The Ga4p family of yeast zinc cluster proteins comprises regulators of multidrug resistance genes. For example, Pdr1p and Pdr3p bind as homo- or heterodimers to pleiotropic drug response elements (PDREs) found in promoters of target genes. Other zinc cluster activators of multidrug resistance genes include Stb5p and Yrr1p. To better understand the interplay among these activators, we have performed native co-immunoprecipitation experiments using strains expressing tagged zinc cluster proteins from their natural chromosomal locations. Interestingly, Stb5p is found predominantly as a Pdr1p heterodimer and shows little homodimerization. No interactions of Stb5p with Pdr3p or Yrr1p could be detected in our assays. In contrast to Stb5p, Yrr1p is only detected as a homodimer. Similar results were obtained using glutathione S-transferase pull-down assays. Importantly, the purified DNA binding domains of Stb5p and Pdr1p bound to a PDRE as heterodimers in vitro. These results suggest that the DNA binding domains of Pdr1p and Stb5p are sufficient for heterodimerization. Our data demonstrate a complex interplay among these activators and suggest that Pdr1p is a master drug regulator involved in recruiting other zinc cluster proteins to fine tune the regulation of multidrug resistance genes.

Toxic compounds such as drugs are used to treat many diseases by killing the harmful target cells, which can be either foreign pathogenic organisms or the tumor cells of the patients. However, both prokaryotic and eukaryotic cells can acquire the ability to become resistant to toxic compounds through the phenomenon of multidrug or pleiotropic drug resistance (PDR).1 Saccharomyces cerevisiae can also acquire PDR, making it a valuable tool in the study of this phenomenon so that we may gain insights into the mechanisms behind PDR in pathogenic fungi and in higher eukaryotes.

Cells that have acquired PDR have consistently shown higher levels of expression of drug efflux pumps (reviewed in Refs. 1 and 2). These pumps fall within two protein families: ATP-binding cassette (ABC) transporters and major facilitator superfamily (MFS) transporters. Their increased expression allows expulsion of drugs from within the cell and, as a result, survival in the presence of these drugs. These higher levels of expression are often due to mutations in the transcription factors that regulate the expression of these pumps.

A complex network of various transcription factors is involved in the regulation of the expression of genes encoding ABC or MFS proteins. There are two major families of transcription factors involved in PDR: 1) the bZip protein family (Yap family), and 2) zinc cluster proteins. Yap1p is the best characterized member of the bZip family and is an important regulator in the stress response (3–5). Yap1p regulates the expression of YCF1, which encodes an ABC transporter (6). The other class of transcription factors involved in PDR is composed of a subclass of zinc finger proteins, the zinc cluster or binuclear zinc cluster proteins (7–10). These proteins contain a DNA binding domain (DBD), which possesses the well-conserved motif Cys-X2-Cys-Xp-Cys-Xn,16-Cys-Xn,2-Cys-Xn,9-Cys, with cysteines binding to two zinc atoms, coordinating folding of the domain involved in DNA recognition (11). Two highly homologous zinc cluster proteins, Pdr1p and Pdr3p, positively control the expression of genes involved in multidrug resistance (1, 2, 12). Target genes of Pdr1p and Pdr3p include the ABC transporters genes PDR5, SNQ2, and YOR1 (13–16). Other targets include HXT9 and HXT11, which encode hexose transporters belonging to the MFS family (17). Another zinc cluster protein, Yrr1p, regulates the expression of SNQ2 and YOR1 (18–20).

In addition to these three zinc cluster proteins, Stb5p and Rdr1p have been recently implicated in the regulation of expression of PDR5 and/or SNQ2 (8, 21). Pleiotropic drug response elements (PDREs) present in the promoters of genes encoding ABC transporters, as well as in the PDR3 promoter have been shown to be important in the regulation of these genes. Pdr1p, Pdr3p, Stb5p, and Rdr1p all act through this element, with Pdr1p, Pdr3p, and Stb5p able to bind to an everted repeat CCGCGG (8, 14, 15, 22–25). Characterization of PDREs in the PDR3 promoter indicates that autoregulation can occur at this gene (22).

