proteins bound between the UAS and TATA elements also repress transcription, presumably by sterically inhibiting the communication between upstream activators and the basic machinery. As exemplified by the GAL80–GAL4 interaction, repression can also be mediated through specific protein–protein associations that mask the activation domain of the DNA-bound activator. In addition to proteins that block the function of activators, there are negative transcriptional regulators that appear to repress promoter activity either by directly inhibiting the transcription machinery or by causing subtle changes in chromatin structure.

Glucose and mating-type repression can occur even when the negative regulatory sites are located upstream of an intact promoter, thus arguing against a steric hindrance mechanism. Consistent with this idea, occupancy of the negative regulatory sites by the relevant DNA-binding proteins (MCM1/α2, **a**1/α2, MIG1) is not sufficient for repression [55]. In addition to the DNA-binding proteins, transcriptional repression also requires two negative regulators, CYC8 and TUP1, that physically associate with each other [56]. The CYC8/TUP1 complex can repress transcription when brought to the promoter via a heterologous DNA-binding domain. These observations suggest that glucose and mating-type repression is mediated by DNA-binding proteins that recruit the CYC8/TUP1 complex to the promoter where it may directly interfere with the transcription machinery [55].

The mating-type silencer represents a dramatic example of long-distance repression; it functions when located more than 2 kb upstream or downstream of promoters. Silencer function requires the binding of RAP1 and ABF1, proteins that are transcriptional activators in other promoter contexts. The repression and activation functions of RAP1 are separable by mutation [24]. RAP1 associates with RIF1, and this protein–protein interaction is critical for silencing and for telomere length regulation, but not for activation [57]. It is very likely the mechanism of silencing involves the establishment of a repressed chromatin state. Silencing is abolished by mutations in the amino terminus of histone H4 [58,59], and the repressed state can be epigenetically inherited under certain conditions [60,61].

Another class of negative regulators affects transcription of many apparently unrelated genes, probably by a variety of mechanisms. CDC39 differentially represses transcription by the functionally distinct TATA elements in the *HIS3* promoter, suggesting that it might affect TBP action [62]. SIN1 may function through the CTD of the largest RNA polymerase II subunit [63]. SIN4 may affect chromatin structure because mutations cause a decrease in superhelical density of circular plasmids [64]. The SPT4, SPT5 and SPT6 proteins function together as negative regulators, possibly through chromatin because mutations in these genes cause similar phenotypes to mutations in histones [65].

Regulation

The amounts or activities of many yeast transcription factors are regulated in response to environmental or developmental stimuli. A novel translational control mechanism ensures that the GCN4 activator is synthesized only under conditions of amino acid starvations [66]. Regulated expression of the GAL4 activator provides a sensitive switch for glucose repression, particularly in promoters where GAL4 binds cooperatively to multiple sites [67]. Regulation of mating-type genes is achieved by the appropriate transcription factors being present only in the correct cell type.

The DNA-binding activities of some yeast transcription factors are regulated by small molecules. Binding of HAP1, a transcriptional activator that regulates many genes in response to oxygen, requires heme. Heme unmasks the HAP1 DNA-binding domain by binding to an adjacent region of the protein [68]. ACE1, a transcriptional activator of the metallothionein gene whose product is critical for metal detoxification, requires copper for folding of the DNA-binding domain [69].

The transcriptional activities of proteins can be regulated by a variety of mechanisms. LEU3 transcriptional activation, but not DNA-binding, depends on a metabolic intermediate, α-isopropylmalate [70]. PUT3, an activator of genes involved in proline metabolism, is constitutively bound to promoters *in vivo* and activates transcription only in response to proline [71]. The heat shock factor activation domain is rapidly phosphorylated in response to high temperature, with the degree of phosphorylation being strongly correlated with transcriptional activity [38]. Similarly, STE12 becomes transcriptionally active upon the rapid phosphorylation of its activation domain in response to mating pheromones [39]. Phosphorylation of the GAL4 activation region is also observed, but in this case it appears to be a consequence rather than a cause of increased transcriptional activity in the presence of galactose [72]. Instead, galactose induction of GAL4 activity is mediated by a regulated interaction of its activation domain with GAL80. Interestingly, GAL80 is always associated with GAL4, suggesting that galactose induction is due to a conformational change that unmasks the GAL4 activation region [73,74].

Regulation of SWI5, a transcription factor that controls mating-type switching through its influence on the *HO* endonuclease, occurs at the level of nuclear entry. The protein is cytoplasmically localized throughout most of the cell cycle, but is translocated into the nucleus as cells enter G_1 [75]. Three serine residues in the SWI5 nuclear localization signal are phosphorylated, probably by the CDC28 kinase, when the protein is in the cytoplasm, but not in the nucleus [76]. Thus, dephosphorylation of the nuclear localization signal due to the cell cycle dependent destruction of the CDC28 kinase is likely to regulate transcriptional activation by SWI5.

Concluding comments

It is clear that transcriptional regulation in yeast follows the same principles and uses the same basic mechanisms as in other eukaryotes. Indeed, yeast has contributed much of our current knowledge about eukaryotic transcriptional regulatory mechanisms. At present, the broad outlines of these mechanisms are fairly well understood, and there are an increasing number of examples where detailed information is available. Aside from refining this knowledge and dissecting more regulatory circuits, what does the future hold?

There are three major areas of interest. First, from the perspective of initiation mechanisms, the critical and time-honored issue is how activators and repressors affect the activity of the basic transcription machinery. Although hypotheses and data abound, molecular understanding is remarkably limited. The central question is whether the regulators function at the level of the transcription machinery itself or at the level of the chromatin template; the answer is likely to differ depending on the regulator. Further, the biochemical mechanisms involved in either of these processes remain to be elucidated. The second area concerns how the activities of transcription factors are altered to stimulate or repress gene expression. In nearly all cases, not much is known about the physiologically relevant signals, or the pathways by which these signals are transmitted to the transcription factors. The structural bases and biochemical consequences of protein modification and/or association with small molecules or other proteins are largely unknown. Third, on the level of the organism, it is likely that separate lines of enquiry will converge ever more rapidly, thus yielding a better understanding of the overall logic in regulating the genome. The awesome power of yeast molecular genetics combined with *in vitro* transcription and chromatin assembly systems will keep many investigators occupied on these questions, at least until the end of the millennium.

Acknowledgements

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