Genesis of Chromatin and Transcription Dynamics in the Origin of Species

Maria J.E. Koster,[1] Berend Snel,[2] and H.Th. Marc Timmers[1,*]
[1]Molecular Cancer Research, Center for Molecular Medicine, University Medical Center Utrecht, Universiteitsweg 100, 3584 CG Utrecht, The Netherlands
[2]Theoretical Biology and Bioinformatics, Utrecht University, Padualaan 8, 3584 CH Utrecht, The Netherlands
*Correspondence: h.t.m.timmers@umcutrecht.nl
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Histone proteins compact and stabilize the genomes of Eukarya and Archaea. By forming nucleosome(-like) structures they restrict access of DNA-binding transcription regulators to *cis*-regulatory DNA elements. Dynamic competition between histones and transcription factors is facilitated by different classes of proteins including ATP-dependent remodeling enzymes that control assembly, access, and editing of chromatin. Here, we summarize the knowledge on dynamics underlying transcriptional regulation across the domains of life with a focus on ATP-dependent enzymes in chromatin structure or in TATA-binding protein activity. These insights suggest directions for future studies on the evolution of transcription regulation and chromatin dynamics.

''Nothing in biology makes sense except in the light of evolution'' is the title of an influential essay (Dobzhansky, 1973), which appeared in 1973 from the hand of the famous geneticist Theodosius Dobzhansky to empower American teachers for the creation-evolution debate in their class rooms. As a comparative zoologist, Dobzhansky was fascinated by the diversity of species. Nevertheless, he was well aware that the unity of life resides in ''biochemical universals'' like DNA, RNA, proteins, and certain metabolites. How could Dobzhansky know that around the time of his writing Fred Sanger was developing a rapid method for sequencing DNA (Sanger et al., 1977) and that ''Sanger'' sequencing of genomic DNA was about to transform his comparative zoology into comparative genomics?

Different branches of the tree of life developed distinct strategies to accurately express their genes. With increased genome size and biological complexity comes an increase in complexity of gene regulation mechanisms. The most pervasive is regulation at transcription initiation, which will be the focal point for our discussions. Transcriptional pausing is a later evolutionary invention, and excellent reviews on this appeared recently (Adelman and Lis, 2012; Yamaguchi et al., 2013). Here, we discuss the molecular functions and genomic occurrences of key components of the DNA transcription machinery across the archaeal and eukaryotic lineages in light of ''adaptive'' gene expression and transcriptional dynamics. In particular, we focus on evolutionary retention and expansion of the class of ATP-dependent enzymes, which are relevant for gene transcription by mammalian RNA polymerase II (pol II) and control the dynamics of chromatin structures or of basal transcription complexes. In the spirit of Dobzhansky, we aim to understand the dynamics of transcriptional regulation from an evolutionary perspective.

Transcriptional Mechanisms across the Domains of Life

The regulated action of DNA-dependent RNA polymerases in gene transcription underlies all life processes. Early studies on adaptive gene expression in the colon bacterium, *Escherichia coli,* and its bacteriophage λ (Jacob and Monod, 1961; Ptashne, 2005) revealed that facilitated access of RNA polymerase (RNAP) to promoter DNA is regulatory for gene expression. This paradigm proved valid for all Bacteria and is also central in understanding of gene regulation in Archaea and Eukarya (Jun et al., 2011; Ptashne, 2005; Struhl, 1999). Whereas archaeal transcription units are typically of an operon-type and archaeal gene-specific regulators preclude or enhance promoter binding of RNAP and its associated factors via direct interactions, the archaeal basal transcription machinery is more similar to eukaryotic than to bacterial systems (Figure 1) (Grohmann and Werner, 2011; Jun et al., 2011). Orthologs of the basal transcription factors TATA-binding protein (TBP) and TFIIB (called TFB) direct promoter recruitment of archaeal RNAP, whereas bacterial RNAP requires a single specificity (σ) factor for promoter recognition (Grohmann and Werner, 2011; Jun et al., 2011). It was proposed that analogous to bacterial σ-factors, different combinations of TBP/TFB paralogs could be used for subsets of genes in Archaea (Grohmann and Werner, 2011; Jun et al., 2011). However, little proof for this attractive model has been obtained and a significant functional redundancy may exist between archaeal TBP and TFB paralogs (Santangelo et al., 2007). In addition, the histone proteins essential for packing chromatin into the eukaryotic nucleus are present in some Archaea (Malik and Henikoff, 2003; Reeve, 2003). It was recently proposed that the eukaryotic nuclear lineage potentially originated within present-day Archaea (Williams et al., 2013). In contrast to archaeal organisms, eukaryotes contain three RNA polymerases for the transcription of nuclear genes, which are the result of a massive ''big-bang'' of gene duplications during the transition from an archaeum to a fully fledged eukaryote (Koonin, 2007). Each eukaryotic RNA polymerase has a dedicated set of transcription initiation factors, which recruit the enzymes and assist in formation of the open complex competent for transcription initiation.

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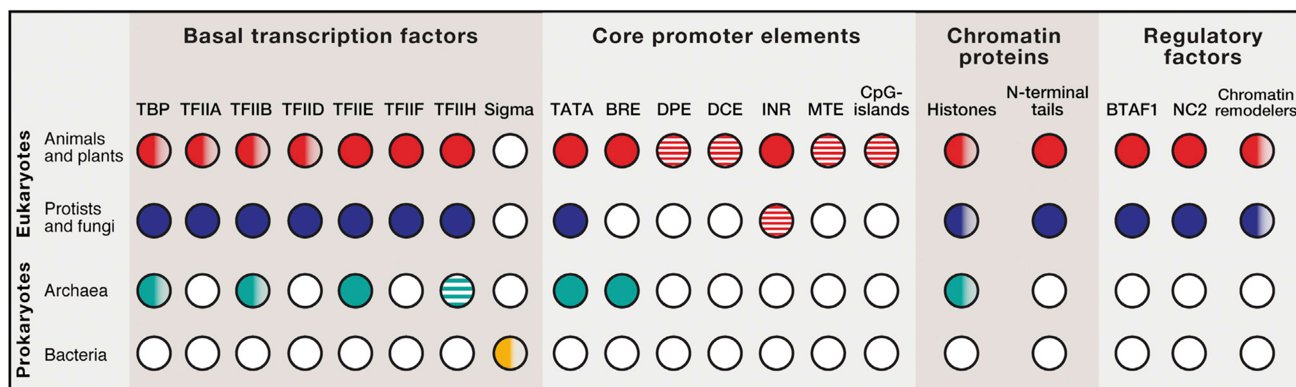

Figure 1. The Evolution of Gene Transcription

Simplified overview of the evolutionary conservation and diversification of factors important for gene transcription in the domains of life: Archaea, Bacteria, and Eukarya (split into two groups: Animals and Plants and Protists and Fungi). Filled bullets indicate orthologous proteins or sequences in the whole lineage, striped bullets the presence in part of the lineage, and open bullets that no homologs have been found. Gradient colors denote presence of paralogs. Although TFIIH subunits are present in Archaea, their role is probably restricted to DNA repair. Please note that in *S. cerevisiae* the TATA and INR elements are at variable distance and it is unclear whether yeast TFIID directly contacts the INR. Also, several members of the Apicomplexa lineage lack TAFs and basal transcription factor genes (see text).