Even though they act through the same element, all these zinc cluster proteins may perform different functions. Pdr1p and Pdr3p have recently been shown to be able to form homo- and heterodimers (26). Different combinations of homo- and heterodimers may regulate the expression of different genes, which might help explain how these two proteins act differently. We were interested in determining if Stb5p acts by itself or if it regulates gene expression in concert with other zinc cluster proteins involved in PDR. We show that Stb5p interacts predominantly with Pdr1p (but not Pdr3p or Yrr1p) in vitro and that Yrr1p forms homodimers.
Experimental Procedures

Strains—Wild-type strains used were BY4741, MATa his3Δ1 leu2Δ0 met15Δ0 ura3Δ0, and BY4742, MATa his3Δ1 leu2Δ0 lys2Δ0 ura3Δ0 (27). Strains for the TRFIP assay were isogenic with BY4742 and the PCR products generated with the following oligos using pXMyc and pXHA as templates (28). Oligos were obtained from AlphaDNA (Montréal) and purified on a denaturing polyacrylamide gel. PDR1, PDR3, STB5, and YRR1 were PCR amplified with the PCR products digested with BglII and subcloned into the BamHI site of pHis-Pdr1-(152) (24). Half of the GST proteins attached to glutathione Sepharose beads were mixed with the yeast lysates and left overnight at 4°C. The beads were washed with IP-1 buffer, and the proteins were suspended by adding 50 μl of 1× Laemmli buffer and boiling. The proteins were resolved on 7.5% SDS-polyacrylamide gels, and analyzed by immunoblotting with the HA antibody (12Ca5, Roche Applied Science).

In Vivo Co-immunoprecipitation Assays—Diploid strains described above were grown in YPD to an OD600 of ~1 in a volume of 200 ml. Proteins were isolated as described above and incubated for 2 h with 4 μg of Myc antibody (9E10, Upstate Technologies). Then 20 μl of a 50% protein G-Sepharose slurry were added to the lysates and incubated overnight at 4°C. The samples were washed five times with the IP-1 buffer, and then the proteins were dissociated from the beads by boiling the sample for 5 min in 1× Laemmli buffer. The samples were run on a 7.5% SDS-polyacrylamide gel and analyzed by immunoblotting with a HA antibody (12Ca5, Roche Applied Science).

Results

Pdr1p and Pdr3p activate transcription through PDRs by forming homo- and heterodimers (28). Since STB5 also activates transcription by binding to PDRs (8), we tested if it could dimerize with either Pdr1p, Pdr3p, Yrr1p, or itself using co-immunoprecipitation assays. Triple Myc or HA epitopes were inserted into chromosomal DNA at the loci encoding these proteins and at the DAL81 and UGA3 loci. Uga3p, another member of the family of zinc cluster proteins, activates expression of genes involved in γ-aminobutyrate (GABA) catabolism by binding to promoters of target genes (31, 32) while the zinc cluster protein Dal81p is a general activator of nitrogen regulated genes (33, 34). Tagged Uga3p and Dal81p were used as negative controls since they do not play any role in conferring drug resistance and, as a result, they should not interact with STB5, Pdr1p, Pdr3p, or Yrr1p. All tagged proteins were fully functional since the haploid strains expressing these tagged proteins had a wild-type phenotype when tested on drugs for PDR1, PDR3, STB5, and YRR1 and when assayed with the reporter UGA1-lacZ (31) for UGA3 and DAL81 (data not shown). Since the tagged proteins are expressed from their natural promoters, levels of these proteins should not differ from those normally present in wild-type cells.

