A Dominant Allele of PDR1 Alters Transition Metal Resistance in Yeast*

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A yeast mutant was found to have defective growth on low iron medium despite a normal high affinity iron transport system. The phenotype results from a gain of function mutation in PDR1, which encodes a transcription factor that acts as a regulator of pleiotropic drug resistance. The mutation in the PDR1 allele, PDR1(R821H), was found to result in increased expression of at least 19 genes, three of which are ATP-binding cassette (ABC) transporters. Expression of at least six genes was required to show the low iron growth defect. Wild type cells transformed with the PDR1(R821H) allele or a PDR1 dominant allele (PDR1–3) showed the low iron growth defect as well as increased resistance to drugs such as cycloheximide and oligomycin. Transformation of PDR1(R821H) into Δccc1 cells, which were previously shown to have increased sensitivity to high iron medium because of defective vacuolar iron storage (Li, L., Chen, O. S., Ward, D. M., and Kaplan, J. (2001) J. Biol. Chem. 276, 29515–29519), conferred resistance to high iron medium. Cells expressing PDR1(R821H) also showed increased resistance to copper and manganese because of increased metal export. These results suggest that expression of PDR1-regulated genes affects both efflux and storage of transition metals.

Investigations of the budding yeast Saccharomyces cerevisiae have provided many insights into general principles of eukaryotic transition metal metabolism (for review see Ref. 1). Analyses of yeast mutants that show defective growth under iron-limited conditions have shown that growth on low iron medium requires a functioning high affinity iron transport system (2, 3). The structural components of the high affinity transport system are the products of the FET3 and FTR1 genes, which are induced in response to iron deprivation by the iron-sensing transcription factor AHR1 (4). Fet3p mediates iron transport by acting as a ferroxidase, converting ferrous iron to ferric iron, which is then transported by the permease Ftr1p (5). Many mutants have been found to be unable to grow on low iron as a consequence of defects in genes that encode components of the high affinity iron transport system or in genes required for assembly of the system (6).

Other mutants have been found to be unable to grow on low iron media, despite having a functional high affinity iron uptake system. The gene for one such mutant was identified to encode a methyl sterol oxidase, Erg25p, an oxo-diiron containing enzyme that catalyzes an oxygen-dependent step in ergosterol biosynthesis (2). The gene was cloned because the erg25 mutant enzyme has a low affinity for iron. When cellular iron levels were low, the mutant enzyme lost activity resulting in sterol deficiency.

Because little is known regarding intracellular iron metabolism, we have pursued the identification of genes that lead to defective intracellular iron metabolism. In this article we describe a mutant that is unable to grow on low iron media despite normal high affinity iron uptake. We show that the mutation is a gain of function allele of the transcription factor PDR1, which regulates a diverse set of genes, many of which are multidrug resistance genes. We suggest that expression of this dominant allele results in transition metal efflux and storage.

MATERIALS AND METHODS

Strains and Media—The S. cerevisiae strains used in this study were derived from DY150 and DY1457 of the W303 background. MS55 is a mutant derived from DY150 that was isolated in a screen that selected for resistance to streptomycin (3). The mutant was backcrossed twice to ensure that the phenotypes were caused by a single gene. The Δccc1 strain was made as previously described (7). A library of strains with deletions of each of the nonessential genes in homozygous diploid (BY4743) backgrounds was purchased from Research Genetics.

Luziria-Bertani medium was used to propagate Escherichia coli strain DH5α. The strain was supplemented with antibiotics as required (8). Yeast extract-peptone-dextrose (YPD) and yeast nitrogen-base synthetic complete media (CM) were used for the standard growth of S. cerevisiae and were supplemented as needed (9). Cycloheximide containing medium was prepared by adding 0.7 μg/ml cycloheximide to standard growth media (10). Oligomycin containing medium was prepared by adding 0.7 μg/ml oligomycin to yeast extract-peptone-glycerol ethanol (YPGE) (11). Low iron growth medium was made by adding 40 μM bithiophenanthrolinium disulfonate (BPS), an iron chelator, to standard growth medium and then adding back varying amounts of FeCl3 (3). Synthetic low iron medium (LIM), supplemented with varying amounts of FeCl3 and CuSO4, was used to limit both iron and copper (12). The various LIM and BPS media used in this work are referred to as LIM(x) and BPS(x), where x equals the concentration in micromol of added FeCl3. High metal growth media was made by adding the indicated amount of Fe(NO3)3·9H2O, ZnSO4, MnCl2, CoCl2, or CuSO4 to standard CM.

The Δpdr1 strains were generated by double fusion polymerase chain reaction (13). The primers were: 5′-GGTTGACTGCCAGAATTTCAG-3′, 5′-CATAGTACGCCGAAACGAACACCG-3′, 5′-
TCCTGTGAAATTGTTACCTCGGTACGATCCGCTGGACAGGGACGT-3', and 5'-GACTGACAGGATTGTCG-3'. The HIS3 gene was used as the selectable marker. The PCR fusion products were transformed into DY150 and MS35 cells, and the deletion of the PDR1 gene was confirmed by PCR.