However, each RNA polymerase initiation system depends on TBP and TFIIB paralogs (Akhtar and Veenstra, 2011; Gazdag et al., 2007; Vannini and Cramer, 2012). Of all RNA synthesis machineries, eukaryotic pol II is the most versatile as it serves the largest diversity of gene promoters. It is also the most tightly controlled serving the widest dynamic range of RNA expression levels (Levine et al., 2014).

Control and Dynamics of RNA Polymerase II-Mediated Transcription

Transcription initiation by pol II is controlled roughly at three different levels. First, gene-specificity is achieved through DNA-sequence-specific binding by activator and repressor proteins (gene-specific transcription factors [GSTFs]), which serve to mark a gene promoter or enhancer for activity (Figure 2). In general, GSTF binding to DNA is highly dynamic with in vivo residence times ranging from milliseconds to a few minutes (Chen et al., 2014; Dinant et al., 2009; Hager et al., 2009). This corresponds well with FRAP (fluorescence recovery after photobleaching) experiments indicating that diffusion is the prime means for GSTF movement in living cells. It allows a GSTF to scan the entire volume of a mammalian nucleus in a matter of minutes (Hager et al., 2009). GSTF binding to its DNA target sequence in chromatin is mostly transient, but exceptions exist like yeast Rap1p and activated *Drosophila* HSF (Lickwar et al., 2012; Yao et al., 2006). DNA residence time is correlated with transcriptional output as slower exchanges correlate with increased mRNA levels (Lickwar et al., 2012; Stavreva et al., 2004).

The second level of control is exerted by transcriptional co-activator and co-repressor complexes, which often act through chromatin structures and modifications (Figure 2). These complexes are recruited to specific genomic elements by GSTFs, by chromatin modifications, by DNA, and in some cases by regulatory RNAs. While genomic binding of these chromatin-regulatory complexes is dynamic (Hager et al., 2009; Johnson et al., 2008), their effect on chromatin function can be lasting due to the immobile character of histones and the DNA fiber in the eukaryotic nucleus (Kimura and Cook, 2001). Archaea seem to lack chromatin-remodeling and -modifying complexes, but most archaeal species contain histone-type or nucleoid proteins (Figure 1) (Sandman and Reeve, 2005). Archaeal histones are also characterized by a histone-fold domain (HFD) comprised of three α helices, but they lack the extensively modified extensions of their eukaryotic counterparts (Jun et al., 2011; Malik and Henikoff, 2003). Archaeal histones are more similar to the eukaryotic histones H3/H4 than the H2A/H2B pair (Malik and Henikoff, 2003; Sandman and Reeve, 2005). Nuclease digestion of archaeal chromatin indicates that DNA follows a spiral path on the surface of multimeric histone dimer cores with a periodicity of 30 or 60 bp (Ammar et al., 2012; Maruyama et al., 2013). Archaeal chromatin proteins seem to increase the melting temperature of DNA (Reeve, 2003), and it is tempting to speculate that a prime function of archaeal histone proteins has been to protect DNA from thermal denaturation. Several archaeal lineages like hyperthermophilic Crenarchaea lack histones but instead contain other chromatin proteins like Alba, which may perform similar functions (Sandman and Reeve, 2005). Eukaryotic histones are derived from an ancestor shared with Archaea, which duplicated the histone-fold to form a “doublet histone” (Malik and Henikoff, 2003). The ancestral gene split into histone H3 and H4 to form a H3-H4 tetramer, and after duplication it also diverged into the histone H2A-H2B heterodimer. While histone H4 is remarkably conserved, variants of H3, H2A, and H2B appeared to allow functional specialization (Malik and Henikoff, 2003). The nucleosomal repeating unit of eukaryotic chromatin consists of two copies of histone H3, H4, H2A, and H2B wrapping ~150 bp of DNA in 1.7 left-handed turns (Luger et al., 1997). Depending on linker length, nucleosomes can form higher-order structures with di-nucleosomes in head-to-head arrangements (Song et al., 2014). Eukaryotic chromatin is inherently stable and has been proposed to “maintain the restrictive

Figure 2. The Control of Transcription Initiation and Dynamics

Gene-specific transcription factors (GSTFs) bind to DNA elements to recruit regulatory complexes such as Mediator, histone acetyltransferases, and chromatin remodelers (SWI/SNF) altering chromatin structure. Pre-initiation complex (PIC) assembly starts with binding of TFIID, including TATA-binding protein (TBP) to the core promoter. Promoter association of TFIID is stabilized by TBP-associated factors (TAFs) binding to (dynamically) modified histone tails. BTAF1/Mot1p and NC2 can remove TBP from the promoter. Intrinsically mobile proteins are indicated in red, while the more stably bound are colored blue.

ground state of promoters by blocking association of the basal pol II machinery with the core promoter, while permitting many GSTFs to bind their target sites" (Struhl, 1999). Interestingly, transcription regulatory regions display a paucity of nucleosomes (see below). In contrast, archaeal chromatin is relatively flexible and unstable, which allows its promoters to be accessible (Reeve, 2003; Sandman and Reeve, 2005).

The third level is formed by the pol II pre-initiation complex (PIC), which besides pol II itself consists of six basal (or general) transcription factors (Thomas and Chiang, 2006; Vannini and Cramer, 2012). PIC assembly in vitro is sequential (Buratowski et al., 1989) and starts with core promoter binding by the TFIID complex, which consists of TBP and 13 highly conserved TAFs (TBP-associated factors) (Papai et al., 2011). While TBP in vitro directly recognizes the TATA box, promoter binding by TFIID can be stabilized by binding of TAFs to core promoter DNA sequences, like the INR, DPE, MTE, and DCE (Juven-Gershon and Kadonaga, 2010) and/or binding to acetylated and methylated histone tails (Jacobson et al., 2000; Vermeulen et al., 2007). TFIID binding is stabilized by TFIIA and subsequently the remaining four basal transcription factors (TFIIB, TFIIF, TFIIE, TFIIH) and pol II itself enter to complete PIC assembly (Figure 2). It is important to note that TAFs are eukaryotic inventions, which are lacking from Archaea. The occurrence of core promoter sequences other than TATA and INR differs between eukaryotic species (Figure 1). Most of mammalian promoters reside in CpG-islands and lack a canonical TATA box (Sandelin et al., 2007). The combination of nucleosome depleted regions (NDRs), core promoter sequence elements and histone tail interactions positions TFIID onto mammalian core promoters (Cler et al., 2009; Lauberth et al., 2013; Müller and Tora, 2014; Vermeulen et al., 2007). It is interesting to note that yeast pol II promoters contain AT-rich sequences and that TATA-less promoters predominate in larger genomes (Juven-Gershon and Kadonaga, 2010; Rhee and Pugh, 2012; Tora and Timmers, 2010). Biochemical experiments indicate that binding of eukaryotic TBP to TATA occurs in a linear three-step pathway resulting in severe DNA bending (Delgadillo et al., 2009). Minor groove deformation results from insertion of two pairs of phenylalanines between the first and last di-nucleotides of the TATA box, which is compensated by a ~90° bend in promoter (Delgadillo et al., 2009). While TBP binding is rapid, TATA box complexes with eukaryotic TBP or TFIID are long-lived (30–45 min) in vitro (Hoopes et al., 1998; Timmers and Sharp, 1991; Workman and Roeder, 1987). Whereas nucleosomes can obstruct TFIID binding, the opposite is also true as template pre-incubation with TFIID or TBP renders promoter activity resistant to nucleosome repression (Meisterernst et al., 1990; Workman and Roeder, 1987). This competition also seems to occur in living cells (Tirosh and Barkai, 2008; van Werven et al., 2009). Besides nucleosome organization and interaction, the assembly rate of the pol II PIC is influenced by the combination of core-promoter elements and by PIC composition (Levine et al., 2014; Sikorski and Buratowski, 2009). It is interesting to note that live-cell imaging showed that only a few of the promoter-binding events of pol II are productive (Darzacq et al., 2007). At present, much less is known of the archaeal PIC. While TATA-interaction of archaeal TBP also results in bent DNA, this interaction is extremely dynamic with on-off rates in the (sub)second range (Gietl et al., 2014). Similarly to eukaryotes, archaeal TFB can stabilize TBP/promoter interactions, but TFIIA orthologs are absent (Figure 1).