We assayed the relative expression of tagged Pdr1p, STB5, YRR1p, and PDR3p. Diploid strains expressing tagged proteins of interest were grown in rich medium (YPD) to mid-log phase, and extracts were used for immunoprecipitation followed by Western blot analysis using an anti-Myc antibody (Fig. 1). Tagged proteins were detected at positions expected from their predicted molecular weight. STB5p, YRR1p, and PDR3p were expressed at somewhat similar levels while PDR1p was expressed at much higher levels (Fig. 1) as observed by Ghaemmighami et al. (35) who showed that Pdr1p is expressed at higher levels than STB5p and PDR3p. Multiple forms of PDR3p were detected in agreement with another study that showed that the bands correspond to non- and phosphorylated forms of the protein (26). Similarly, multiple forms of PDR1p were detected. However, we have not yet differentiated the various forms of PDR1p that are expressed at higher levels than STB5p and PDR3p. The expression of tagged proteins of interest was confirmed by western blotting with an anti-Myc antibody (Fig. 1, lane 1). Diploid strains expressing Myc-STB5p along with various HA-tagged zinc cluster proteins were used for co-immunoprecipitation with an anti-Myc antibody followed by Western blot analysis using an anti-HA antibody. A strong signal was obtained when Myc-PDR3p co-immunoprecipitated with HA-STB5p (Fig. 2, top panel, lane 5) while there was no signal for HA-YRR1p or HA-
Moreover, no signal was detected in the absence of tagged Pdr1p (Fig. 2, top panel, lanes 1–3). Control experiments showed that HA-tagged Uga3p, Stb5p, and Yrr1p were detected when immunoprecipitated with an anti-HA antibody (Fig. 2, bottom panel, lanes 1–6). In summary, our results strongly suggest that Stb5p specifically interacts with Pdr1p in vivo.

To ensure that Stb5p does interact with Pdr1p and to test if it can form homodimers, we performed additional experiments where Myc-tagged zinc cluster proteins were used for immunoprecipitation. As shown previously, a strong signal was observed when Myc-Pdr1p was used for co-immunoprecipitation with HA-Stb5p (Fig. 3A, top panel, lane 6). To test the formation of a Stb5p homodimer, we performed co-immunoprecipitation experiments with Myc-Stb5p and HA-Stb5p. Only a small fraction of Stb5p could be detected as a homodimer (Fig. 3A, top panel, compare lanes 5 and 6). No interaction between Stb5p and the PDR regulator Pdr3p could be detected in this assay (Fig. 3A, top panel, lane 4). In addition, Dal81p, a zinc cluster protein not involved in PDR (33, 34), did not interact with Stb5p (Fig. 3A, top panel, lane 3). Control experiments showed that all Myc-tagged proteins tested above could be detected.
when immunoprecipitated and immunoblotted with an anti-Myc antibody (Fig. 3A, bottom panel, lanes 1–6). In summary, our co-immunoprecipitation experiments strongly suggest that Stb5p does not efficiently homodimerize and is predominantly found as a heterodimer with Pdr1p in vivo.

To test if the DBD of Pdr1p is sufficient for interaction with Stb5p, in vitro GST pull-down assays were performed. As a negative control, we used the zinc cluster protein Gal4p that is involved in galactose metabolism and unrelated to PDR (36). The DBDs of Pdr1p and Gal4p fused to GST were expressed in bacteria, purified, and bound to glutathione-Sepharose beads. A protein extract was prepared from a haploid yeast strain expressing HA-Stb5p and added to the GST fusion proteins bound to beads. After washing, bound proteins were dissociated by boiling, run on a gel and visualized by immunoblotting. GST-Pdr1p interacted with HA-Stb5p while GST-Gal4p did not (Fig. 3B). The results from these GST pull-down assays are in agreement with the co-immunoprecipitation experiments and suggest that the DBD of Pdr1p (amino acids 1–152) is sufficient for dimerization with Stb5p.

Since Yrr1p is also involved in PDR, we were interested in determining if it could interact with itself as well as with other PDR activators such as Pdr1p, Pdr3p, and Stb5p. Co-immunoprecipitation experiments similar to those described above were performed with Myc- and HA-tagged Yrr1p. Results show that Yrr1p forms homodimers in vivo (Fig. 4A, top panel, lane 6). No interaction of Yrr1p with Dal81p, Pdr3p, and Stb5p was detected in this assay (Fig. 4A, top panel, lanes 3–5). Control experiments showed that Myc-tagged Yrr1p, Dal81p, Pdr3p, and Stb5p were detected when immunoprecipitated and immunoblotted with an anti-Myc antibody (Fig. 4A, bottom panel, lanes 2–5). Results were confirmed using a GST pull-down assay (Fig. 4B). HA-Yrr1p was pulled down with GST-Yrr1p but not GST-Gal4p. Thus, the GST pull-down assay with Yrr1p is also in agreement with the co-immunoprecipitation experiment, as observed with Stb5p.

