

A systems approach to delineate functions of paralogous transcription factors: Role of the Yap family in DNA damage response

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Abstract

Duplication of genes encoding transcription factors plays an essential role in driving phenotypic variation. One of the best examples of gene duplication in *S. cerevisiae* is the Yap (Yeast AP-1) family of transcription factors, which has a total of eight members. The Yap family belongs to the bZIP superfamily of TFs that is widely-conserved from yeast to human. Functionally, the Yap family is involved in a variety of stress-related programs, including the response to DNA damage as well as oxidative, osmotic, and toxic metal stresses. In all stress types, they have been shown to carry out overlapping but distinct biological functions. With regard to DNA damage, as many as four Yaps (1, 4, 5, 6) have been implicated in the cellular response to methyl methanesulfonate (MMS, a DNA alkylating agent) and cis-diamminedichloroplatinum (CDDP, a DNA crosslinking agent). Although these studies have established the strong role of the Yap family in the stress response, a systematic examination of the different family members with regard to transcriptional regulation has not yet been conducted.

Because regulation can occur at multiple levels, it is often difficult to discern how each duplicated factor achieves its regulatory specificity. In these cases, a “systems approach” may distinguish the role of each factor by integrating complementary large-scale measurements of the regulatory network. To explore such an approach, we performed a series of systematic measurements to characterize the Yap transcriptional network in response to DNA damage,

including a genome-wide screen to identify Yap family members involved in the cellular response to MMS or CDDP, genome-wide promoter binding profiles, and mRNA expression patterns.

Integration of these data revealed that YAP regulatory specificity is achieved by at least three mechanisms: (a) Divergence of DNA-binding sequences into two subfamilies, one describing Yaps 4/6 and one describing Yaps 1/2/5, with motifs of the first group having an additional base pair in the spacer region (Fig. 1); (b) Condition-specific combinatorial regulation by multiple Yap factors. As illustrated in Fig. 2, the pair Yap1/Yap2 co-associates in response to both types of damage, the pair Yap2/Yap6 co-associates predominantly in MMS damage, and the pair Yap4/Yap5 co-associates only in nominal conditions; and (c) Interactions of Yap 1, 4, and 6 with chromatin remodeling proteins. The model further highlights differences among Yap paralogs in terms of regulatory mode (activation vs. repression) and strength on target gene expression.

Figure 1. DNA binding motifs of five Yaps and their phylogeny. Core regions of the motifs are highlighted by a box. IC, information content in bits. Numbers at each branch point are percentages of trees having the observed branching pattern using 500 sets of randomized data. The unrelated transcription factor Gcn4 was used as the outgroup to root the tree.

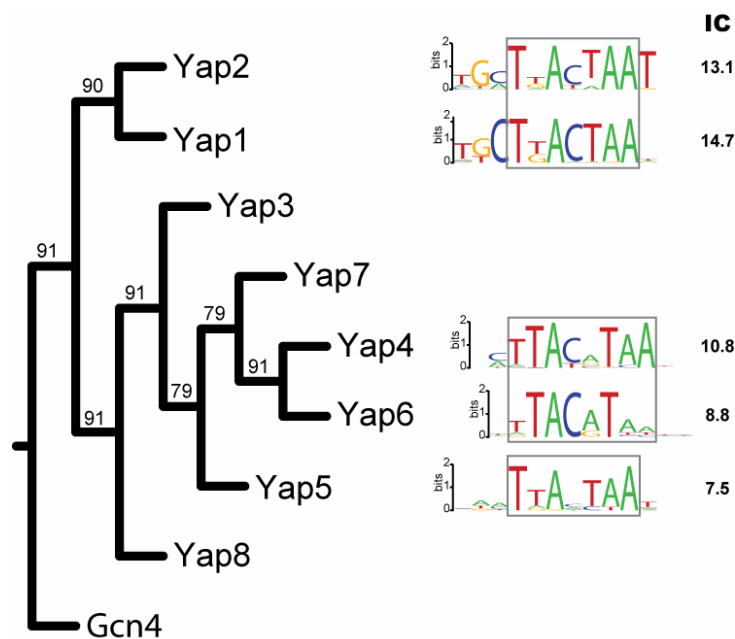


Figure 2. Significant overlaps between Yap target gene sets. Significance threshold $P < 0.001$. Line width is proportional to $-\log P$. **A.** MMS treatment. **B.** CDDP treatment. **C.** Nominal growth conditions. **D.** Enriched functional categories of genes co-regulated by pairs of Yaps. Blue, MMS response; orange, CDDP response, green, nominal growth condition.