In conclusion, the general mechanisms of transcriptional regulation display similarities in organisms from the distinct domains of life and the major differences relate to fine-tuning and the dynamic behavior of chromatin structures and of TBP/TFIID complexes.

Sources of Stochastic Gene Transcription

Gene transcription has to be dynamic to meet changing environmental and cell-intrinsic demands. A highly relevant aspect for dynamic gene regulation is the stochastic nature of pol II-mediated transcription, which relies on (in)stability of DNA-transcription factor complexes (Hager et al., 2009; Munsky et al., 2012). Analysis and modeling of mRNA abundance on a single-cell basis indicated that mRNAs from constitutively expressed genes follow Poisson distributions. In contrast, regulated mRNAs follow a two-state model, in which the promoter frequently alternates between active and inactive states (Munsky et al., 2012; van

Werven et al., 2008). This behavior increases gene expression ''noise,'' which may enable rapid differential cellular responses to cell-external and -internal cues (Newman et al., 2006). Mutational analyses of the regulated *GAL1* promoter from yeast revealed that mutations in its canonical TATA box reduce transcriptional bursting and cell-to-cell variability in expression (Blake et al., 2006). Interestingly, genome-wide analysis in yeast cells showed that TBP turnover is higher at TATA-containing promoters compared to promoters lacking a canonical TATA box (van Werven et al., 2009). FRAP experiments in human and yeast cells indicated that TBP exists in (at least) two pools of different mobility (de Graaf et al., 2010; Sprouse et al., 2008). Another attribute of regulated promoters is that the TATA box is often occluded by nucleosomes (Tirosh and Barkai, 2008) and that assembly of a functional PIC requires (transient) removal of this +1 nucleosome. Interestingly, the TATA box is enriched in (developmentally) regulated promoters from yeast or humans (Basehoar et al., 2004; Sandelin et al., 2007). With the bulk of histone proteins being immobile in vivo (Kimura and Cook, 2001), remodeling of nucleosome structures at DNaseI-hypersensitive sites (DHSs) like promoters and enhancers, is a continuous process in cells (Hager et al., 2009). Also, histone H3 turnover analysis in yeast showed that this histone is replaced more rapidly at promoters than at coding regions and that H3 turnover rate in coding regions correlates with pol II density (Dion et al., 2007).

Together, this indicates that the biochemical stabilities of the eukaryotic histone/DNA and TBP/TATA box complexes are countered in vivo by specific dynamic processes. This may contribute to stochastic and transient promoter activation and to transcriptional noise of pol II-transcribed genes.

Moving the Immobile to meet Dynamic Demands Requires Energy

The molecular processes responsible for chromatin and PIC dynamics remained elusive until April 1992, when *Molecular and Cellular Biology* published two landmark studies identifying the yeast transcription regulators *SNF2* and *MOT1* as ATP-consuming enzymes (Davis et al., 1992; Laurent et al., 1992).

Mutations in the *SNF2* gene had been isolated in genetic screens for loss of growth on sucrose by Carlson and coworkers (Neigeborn and Carlson, 1984). Suppressor analyses of *snf2* alleles provided links with histone proteins and chromatin regulation (Hirschhorn et al., 1992). Soon after, biochemical studies showed that binding of the Gal4p GSTF to nucleosomal DNA was stimulated by a Snf2p-containing complex in an ATP-hydrolysis dependent manner (Côté et al., 1994; Kwon et al., 1994). It rapidly became clear that *SNF2* is identical to *SWI2*, which had been isolated in screens for defective mating-type switching (Stern et al., 1984). The Swi2p/Snf2p ATPase became the primogenitor of the family of ATP-dependent chromatin remodelers (Clapier and Cairns, 2009). In metazoans, *SWI2/SNF2* orthologs play important roles in development and cancer (Hargreaves and Crabtree, 2011; Shain and Pollack, 2013).

Using a genetic screen for regulators of basal activity of the yeast *CYC1* promoter the Thorner group isolated *MOT1* alleles to realize that its gene product contains a helicase domain, which is homologous to Snf2p and Rad54p (Davis et al., 1992). Subsequently, Auble and Hahn showed that Mot1p binds with high affinity to TBP-TATA complexes in vitro and uses ATP-hydrolysis to dissociate the complex (Auble and Hahn, 1993; Auble et al., 1994). Stable Mot1p-TBP complexes were isolated from yeast cell extracts (Poon et al., 1994). Parallel work with human cells showed that the orthologous complex, B-TFIID (BTAF1/hMot1p plus human TBP), can replace TFIID and TBP in in vitro transcription assays. B-TFIID rapidly exchanges between TATA boxes and contains a potent (d)ATPase activity (Timmers et al., 1992; Timmers and Sharp, 1991).

Identification of *SNF2* and *MOT1* as ATP-dependent remodelers opened studies toward the dynamics of inherently stable nucleosomal and TBP/TATA complexes. While first classified as a *SWI2/SNF2* family member, phylogenetic comparisons indicate that *MOT1* and its human ortholog *BTAF1* belong to a separate lineage within the SNF2 family of ATPases (Eisen et al., 1995; Flaus et al., 2006). This lineage includes the RAD54 ATPase involved in DNA repair and RAD54 orthologs, RAD54L2 and ATRX/RAD54L. Interestingly, the eukaryotic BTAF1/RAD54 lineage relates to a different archaeal homolog than *SWI2/SNF2* (Figure 3). In the following sections we discuss function, evolutionary retention, and expansion of gene families encoding ATP-dependent enzymes relevant for transcription and chromatin regulation in the context of their substrates. In this discussion our viewpoint will be the human genome.