We also wished to determine if the interaction of Stb5p with Pdr1p seen in vivo could be observed in vitro using purified components in an EMSA. We used the approach of Hope and Struhl (37) that relies on proteins with different electrophoretic mobilities in order to detect an intermediate complex corresponding to a heterodimer. Various polypeptides encoding the DBDs of Stb5p and Pdr1p showed similar mobilities as tested in EMSA (data not shown). To circumvent this problem, a fusion of the DBD of Pdr1p with 6 histidines and a triple HA epitope (His-HA-Pdr1p) was expressed in E. coli and purified on a nickel column. Similarly, GST-Stb5p was expressed in E. coli, purified and the GST moiety removed by thrombin cleavage. Binding in vitro of the purified proteins was assayed by EMSA using a probe corresponding to the PDRE number 1 found in the SNQ2 promoter (see “Experimental Procedures”). With the DBD of Stb5p alone, two major retarded complexes of fast mobility were observed (Fig. 5, lanes 2–5). With the DBD of Pdr1p alone, a retarded complex was observed only at high protein concentration (Fig. 3, lanes 6–9). Smearing suggests that the DNA-Pdr1p complex dissociated during electrophoresis. Interestingly, a complex of intermediate mobility was observed when mixing the DBDs of Pdr1p and Stb5p, strongly suggesting the formation of a heterodimer (Fig. 5, lanes 10–13). These results suggest that the DBDs of Stb5p and Pdr1p bind in vitro as a heterodimer to a target DNA sequence.

**DISCUSSION**

At least four zinc cluster proteins activate transcription of multidrug resistance genes. Initially, it was shown that the expression of these genes was activated by Pdr1p, Pdr3p, and Yrr1p through the PDREs found in their promoters (1, 12, 18, 20). Recently, Stb5p has been identified as an additional transcriptional activator of multidrug resistance genes (8). Stb5p activates transcription by binding to PDREs, the same elements found to be critical for Pdr1p and Pdr3p activity. It has been shown that Pdr1p and Pdr3p homo- and heterodimerize (26). Since Stb5p and Yrr1p have similar roles and act through the same elements as Pdr1p and Pdr3p, we tested the ability of these four proteins to dimerize with each other. Interestingly, Stb5p dimerizes with Pdr1p while Yrr1p forms homodimers. The interactions among these various transcriptional activators are summarized in Fig. 6.

Using native co-immunoprecipitation experiments, we determined that Stb5p was found predominantly as a heterodimer with Pdr1p (Figs. 2A and 3A). Only a small fraction of Stb5p was found as a homodimer and no Stb5p-Pdr3p or Stb5p-Yrr1p heterodimers were detected in our assay. The Stb5p-Pdr1p interaction was also observed when a GST-Pdr1p(DBD) fusion

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**Fig. 4. Yrr1p interacts with itself in vivo and in a GST pull-down assay.** A, top panel, strains expressing various tagged proteins (as indicated by + on the top of the figure) were used to prepare extracts for immunoprecipitation (IP) with an anti-Myc antibody. Immunoprecipitated proteins were then detected by Western blot analysis with an anti-HA antibody. Bottom panel, same as above except that Western blot analysis was performed with an anti-Myc antibody. B, extract was prepared from a strain expressing HA-Yrr1p and incubated with GST fusion proteins (as indicated at the bottom) for pull-down assay. After washing, bound proteins were eluted and analyzed by Western blot with an anti-HA antibody.
Formation of heterodimeric complexes by zinc cluster proteins may therefore be a more predominant mechanism for regulation of gene expression than initially anticipated. Regulation of a relatively simple pathway, such as the one triggered by galactose, is efficiently performed by Gal4p homodimers, while more complex processes, like PDR, must require various combinations of homo- and heterodimers to integrate different signals allowing for precise expression of target genes. Taken together, the data suggest that Pdr1p is a master PDR regulator involved in recruiting other zinc cluster proteins to fine-tune the regulation of multidrug resistance genes. This is reminiscent of the mammalian nuclear receptor RXR, which forms heterodimers with the receptors for 9-cis retinoic acid, thyroid hormone, and vitamin D, as well as peroxisome proliferator activators to differentially regulate expression of target genes (41).

