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The evolution of G1/S transcriptional network in yeasts

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Abstract

The G1-to-S cell cycle transition is promoted by the periodic expression of a large set of genes. In *S. cerevisiae* G1/S gene expression is regulated by two transcription factor (TF) complexes, the MBF and SBF, which bind to specific DNA sequences, the MCB and SCB, respectively. Despite extensive research little is known regarding the evolution of the G1/S transcription regulation including the co-evolution of the DNA binding domains with their respective DNA binding sequences. We have recently examined the co-evolution of the G1/S TF specificity through the systematic generation and examination of chimeric Mbp1/Swi4 TFs containing different orthologue DNA binding domains in *S. cerevisiae* (Hendler, et al. 2017). Here, we review the co-evolution of G1/S transcriptional network and discuss the evolutionary dynamics and specificity of the MBF-MCB and SBF-SCB interactions in different fungal species.

In eukaryotes, different steps of the cell cycle are promoted by waves of expression of large sets of genes (Granovskaia, et al. 2010, Spellman, et al. 1998, Whitfield, et al. 2002). Co-regulated genes whose expression peaks at the G1-to-S transition promotes entry into S phase and enables the initiation (Start) of a new cell cycle. Although G1-to-S gene expression is regulated in many eukaryotes (Bahler 2005, Bar-Joseph, et al. 2008, Bertoli, et al. 2013, Côte, et al. 2009), some regulators of the G1-to-S transition (e.g. transcription factors) are not conserved between Fungi and Metazoans (Cross, et al. 2002, Medina, et al. 2016). Currently, little is known regarding the evolution and specificity of the key TFs promoting G1/S gene expression in Fungi. In *S. cerevisiae* (*Sc*) budding yeast, MBF and SBF are the two protein complexes regulating G1/S transcription program (Amon, et al. 1993, Bean, et al. 2005, de Bruin, et al. 2006). The MBF and SBF complexes contain a common Swi6 protein and the Mbp1 and Swi4 DNA binding proteins, respectively. In *C. albicans*, both MBF and SBF complexes were identified, however, the mechanism and control of the G1/S transcription program are different from those in *Sc* (see below for details) (Côte, et al. 2009, Hussein, et al. 2011, Ofir, et al. 2012). Finally, in the *S. pombe* fission yeast, a related tetrameric complex containing the Cdc10 subunits with Res1 and Res2 DNA binding proteins regulates G1/S gene expression (Bahler 2005).

In budding yeast, the SBF and MBF were shown to regulate distinct branches of the G1/S transcriptional network where SBF promotes the expression of genes involved in morphogenesis including budding and MBF promotes the expression of genes involved in DNA replication and repair (Bean, et al. 2005, Ferrezuelo, et al. 2010, Wittenberg and Reed 2005). The MBF complex can bind promoter sequences containing the MCB (***M****luI* **C**ell-cycle **B**ox) recognition sequence *ACGCGT* that is conserved across many fungal species including *C. albicans* (Côte, et al. 2009) and *S. pombe* (Rustici, et al. 2004). In contrast, the SCB (**S**wi4 **C**ell-cycle **B**ox) recognition sequence *CRCGAAA*, bound by the SBF complex, is only found in budding yeasts including *Sc*. Thus, it is generally assumed that ancestral Res (the progenitor of Swi4 and Mbp1 in Hemiascomycetes) bound an MCB-like motif (which we will call RCB) and that SCB is the more specialized DNA-binding motif that emerged after Res duplication. This scenario represents a classic case of neofunctionalization after gene duplication, where one of the paralogs (Swi4) evolves

a new function and DNA-binding specificity (SCB) to regulate old and new G1/S target genes (Voordeckers, et al. 2015).