Chromatin Remodelers Move and Restructure Nucleosomes

The *SWI2/SNF2* gene family expanded to 27 members in humans (Hargreaves and Crabtree, 2011). Of this family 16 of the ATP-dependent remodelers are currently implicated in controlling chromatin structures relevant for pol II transcription. The catalytic domain of all remodelers consists of two RecA-like lobes and is highly similar to that of DNA translocases (Becker and Workman, 2013). Recent models indicate that ATP-dependent remodelers employ a DNA translocation mechanism to modify chromatin structure (Bartholomew, 2014; Clapier and Cairns, 2009; Narlikar et al., 2013). Depending on the ATPase and its associated proteins, the action can be chromatin assembly, accessibility, and/or editing. Transcription-relevant remodelers have been divided into four distinct families (SWI/SNF, ISWI/SNF2L, CHD/Mi-2, INO80), which are genetically and functionally non-redundant, and we restrict our discussion to these groups (Bartholomew, 2014; Clapier and Cairns, 2009; Hargreaves and Crabtree, 2011). The combined cellular abundance of remodelers is estimated to be of one remodeling complex per four nucleosome substrates (Moshkin et al., 2012), suggesting that chromatin remodeling is a continuous process. Mutations in several remodelers or their associated subunits are causative to defects in metazoan development and to cancer in human cells, which underscores the importance of chromatin remodeling for biological processes (Hargreaves and Crabtree, 2011; Kadoch et al., 2013; Shain and Pollack, 2013). Below, we shortly describe the four distinct families, and we refer to excellent reviews with more details (Becker and Workman, 2013; Clapier and Cairns, 2009; Hargreaves and Crabtree, 2011; Narlikar et al., 2013).

SWI/SNF Group

The mammalian orthologs of yeast *SWI/SNF2* are Brg1 (*SMARCA4*) and Brm (*SMARCA2*), which form BAF complexes

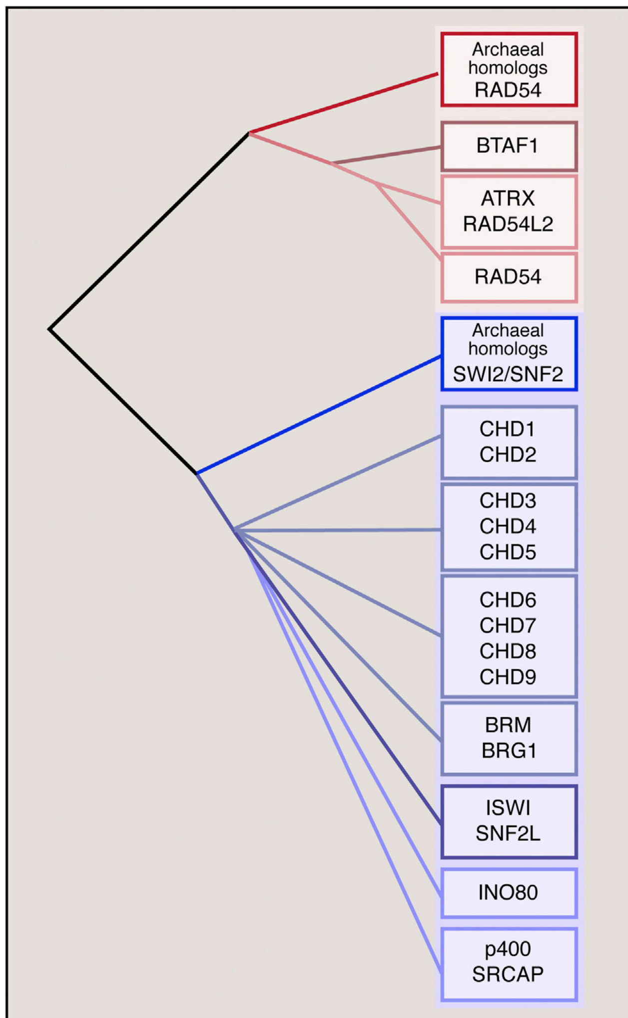

Figure 3. The Evolution of ATP-Dependent Enzymes in Transcription and Chromatin Regulation

Schematic representation of the tree of life for ATPase subunits representing the origin of the BTAF1/Mot1p-ATRX-RAD54 and CHD-SNF2-INO80-SWR lineages. The colors represent two groups that duplicated and diverged early in an archaeal and eukaryotic ancestor.

with either Brm or Brg1. Brg1 is also the catalytic subunit of the PBAF remodeler. The ATPase domain of *SWI2/SNF2* orthologs is abutted by an upstream HSA domain and a C-terminal bromo-domain, which can bind to acetylated lysines. Both in mammals and yeast, SWI2/SNF2 proteins assemble into large remodeling complexes. Whereas only one SWI2/SNF2 isoform is present in yeast, mammalian BAF complexes can differ in subunit make-up. Subunit exchange is used to regulate specific gene expression programs during development. Besides SWI2/SNF2, budding yeast also contains the RSC complex and mammalian PBAF is presumed to be the counterpart of yeast RSC (Bartholomew, 2014; Clapier and Cairns, 2009; Hargreaves and Crabtree, 2011). Recent evidence indicates that RSC action rather than AT richness is responsible for nucleosome depletion from intergenic regions in yeast (Lorch et al., 2014).

ISWI/SNF2L Group

ISWI/SNF2L remodelers also form distinct functional complexes by assembling with different homologous subunits (Hargreaves and Crabtree, 2011). ATPases of this group are characterized by SANT and SLIDE domains at their C terminus, which form a nucleosome recognition module (Clapier and Cairns, 2009). ISWI/SNF2L proteins assemble in different complexes with one to four subunits. The ISWI/SNF2L family is involved in repression of non-coding RNA transcription, heterochromatin formation, DNA replication, and ES cell pluripotency (Hargreaves and Crabtree, 2011; Koster et al., 2014). Interestingly, the fission yeast *Schizosaccharomyces pombe* lacks any ISWI/SNF2L ortholog (Pointner et al., 2012).

CHD/Mi-2 Group

Defining features for this group are two tandemly arranged chromo-domains, which lie N-terminal to the ATPase domain. Chromo-domains can interact with methylated histones and/or DNA (Clapier and Cairns, 2009). A single *CHD1* gene is present in *Saccharomyces cerevisiae* and the fission yeast genome contains three paralogs (Pointner et al., 2012), which may compensate for the absence of ISWI/SNF2L orthologs. CHD remodelers have expanded during evolution. Nine CHD genes are present in mammalian genomes, divided over three subfamilies. The first subfamily consists of CHD1 and CHD2, which contain a C-terminal DNA-binding domain. The second subfamily includes the PHD finger-containing CHD3 and CHD4. The third group is more diverse and consists of CHD5-CHD9, which have additional functional domains. Overall, the CHD/Mi-2 family is very versatile, and its members promote or repress transcription and participate in other events like mRNA processing (Murawska and Brehm, 2011).

INO80 Group

This group consists of three members in humans: INO80, SRCAP, and p400. These enzymes are characterized with a large insertion between the RecA-like lobes (Clapier and Cairns, 2009; Hargreaves and Crabtree, 2011). They form large assemblies with 8–14 subunits. SRCAP and p400 complexes exchange histone H2A.Z/H2B dimers for canonical H2A/H2B, and the INO80 complex performs the reverse reaction. The yeast SWR1 exchanger may collaborate with RSC to deposit H2A.Z/H2B abutting NDRs (Ranjan et al., 2013). An evolutionary conserved function of INO80 family members is chromatin editing. Furthermore, INO80 enzymes have been implicated in DNA repair and replication (Clapier and Cairns, 2009; Hargreaves and Crabtree, 2011).