An EMSA showed that the purified DBDs of Pdr1p and Stb5p bound as a heterodimer to a PDER 

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in vitro

Fig. 5. The DBDs of Pdr1p and Stb5p bind in vitro to a PDER as heterodimers. The purified DBD of Stb5p (1–163) and the DBD of Pdr1p (amino acids 1–152) fused to His6 and a triple HA epitope (see “Experimental Procedures”) were used in an EMSA with a probe corresponding to PDER 1 of SNQ2 (see “Experimental Procedures”). Lane 1, probe alone; lanes 2–5, EMSA performed with increasing amounts (0.5, 1, 2, and 4 μl) of the DBD of Stb5p; lanes 6–9, EMSA performed with increasing amounts (0.5, 1, 2, and 4 μl) of the Pdr1p fusion protein; lanes 10–13, same as lanes 6–9 except that 1 μl of the DBD of Stb5p was added in each lane. Arrows on the right part of the figure indicate positions of the various complexes. The Stb5p-DNA complex is assumed to be a monomer.

Fig. 6. Summary of interactions among zinc cluster proteins Pdr1p, Pdr3p, Stb5p, and Yrr1p. Arrows indicate zinc cluster protein interactions identified in this report and by Mamnun et al. (26). A weak Stb5p-Stb5p interaction was also detected (see “Results”).

Many zinc cluster proteins (Gal4p, Leu3p, Hap1p, Ppr1p, Put3p, etc.) initially characterized in Saccharomyces cerevisiae were shown to bind to DNA as homodimers (7, 9, 10). More recently, Oaf1p and Oaf2p (Pip2p) were shown to bind as heterodimers to target sequences of genes for peroxisome proliferation (38, 39). Moreover, Uga3p, the activator of GABA-responsive genes, interacts in vitro with the zinc cluster protein Dal81p.2 The zinc cluster protein ArgRIIp heterodimerizes with members of the MADS family to activate genes for arginine metabolism (40). Our results combined with those of Mamnun et al. (26) demonstrate that Pdr1p can dimerize with itself, Pdr3p and Stb5p. In addition, we have previously shown that another zinc cluster protein, Rdr1p, represses the expression of some PDR genes such as PDR5 and PDR16 (21). We also demonstrated that the repressive effect of Rdr1p is mediated by PDERs. Interestingly, Rdr1p interacts in vivo with both Pdr1p and Pdr3p.3

2 M.-A. Sylvain and B. Turcotte, unpublished results.

3 S. MacPherson and B. Turcotte, unpublished results.

4 B. Turcotte, unpublished results.
Pdr3p expression (52). Moreover, activity of Yrr1p is negatively regulated by overexpression of the zinc cluster protein Yrm1p (53). The observation that zinc cluster proteins form various combinations of dimers will be invaluable in better understanding the complex regulation of PDR genes.

In conclusion, we have shown that the four zinc cluster protein activators of multidrug resistance genes do not act individually. Instead, they form various populations of homo- and heterodimers (Fig. 6). There may be differences in the binding specificity or activity of each of these populations, allowing for a very specific and varied expression of genes involved in PDR. Pdr1p was the only protein able to show multiple interactions indicating that it is similar to mammalian nuclear receptor RXR in its ability to recruit various partners. With at least four different zinc cluster proteins regulating the expression of PDR genes via different PDREs, the cellular ability to respond to drugs is much more adaptable and flexible.

These discoveries present many more questions regarding PDR. For example, would various environmental signals cause a shift in the balance of the various populations of homo- and heterodimers? Is the hyperactivity of the Pdr1p and Pdr3p mutants caused by a change in the activity of the protein or to a change in the partner of the protein? Are other regulators of drug resistance, such as members of the Yajp1 family, able to dimerize with these zinc cluster proteins?

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