New insights regarding MBF and SBF evolution

Despite extensive studies in different organisms, relatively little was known regarding how Swi4 and Mbp1 DNA binding domains (DBDs) co-evolved to recognize the SCB and MCB DNA binding sequences, respectively, to synchronize the expression of a large set of genes during the G1 to S transition. To address these questions, we recently generated and examined the function of different chimeric Mbp1 and Swi4 TFs in *Sc* (Hendler, et al. 2017). Specifically, we generated 16 different chimeric TFs by systematic replacements of native *Sc* DBD in Mbp1 and Swi4 with orthologs from different fungal species of different clades. Examination of these chimeric TFs revealed that all TFs containing the DBD of orthologs of distant Hemiascomycetes and other fungi fused to *Sc* Mbp1 activation domain (AD) were unable to complement the *Sc* Mbp1 suggesting that the Mbp1 regulator in *Sc* evolved relatively recently. In contrast, we found that chimeric TFs containing the DBD of distant orthologs fused to *Sc* Swi4 AD can complement the native *Sc* Swi4. Detailed examination of the phenotype of *Sc* strains expressing the different chimeric TFs lacking the endogenous Mbp1 and Swi4 showed different levels of complementation. We found that while chimeric TFs containing closely related DBDs (e.g. from *K. lactis*, *C. albicans*) did not lead to significant phenotypic defects, chimeric TFs containing distantly related DBDs (e.g. from *Y. lipolytica*, *N. crassa*, *S. pombe*) led to slow growth rate and severe morphological defects upon cell growth, budding and division (Hendler, et al. 2017).

Using genome wide expression analysis, we found that these chimeric TFs lead to the expression of a progressively limited subset of SBF-dependent target genes (**Figure 1**). Interestingly, bioinformatics analysis of these transcription programs showed that the subset of SBF-targets regulated by the chimeric TFs contain motifs more closely related to MCB consistent with a Res-like ancestor found in *S. pombe*. These findings suggest that Swi4 network expansion took place by expanding the ancestral SBF regulon, which contained MCB motifs, via inclusion of the modern SCB motif (**Figures 1-2**). Further support for the functional division of the SBF regulon to "modern" genes containing SCB motifs and "ancient" genes containing MCB motifs came from chromatin

immunoprecipitation (ChIP) experiments. We found that *Sc* Swi4 exhibits much higher affinity for the SCB motif relative to the MCB-like motif while the chimeric TFs containing distantly related DBDs can only bind the MCB-like motif (Hendler, et al. 2017). These results suggest that the *Sc* Swi4 evolved for optimized binding to the SCB motif to enable normal cell growth and morphogenesis. In general, these results reveal that transcription network expansion can depend on gradual co-evolution of the DBD with diverse promoters to include genes containing new regulatory motifs for optimizing cellular fitness.

Conservation of Swi4 function and regulation

In *Sc*, the SBF and MBF complexes exhibit high functional overlap. It was shown that a single *swi4*- or *mbp1*-deletion leads to moderate phenotypic effects, however, the double *swi4*- and *mbp1*-deletion leads to non-viability. Despite the high functional overlap between SBF and MBF complexes, extensive research in the past decade revealed significantly different mechanism of regulation between the two complexes (Costanzo, et al. 2004, de Bruin, et al. 2006, de Bruin, et al. 2004). While SBF is a transcriptional activator required to activate G1/S transcription during G1, MBF is a transcriptional repressor that inhibits transcription outside of G1. In accordance, inactivation of SBF inhibits the expression of G1/S targets, while inactivation of MBF leads to constitutively high levels of its G1/S targets. In *Sc*, two repressors, Whi5 and Nrm1, were previously shown to regulate SBF and MBF transcription, respectively (de Bruin, et al. 2006, de Bruin, et al. 2004). Whi5 was shown to bind and repress SBF activity in G1 and transcription is activated by G1-cyclin/CDK phosphorylation of Whi5, which shuttles it out of the nucleus (Costanzo, et al. 2004, de Bruin, et al. 2004). Upon S phase entry SBF-dependent transcription is inactivated via Clb/CDK phosphorylation of Swi4, which disrupts promoter binding. MBF-dependent transcription is inactivated by Nrm1 via an auto-regulatory negative feedback loop that is present in both *Sc* and *S. pombe* (de Bruin, et al. 2006). Nrm1, a G1/S target itself, is a co-repressor that accumulates upon S phase entry and binds MBF to repress transcription. Nrm1/Whi5 homologues are also identified in *C. albicans* and have been shown to complement the *whi5*- and *nrm1*-deletion in Sc (Ofir, et al. 2012). However, functional analysis indicated that the *Ca*Nrm1 is more similar to *Sc*Whi5 due to its direct binding to *Ca*Swi4 (Ofir, et al. 2012). In addition, the

intracellular localization of *Ca*Nrm1 oscillates through the cell cycle similar to *Sc*Whi5. Additional studies have revealed the functional importance of SBF in *C. albicans* by examining the phenotypes of *mbp1*- and *swi4*-deletion strains. This study showed that while *swi4*-deletion leads to significant phenotypic defects *mbp1*-deletion had mild phenotypic defects (Hussein, et al. 2011). Overall, these studies highlight the importance of SBF complex in *C. albicans* and highlight the plasticity of G1/S regulation within Hemiascomycetes.