The mechanism, which couples ATP hydrolysis to nucleosome translocation, is not well understood (Bartholomew, 2014; Narlikar et al., 2013). Various models have been proposed: "the twist diffusion" model, the "loop propagation" model, and the "octamer swiveling" model. A recent single-molecule FRET (fluorescence resonance energy transfer) study suggests the following model for nucleosome remodeling by ISWI/SNF2L enzymes: DNA is first translocated in single-bp steps toward the nucleosomal exit side by the ATPase domain; this generates strain on the entry-side DNA; after translocation of seven bps, this triggers DNA at the nucleosomal entry side to be drawn into the nucleosome; an additional three bps of DNA is translocated to the exit side; this step repeats to generate processive DNA translocation

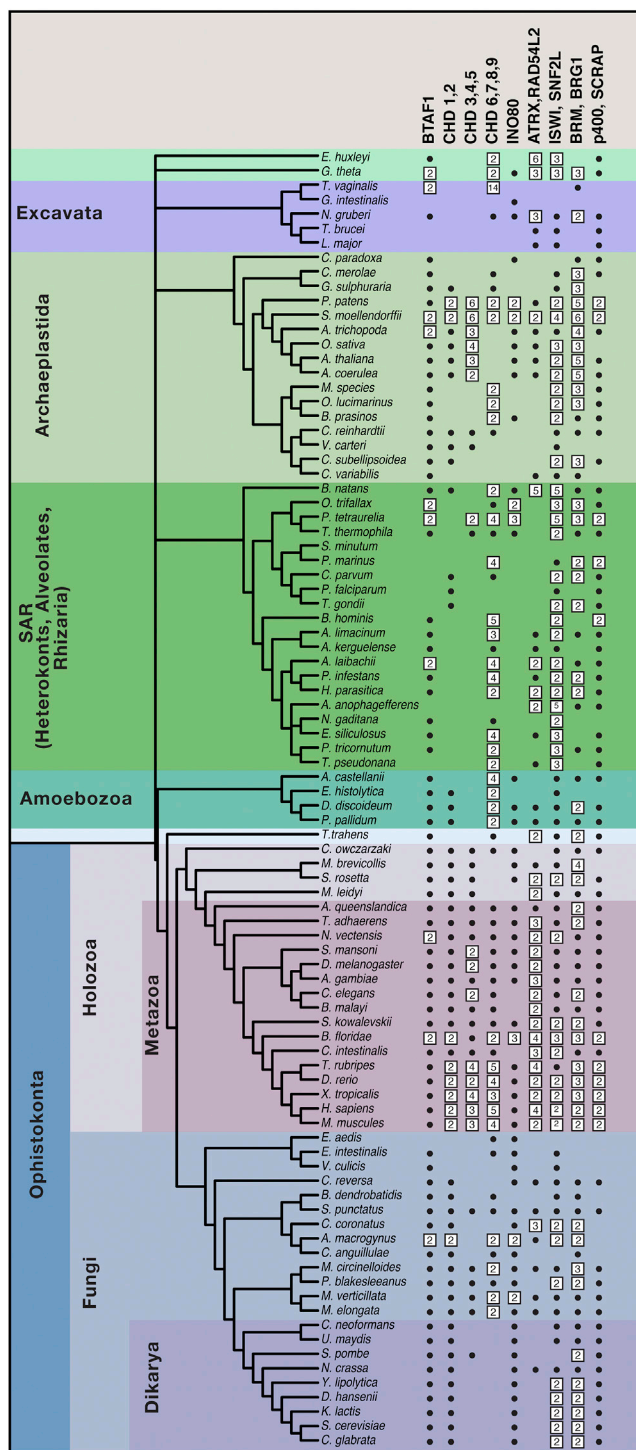

Figure 4. The Evolution of the SWI2/SNF2 Family

Schematic representation of the tree of life with a selection of eukaryotic species from the different supergroups (Excavata; Archaeplastida; SAR; Amoebozoa; Ophistokonta) indicated on the left. The SWI2/SNF2 family member proteins are organized in different functional groups (BTAF1; CHD1,2; CHD3,4,5; CHD6,7,8,9; INO80; ATRX, RAD54L2; SNF2H,SNF2L; BRG1,BRM; SWR1), and whenever present, the number of homologs is indicated in black boxes. A filled bullet indicates presence of a single ortholog.

across the nucleosome (Bartholomew, 2014; Narlikar et al., 2013). It is likely but currently unclear whether different remodeler families utilize distinct mechanisms.

Chromatin Remodeling Complexes: Phylogenetics, Function, and Regulation

Expansion of eukaryotic genomes mandated more extensive DNA condensation and this provided evolutionary pressure to expand the chromatin-remodeling class of enzymes early on. While the catalytic domain of SWI2/SNF2 ATPases seems to have a bacterial ancestor, these domains are equipped with chromatin-binding domains in eukaryotes (Eisen et al., 1995; Flaus et al., 2006; Iyer et al., 2008). We performed phylogenetic comparisons to infer the evolutionary history of gene families encoding ATP-dependent enzymes relevant for eukaryotic transcription regulation (Figure 4). The universality of the chromatin-remodeler families supports their origin soon after the onset of the eukaryotic lineage but before the initial radiation of eukaryotic species. Higher eukaryotes further expanded the number of genes encoding these ATPases and associated subunits through gene duplication (Hargreaves and Crabtree, 2011). Together with the acquisition of novel domains, proliferation of paralogous families led to a diverse set of enzymes. Most eukaryotes have representatives of all four classes of remodelers (SWI/SNF, ISWI/SNF2L, CHD/Mi-2, INO80). This allows higher eukaryotes to form distinct functional complexes that drive and maintain developmental and cell-type-specific gene expression programs. The early divergence and in some cases duplication of plant homologs resulted in plant-specific chromatin remodelers with functions deviating from their metazoan counterparts (Gentry and Hennig, 2014).

Our current knowledge of chromatin-based mechanisms controlling transcriptional permissiveness is derived from a limited set of protozoan and metazoan model organisms, which may not represent the full spectrum. For example, the coral symbiont and dinoflagellate *Symbiodinium minutum* has permanently condensed chromatin and its genome contains both eukaryotic histone genes and prokaryotic histone-like genes (Shinzato et al., 2014). Interestingly, the *S. minutum* genome lacks any chromatin-remodeling enzyme (Figure 4) suggesting that transcriptional regulation of its genes differs from known mechanisms. Of special interest are protozoan parasites, which provide insight into the evolution of transcription and chromatin dynamics. Many organisms belonging to these lineages (Microsporidia [*Edhazardia aedis*, *Encephalitozoon intestinalis*, and *Vavraia culicis*], Kinetoplastida [*Trypanosoma brucei*, *Trypanosoma cruzi*, and *Leishmania major*], Apicomplexa [*S. minutum*, *Perkinsus marinus*, *Cryptosporidium parvum*, *Plasmodium falciparum*, and *Toxoplasma gondii*] and *Giardia*) have a reduced set of chromatin remodelers (Figure 4), which may result from massive gene loss, commonly observed in parasites. The malaria parasite *P. falciparum* is a protist with a very AT-rich genome and with a disconnection between chromatin structure and gene expression (Westenberger et al., 2009). Intriguingly, some of the early branching parasitic protists like Kinetoplastida exert little control at the transcription level, which rather occurs post-transcriptionally (Kramer, 2012). Their protein-coding genes are arranged in long tandem arrays and transcribed as

long poly-cistrons (10–100 genes). Thus, these parasites have limited transcriptional regulation at the level of chromatin, and they also have different nucleosome arrangements and constitutions to support their complex lifestyle and to adapt to their environmental niche.