MBF and SBF specificity

The functional overlap between MBF and SBF complexes in *Sc* as well as the small differences in sequence of the MCB and SCB motifs (Bean, et al. 2005) highlight the difficulty in understanding the promoter specificity of these complexes. Whilst all yeast species contain MCB motifs in their genome it is unclear whether *Sc* MBF is more similar to the ancestral TF complex. Our findings that the SBF regulon in *Sc* contains a subset of targets containing MCB-like sequences and that chimeric TFs containing distantly related DBDs bind MCB-like motifs in *Sc* (**Figure 1**) suggest that SBF is more closely related to the ancestral TF complex and that MCB-like sequences are likely the ancestral MCB/SCB motifs (RCB). Examination of SBF binding to different promoters in *Sc* using ChIP revealed that the binding affinity of *Sc* SBF to SCB motifs is much higher than to RCB motifs (Hendler, et al. 2017) showing that the *Sc* SBF must co-evolved with the SCB to enable high binding affinity.

Previous biochemical studies, examining the binding of Mbp1 and Swi4 DBDs to oligonucleotide duplexes containing one copy of MCB and SCB sequences, showed similar binding affinities of Mbp1 and Swi4 for both sequences (Taylor, et al. 2000). These results suggest that the highly conserved core *CGCG* recognition sequence found in yeast and mammalian cells and is present in both MCB and SCB motifs contributes significantly to DBDs binding affinity. This motif is probably an essential prerequisite for MBF and SBF binding but is not sufficient for achieving MBF and SBF specificity in yeast. Thus, other factors may contribute to specificity in the context of the yeast chromosomes. In addition, natural evolutionary changes in the DBDs protein sequence and promoter sequence may significantly influence MBF and SBF binding specificity in different organisms. It is possible that the accumulated effects of natural mutations in

non-conserved residues of Mbp1 and Swi4 DBDs can affect promoter-binding specificity, however, these changes are very difficult to identify. Previous biochemical studies using protein Nuclear Magnetic Resonance (NMR) allowed the identification of residues in Mbp1 and Swi4 DBDs that change their conformation upon DNA binding (Taylor, et al. 2000). This study showed that the majority of residues that participate in DNA binding are conserved between Mbp1 and Swi4 DBDs except for K60 in Mbp1 where aspartic acid occupies the equivalent position in Swi4. Such residues can contribute to the degree of affinity for MBF and SBF with specific DNA binding sequences. Additional residues that affect binding specificity can be identified by structural and sequence alignment analysis. The recently solved structure of the DBD of PCG2, the orthologue of Mbp1 from *Magnaporthe oryzae*, bound to MCB can shed new light on DNA binding specificity (Liu, et al. 2015). Sequence and structural analysis of PCG2-DNA complex allowed us to identify two residues, T21 and Y85, located near the PCG2 binding pocket that are conserved in most Fungi but change to lysine and phenylalanine, respectively, in the ancestor of *S. cerevisiae* and *K. lactis* (**Figure 3**). To examine whether these residues might affect the specificity of Mbp1, we inserted the Y85F and T21K mutations into Mbp1 DBD orthologues and examined the function of the mutated chimeric TFs in *Sc*. Unfortunately, we found that these mutations do not affect the chimeric TF function in *Sc* (data not shown) suggesting that changes in specificity may be dictated by the contribution of multiple and yet unidentified residues in the Mbp1/Swi4 DBDs.

Previous structural and biochemical studies focused on DBDs binding analysis with small stretches of DNA sequences (Taylor, et al. 2000). However, binding affinity *in vivo* is likely to depend on extended sequences around the binding motif and local chromatin structure. In the context of the chromatin, binding specificity may be dictated by a much larger stretches of DNA sequences, the chromatin structure and the chromosomal location. It is possible that promoters containing MCB/SCB motifs are optimal for MBF/SBF binding at the native chromosomal location and changes in promoter location will result in alteration of binding specificity. In addition, chromatin environment might also dictate the role of SBF as a transcriptional activator and MBF as a transcriptional repressor. With recent advancement in CRISPR/CAS9 technologies in *Sc* (DiCarlo, et al.

2013, Ryan, et al. 2014, Si, et al. 2017), we can now more easily switch SBF and MBF promoters to examine the role of local chromatin in MBF/SBF binding and function.

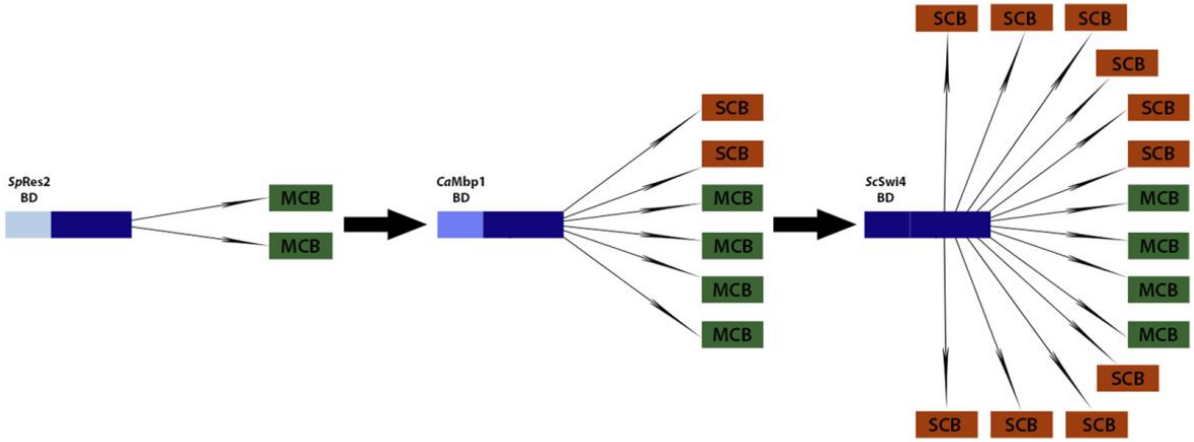

Figure 1: Schematic representation of genome wide transcription analysis in *Sc* of chimeric Swi4 TFs containing orthologs DBDs from different fungal species (Hendler, et al. 2017). The chimeric TF containing orthologue DBD from *S. pombe* (Res2) leads to the expression of ~11% of SBF-dependent target genes while in *Sc* chimeric TF containing Mbp1 DBD from *C. albicans* leads to the expression of ~%40 of SBF-dependent target genes. These subsets of genes are enriched with motifs that are more closely related to MCB consistent with a Res-like ancestor found in *S. pombe*. The expression of a smaller subset of genes, in some chimeric TFs, leads to phenotypic defects including slow growth rate and morphological abnormalities (Hendler, et al. 2017). A small number of genes containing MCB or SCB motifs that are expressed in *Sc* by the chimeric TF are shown for illustration.