The histone variants H3.3, H2A.Z, and H2A.X are almost universally present indicating that they arose early in eukaryotic evolution (Malik and Henikoff, 2003). One would expect that histone variants and specific chromatin remodeling complexes acting upon these variants co-evolved in species. Support for this comes from budding yeast, which expresses only a single H3 protein resembling H3.3 and lacks ATRX (Figure 4). Certain histone lineages are categorized as outliers including: functionally specialized lineages, ancestral eukaryotic lineages that diverged early, and recent lineages subject to relaxed selection. Relaxed selective evolutionary constrains could account for the more rapid rate of histone evolution seen in Microsporidia (Malik and Henikoff, 2003). This strong divergence and accelerated evolution of histones might explain their limited set of chromatin remodeling enzymes (Figure 4). Clearly, detailed phylogenetic comparisons of chromatin remodelers and of their histone substrates provide testable hypotheses and further mechanistic insights.

Restructuring TBP-TATA and Liberating TBP

ATP-dependent remodeling is not unique to histone-DNA complexes. The inherently stable TBP-TATA complex is regulated directly by BTAF1/Mot1p that also uses ATP to mobilize the TBP at core promoters (Figure 2). BTAF1/Mot1p family members are also SWI2/SNF2-family ATPases and they bind to TBP in the presence or absence of DNA (Auble and Hahn, 1993; Auble et al., 1994; Timmers et al., 1992; Timmers and Sharp, 1991). BTAF1/Mot1p relaxes the DNA sequence-specificity of TBP to allow binding to non-TATA sequences (Gumbs et al., 2003; Klejman et al., 2005). BTAF1/Mot1p binds to TBP with its N-terminal HEAT/ARM repeats and contacts DNA upstream of TATA with its ATPase domain (Wollmann et al., 2011). BTAF1/Mot1p function is intimately linked to NC2. In living cells these factors together control the residence time of TBP on chromatin (de Graaf et al., 2010; Sprouse et al., 2008). The NC2 heterodimer consists of NC2α and NC2β, which interact via HFDs, resembling histones H2A and H2B (Kamada et al., 2001). NC2 inhibits PIC formation by competing with TFIIA and TFIIB for TBP binding (Goppelt et al., 1996; Meisterernst and Roeder, 1991; Mermelstein et al., 1996). Structural studies indicate that NC2 may embrace the TBP-TATA complex to close a ring around the DNA (Kamada et al., 2001). In vitro findings support that NC2 induces TBP sliding along the DNA (Schluesche et al., 2007).

Historically, BTAF1/Mot1p and NC2 have been studied in separation, but genome-wide mapping in yeast showed that binding profiles of Mot1p and NC2 strongly overlap (van Werven et al., 2008). Yeast strains with *ts*-mutations in *MOT1, NC2α*, and *NC2β* display similar alterations in mRNA expression (Dasgupta et al., 2002; Sikorski and Buratowski, 2009; Spedale et al., 2012; van Werven et al., 2008). Mot1p-TBP-NC2-TATA complexes can be disrupted in vitro as a result from Mot1p-mediated ATP hydrolysis (van Werven et al., 2008). Compared to TATA-less promoters, TBP turnover at TATA-containing promoters is relatively high (van Werven et al., 2009). This is counterintuitive as the canonical TATA box represents DNA with the highest affinity for TBP (Hahn et al., 1989). We proposed that the bent TATA conformation induced by TBP binding could act as a "spring" for rapid BTAF1/Mot1p-NC2 mediated release from TATA boxes (Tora and Timmers, 2010). Auble and colleagues proposed models involving DNA-translocation by the ATPase moiety of BTAF1/Mot1p coupled to insertion of a latch from the HEAT repeat region into the concave surface of TBP to compete with DNA binding (Pereira et al., 2001; Viswanathan and Auble, 2011). The combined action of Mot1p and NC2 mobilizes TBP from intrinsically preferred TATA-containing promoters, which allows TBP redistribution to intrinsically disfavored TATA-less promoters (Zentner and Henikoff, 2013). This explains how Mot1p and NC2 repress SAGA-dependent TATA-containing genes and how they activate TFIID-dependent TATA-less genes (Spedale et al., 2012). It is interesting to note that a recent study on SAGA-bound TBP in yeast indicates that the concave surface of TBP remains largely accessible (Han et al., 2014), which may provide an entry zone for BTAF1/Mot1p and NC2. Given the strong sequence conservation between BTAF1/Mot1p, NC2, and TBP it seems likely that this is a common mechanism in eukaryotes.

TBP and Related Factors: Phylogenetics, Function, and Regulation

Proper TBP function is fundamental to the fidelity of transcriptional programs in both Archaea and Eukarya. The highly conserved C-terminal half of TBP consists of two symmetric pseudo-repeats (the TBP domain) folding into a saddle-shaped structure. While the convex surface interacts with proteins like TAFs, BTAF1/Mot1p, NC2, and basal transcription factors, the concave surface binds to the TATA box via the insertion of two pairs of phenylalanine to induce the bent conformation of TATA (Delgadillo et al., 2009). The evolutionary origin of the TBP domain can be traced back to the last universal common ancestor (LUCA) to Archaea and Eukarya and most likely resulted from an ancestral gene duplication and fusion event (Brindefalk et al., 2013). TBP domains are present in proteins with diverse functions like DNA glycosylases and RNase III (Brindefalk et al., 2013).

The compact nature of eukaryotic chromatin might have mandated a more stable DNA interaction of TBP compared to that in Archaea. Possibly, evolutionary acquirement of the critical phenylalanines provided stability to eukaryotic TBP-DNA complexes and resulted in the deformability of the TATA-sequences. Interestingly, promoter bending by eukaryotic and archaeal TBP and TFB/TFIIB occurs via molecularly distinct mechanisms (Gietl et al., 2014). The rapid on- and off-rates of archaeal TBP on DNA allows regulation directly at the recruitment stage. In line with this, archaeal transcription initiation is inhibited by sequence-specific regulators that compete with TBP and TFB for binding to the TATA box and BRE, or with RNAP for the site of transcription initiation (Reeve, 2003). Archaeal species living at high-temperature and/or high-salt concentrations increased the hydrophobicity of the TBP interior to withstand these extreme conditions (Koike et al., 2004).

Interestingly, most metazoan eukaryotes encode for multiple TBP paralogs, the TBP-related factors (TRFs) (Akhtar and

Veenstra, 2011; Levine et al., 2014; Müller et al., 2010). Independent duplication events gave rise to genes encoding insect-specific TRF1, metazoan-specific TRF2/TLF/TBPL1, and vertebrate-specific TBP2/TRF3/TBPL2 proteins. TRF1 associates with BRF in *Drosophila melanogaster* to form the TFIIIB complex driving pol III-dependent transcription instead of TBP (Takada et al., 2000). The vertebrate-specific TBP2/TRF3 binds to the TATA box and interacts with TFIIA and TFIIB. TBP2/TRF3 can replace TBP for transcription in oocytes. During early development TBP levels increase and TBP2/TRF3 is actively degraded (Akhtar and Veenstra, 2011; Levine et al., 2014; Müller et al., 2010). TBP-like factor (TLF or TRF2) is the most distant paralog that evolved prior to the emergence of the bilateria and subsequent to the split between bilaterian and non-bilaterian animals (Duttke et al., 2014). TLF/TRF2 functions in male germ cell differentiation (male TLF/TRF2 null mice are sterile) and is essential for early embryogenesis in all non-mammalian metazoans studied thus far (Akhtar and Veenstra, 2011; Levine et al., 2014; Müller et al., 2010). TLF/TRF2 interacts with TFIIA and TFIIB, but lost the capacity to bind to the TATA box due to loss of two of the four phenylalanines required for TATA box recognition (Duttke et al., 2014; Teichmann et al., 1999). TLF/TRF2 is targeted to TATA-less promoters including the histone H1 promoter and it activates TCT- and DPE-containing promoters (Duttke et al., 2014; Isogai et al., 2007; Kedmi et al., 2014). The divergence in structure, expression, and function of TBP homologs explains their evolutionary retention. Thus far, most work has focused on TBP-containing complexes and the molecular mechanisms underlying the regulation of TBP paralogs remain to be elucidated.

Interestingly, some protists including *Giardia intestinalis*, *Crypthecodinium cohnii*, *T. brucei*, *T. cruzi*, and *L. major* replaced multiple of the four critical phenylalanine residues in their single-copy *TBP* genes (Best et al., 2004; Das et al., 2005; Guillebault et al., 2002). Thus, these organisms must use different PIC assembly strategies, which still dependent on TBP but not on TATA box interactions. The promoter binding events are probably more dynamic, and to stabilize TBP-DNA interaction these organisms might depend more on the presence of other proteins, like TFIIA and TFIIB. However, this is not the case in *G. intestinalis,* because it seems to lack TFIIB (Best et al., 2004). Possibly, in this organism Brf1p, part of TFIIIB, or a non-conserved protein with similar function, replaces TFIIB in pol II transcription. At present it is unclear how PIC assembly is achieved in these protozoan parasites and certain unicellular eukaryotes as they lack most of the basal transcription factors (Figure 1). Research in this area will be full of surprises.

BTAF1/Mot1 and NC2: Phylogenetics, Function, and Regulation

TBP orthologs play crucial roles in all Archaea and Eukarya, but only eukaryotic genomes contain genes orthologous to *BTAF1/MOT1*, *NC2α* and *NC2β*. Analogous to σ-factors in Bacteria, DNA sequence-specific regulators can compete with archaeal TBP for promoter binding. It is interesting to note that the TBP-interacting protein 26 (TIP26) from *Thermococcus kodakarensis* KOD1 can bind archaeal TBP inhibiting DNA binding (Yamamoto et al., 2006). Proteins with analogous functions to TIP26 might exist in other archaeal species. Alternatively, no additional factors could be required to disrupt archaeal TBP-DNA complexes as they are very dynamic intrinsically (Gietl et al., 2014).

While TBP regulation by BTAF1/Mot1p and NC2 is well studied, their action toward the TBP paralogs of higher eukaryotes is not yet clear. Human BTAF1 was found to interact with both *Caenorhabditis elegans* TRF2/TLF and *D. melanogaster* TRF1 (Pereira et al., 2001). In vitro transcription assays revealed that NC2 does not compete with TFIIA when bound to human TRF2 in contrast to TBP (Teichmann et al., 1999). This is an interesting area of study given the importance of TBP paralogs in germ cells and early embryogenesis (Akhtar and Veenstra, 2011; Duttke et al., 2014; Müller et al., 2010; Torres-Padilla and Tora, 2007).

We proposed previously that BTAF1/Mot1p and NC2 act together on TBP, which implies co-occurrence of their genes across eukaryotes (van Werven et al., 2008). Indeed, testing this hypothesis revealed a clear co-occurrence and similar distribution of *BTAF1/MOT1*, *NC2α*, and *NC2β* genes across the eukaryotic lineage (Figure 5). This provides strong evidence that these genes co-evolved. Interestingly, the Kinetoplastida and Apicomplexa protozoan parasites lack both *BTAF1/MOT1* and *NC2* genes. Unfortunately, little is known about of transcriptional control in Apicomplexa. They contain a primitive transcription machinery lacking most of the TAFs and the basal transcription factors TFIIA and TFIIF (Meissner and Soldati, 2005). Typical eukaryotic promoter elements like TATA boxes are also absent. More is known about transcription regulation in Kinetoplastida. *G. intestinalis*, *T. brucei*, and *L. major* do not employ canonical TATA boxes for transcription initiation (Thomas et al., 2009). These species contain TBP homologs lacking the critical TATA-intercalating phenylalanine residues (Best et al., 2004; Guillebault et al., 2002; Ruan et al., 2004). Most likely, DNA interactions of these TBPs are weak and easily disrupted, which would obviate the need for TBP regulators BTAF1/Mot1p and NC2. In *T. brucei* an alternative mechanism for TBP-promoter dissociation has been described, which involves PIC release from the promoter by TBP phosphorylation (Hope et al., 2014). We analyzed whether absence of the four phenylalanines in TBP is common in organisms lacking *BTAF1/MOT1* and *NC2* orthologs. Organisms that lack the NC2 subunits, but have BTAF1/Mot1p contain at least one *TBP* gene with all four intercalating phenylalanines (Tables S1, S2, S3, S4, S5, and S6). Interestingly, most of the organisms lacking BTAF1/Mot1p do not contain a single TBP paralog with all four intercalating phenylalanines (Tables S1 and S2). In particular, the first phenylalanine (F193 in human TBP) is missing (6 out of 10). We propose that BTAF1/Mot1p dependence is relaxed when TBP lacks the full complement of four phenylalanines. In contrast, organisms carrying the full set of genes orthologous to *BTAF1/MOT1*, *NC2α*, and *NC2β* contain at least one *TBP* gene with all four intercalating phenylalanines. The only two exceptions to this rule (*B. natans* and *T. vaginalis*; Tables S5 and S6) carry an aromatic tyrosine, which could also intercalate into DNA. This persuasive correlation indicates co-evolution of stable TBP-DNA interactions with the enzymatic BTAF1/Mot1p-NC2 machinery to enable dynamic transcriptional responses (Tora and Timmers, 2010; Viswanathan and Auble, 2011).