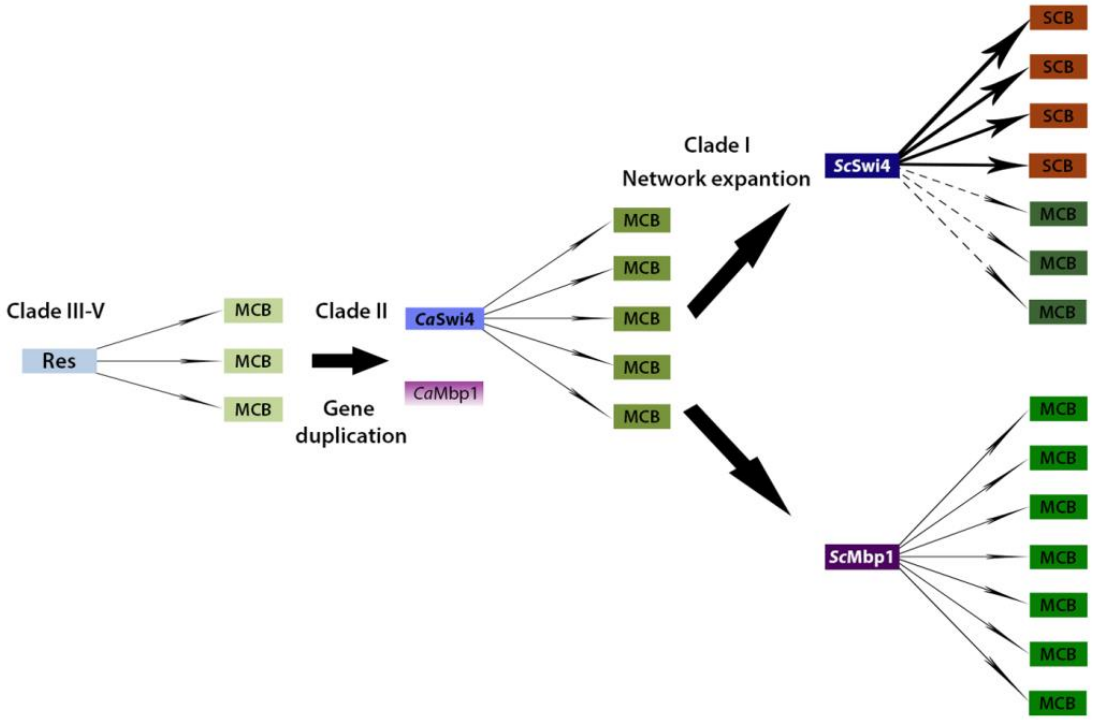

Figure 2: The evolution of Swi4 and Mbp1 in different fungi species. Res TFs (light blue) from clades III-V promote the expression of a smaller set of genes containing MCB motif, relative to *Sc* G1/S targets (Rustici, et al. 2004). Swi4 (blue) in *C. albicans* was shown to mediate the expression of G1/S genes containing MCB motif in their promoter while Mbp1 (pink) was shown to be non-functional (Hussein, et al. 2011). In clade I both Swi4 (dark blue) and Mbp1 (purple) are functional mediating the expression of genes containing SCB and MCB, respectively, in their promoter. Analysis of Swi4/Mbp1 chimeric TFs in *Sc* (Hendler, et al. 2017) indicates that the Swi4 regulon contains both SCB and MCB motifs where the SCB motifs are optimized for binding to Swi4 (bold arrows).

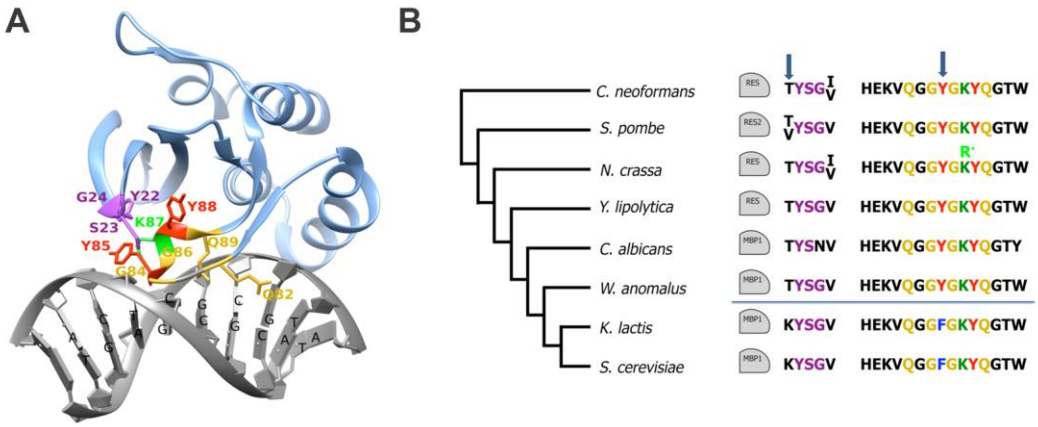

Figure 3: Structure and sequence analysis of PCG2 (Res) binding domain from the rice blast fungus (*Magnaporthe oryzae*) relative to Mbp1 orthologues in hemiascomycetes for the identification of functional residues that may affect DNA binding specificity. (**A**) Structural analysis of PCG2 bound to an MCB DNA binding motif (Liu, et al. 2015) highlights key residues that are in direct contact or located in the close vicinity of the PCG2 DNA binding site (PDB:4UX5). (**B**) Sequence alignment of Mbp1 and Res from different fungal species focusing on key residues in PCG2 (highlighted in **A**). This analysis identifies two residues, T21 and Y85, which differ between *Sc* and *K. lactis* Mbp1 belonging to clade 1 and more distantly related fungal species. These residues could affect the co-evolution of Mbp1-DNA interactions. T21 and Y85 are highlighted by blue arrows.

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