In summary, during evolution different strategies were developed to enable a dynamic binding of TBP orthologs and paralogs

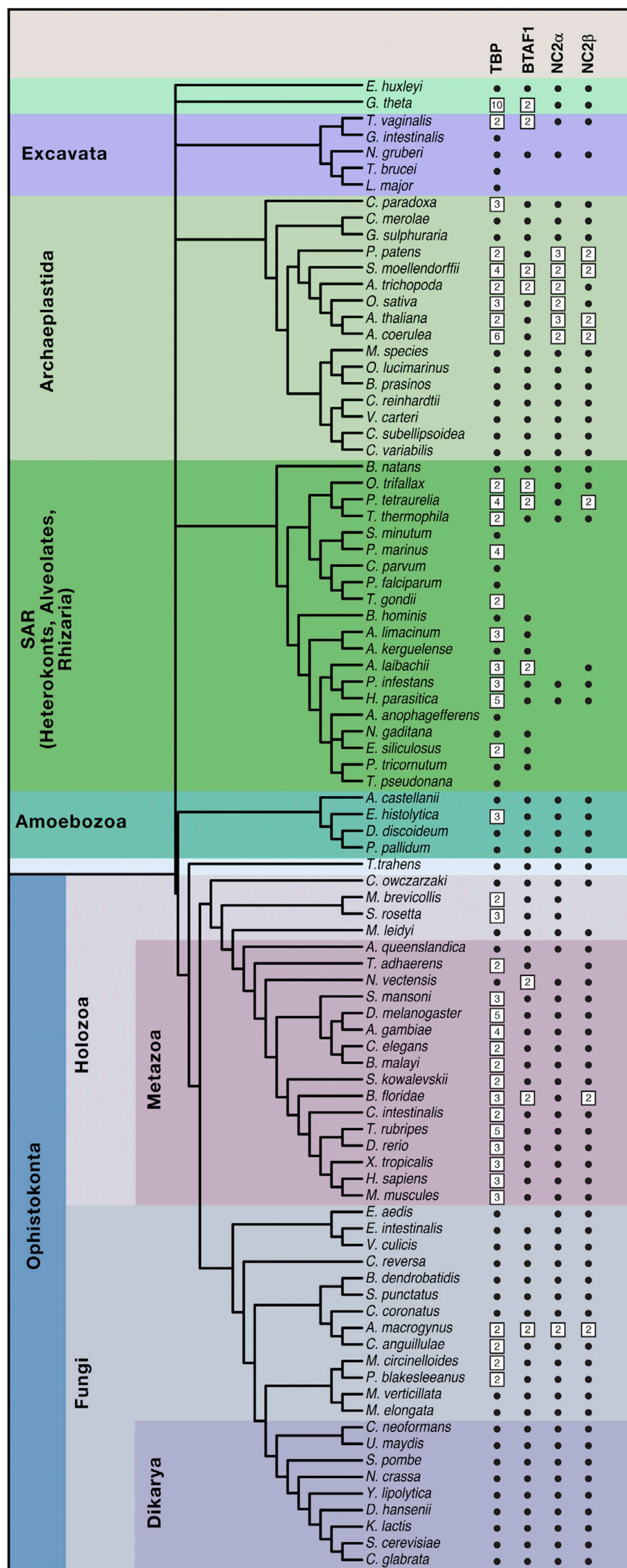

Figure 5. The Evolution of TBP and Its Direct Regulators

Schematic representation of the tree of life with a selection of eukaryotic species from the different supergroups indicated on the left. TATA-binding protein (TBP) and its regulators are organized in different functional groups (TBP; NC2α; NC2β; BTAF1) in a representation similar to Figure 4. These lists have been curated manually (see Supplemental Experimental Procedures).

to control PIC assembly at proper positions in time and space across genomes. Three strategies can be discerned: an inherently unstable TBP-DNA complex due to absence of the four intercalating phenylalanines in TBP, use of non-TATA sequences with limited DNA deformability, and enzymatic disassembly by BTAF1/Mot1p. Clearly, the BTAF1/Mot1p-NC2 pathway offers possibilities for regulation by cell-internal and -external cues, but these remain to be discovered.

Conclusions and Future Directions

The dynamic response of gene expression programs to cellular and environmental signals is a shared property of all living organisms. With the increase of genome size and complexity during the evolution of species came different mechanisms to ensure transcriptional dynamics and regulated accessibility of genomic sequences. In this review we discussed the function and evolutionary history of ATP-dependent enzymes controlling chromatin structure and PIC dynamics. Phylogenetic comparisons between Archaea and Eukarya reveal that histones and SWI2/SNF2 chromatin remodelers as well as TBP and BTAF1/Mot1p originated from an ancestor common to both lineages.

During eukaryotic evolution remodelers diversified into four groups (SWI/SNF, ISWI/SNF2L, CHD/Mi-2, INO80), but not all eukaryotic genomes carry representatives of each group. Given their functional differences complete absence of a group (like ISWI/SNF2L in *S. pombe*) has direct consequences on chromatin structure (Pointner et al., 2012) and gene regulation pathways. ATP-dependent remodelers acquired additional (signature) domains for intra-molecular regulation and/or for chromatin interaction (Clapier and Cairns, 2009, 2012; Hargreaves and Crabtree, 2011). In almost all cases the enzymatic SWI2/SNF2 core has been decorated with many subunits, which modulate its activity, function, and/or localization. Cancer exome sequencing revealed that subunits of human SWI/SNF complexes are particularly prone to mutation and amplification in a variety of human cancers (Kadoch et al., 2013). From both fundamental and translational perspectives, it is important to determine evolutionary conservation and diversification of chromatin remodeler subunits. In addition, it would be interesting to analyze the evolutionary distribution of histone variants in relation to chromatin remodeling complexes.

Phylogenetic comparisons between the ATP-dependent BTAF1/Mot1p and their TBP substrate reveal distinct patterns. Whereas all Eukarya contain one or more TBP genes, several species lack the BTAF1/Mot1p gene. In most of these cases, no NC2 orthologs could be detected, which emphasizes the intimate link between BTAF1/Mot1p and the NC2 complex in controlling TBP dynamics. Besides their TBP-regulatory domains BTAF1/Mot1p and NC2α acquired additional domains during evolution, and their phylogenetic analysis may reveal accessory functions (Goppelt et al., 1996; Wollmann et al., 2011). It is striking to note that most organisms lacking BTAF/Mot1p express TBP orthologs, which are also lacking one or more of the four phenylalanines responsible for intercalating DNA.

Appreciating evolutionary relationships between chromatin and transcription proteins improves our overall understanding of gene and chromatin regulation principles. In these days, we are witnessing an ever-increasing wealth of genomic sequence data from present-day and extinct organisms, which offer unprecedented insight into evolutionary relationships between organisms and processes fundamental to life. Unfortunately, Theodosius Dobzhansky missed the birth of comparative genomics and of phylogenomics as he passed away 7 months after Sanger's first report on modern sequencing (Sanger et al., 1977) propelling this genomics revolution. Nevertheless, Dobzhansky realized the close association between environmental niche and the genome: ''the environment presents challenges to living species, to which the latter respond by adaptive genetic changes'' in (Dobzhansky, 1973). The fact, that the regulatory components of the transcription machinery are evolutionary malleable, should be no surprise as gene regulation steers many diverse processes as enzymatic adaption and organismal development. Understanding evolutionary conservation and diversity of these key components sheds light on the processes of adaptive gene expression and of organismal evolution itself.

Compared to the incredible airlift given by whole-genome sequencing in describing the genomic relatedness of organisms, description of their environmental niche remains grounded. For each organism, genome sequence and environment are inextricably linked, and we advocate attaching a standardized description of the environment to each genome sequence. These descriptions facilitate the linking of comparative zoology and phylogenetics to illuminate the fascinating 4.5 billion-year (bio-) chemical experiment underlying organismal evolution. We are sure that Dobzhansky would have been thrilled to partake in the current developments to understand the diversity of species.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures and six tables and can be found with this article online at http://dx.doi.org/10.1016/j.cell.2015.04.033.

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