Iron Transport Assay—Cells in early exponential phase were grown in either CM or CMBPS(0) for 6–8 h. The cells were washed and iron transport was assayed as previously described (3), with the following modifications. To measure iron uptake, 5 x 10^6 cells were mixed with 1 mM ascorbate and 0.5 μM 59Fe, supplied as 59FeCl3. Cells were incubated at 30 °C for 10 min, placed on filters (Whatman GF/C), and washed with EDTA containing buffer to remove unincorporated iron. The filters were air dried and associated radioactivity was determined. The uptake activity is expressed as femtomole of 59Fe uptake per minute per 10^6 cells.

Assays to measure iron retention were done as described previously (14). Briefly, cells growing exponentially in CMBPS(0) were harvested and incubated in LIM-EDTA (i.e. LIM prepared without EDTA) (12) with 0.5 μM 59Fe at 30 °C for 10 min. Then, 1 mM BPS was added to aliquots of cells to chelate the free 59Fe. The cells were then incubated for up to 5 h. Associated radioactivity was measured at various time points throughout the 5-h incubation.

Microarray Analysis—RNA was isolated from DY150 and MS35 in early exponential phase grown in YPD. Total RNA was isolated using standard techniques (15). Purification of mRNA was done using the Promega PolyATtract mRNA isolation system. Fabrication of DNA microarrays, synthesis of fluorescent-labeled cDNA, hybridization to the microarrays, and subsequent scanning were performed at the Huntsman Cancer Institute Microarray Core Facility.

Northern Analysis—Total RNA was isolated and analyzed using standard techniques (15). All samples were isolated from mid-log phase cultures grown in either CM or CMBPS(0). A 5'-32P-labeled PDR2 probe was generated using random primers and a PDR5 (YOR135W) open reading frame template from the Research Genetics open reading frame/H9262 database. The MS35 strain did show a lower rate of uptake, but this decrease is not expected to result in a growth defect, as we have previously observed that much more substantial reductions (>90%) in high affinity iron transport activity are required to show a phenotype of poor growth on low iron media (22). Thus, increased levels of Fet3p and Ftr1p are synthesized in response to low iron in MS35.

An inability to grow on low iron can also result from defective copper loading of apoFet3p (20). As apoFet3p is copper-loaded in a post-Golgi intracellular compartment, defects in either copper homeostasis or vesicular traffic result in the appearance of apoFet3p on the cell surface. Cell surface apoFet3p can be copper-loaded by addition of high copper and chloride, restoring iron transport (6, 21). Consequently, mutations in genes re-
required for the assembly of Fet3p can be identified through suppression of the low iron growth defect by growth in high copper media in the presence of chloride. MS35 showed poor growth in iron-deficient media that was not suppressed by adding copper and chloride (Fig. 1B). Taken together, these results show that the defect in MS35 is not because of a mutation in the assembly or function of the high affinity iron transport system. Thus, the inability to grow on low iron must be caused by a defect in intracellular iron metabolism.

With the exception of the dominant allele AFT1<sup>up</sup>, all other known mutations in iron transport have been found to be recessive. A diploid from a cross between MS35 and wild type cells, however, showed that the inability to grow on low iron media was semidominant (Fig. 1C). As growth of the heterozygote on low iron media was greater than that of a homozygous mutant diploid but less than that of a wild type diploid. Sporulation of the heterozygote showed a 2:2 segregation pattern for the low iron phenotype (data not shown), indicating that this phenotype is because of a defect in a single gene.

**Mutant MS35 Shows Increased Multidrug Resistance**—We performed a transcript analysis of mRNA isolated from mutant and wild type cells grown in YPD using microarrays. Results from two independent experiments demonstrated that MS35 cells showed increased transcription of at least 19 genes (Table I). Some of these genes are notable as belonging to the ATP-binding cassette (ABC) protein transporter family (23). This transcription pattern is similar to that of the transcription factor PDR1, which regulates a large family of ATP transporters (24). These ATP-driven membrane transporters are homologous to the mammalian multidrug resistance proteins and confer resistance to a variety of structurally and functionally unrelated agents (23). For two of the up-regulated genes, PDR5 (pleiotropic drug resistance) and ICT1 (increased copper tolerance), we verified increased expression in mutant cells using Northern analysis (Fig. 2A), and showed that increased expression of these genes was seen in both high and low iron media. We note that Northern analysis suggests a much greater induction of these genes than microarray. Consistent with their multidrug-resistant transcriptional expression pattern, MS35 cells showed a marked resistance to both cycloheximide and oligomycin, two drugs that are unrelated in structure and function (Fig. 2B).

Similar to the low iron phenotype, increased drug resistance was semidominant in a heterozygotic diploid of MS35 and wild type yeast (Fig. 2C). Sporulation of 15 heterozygotic diploids showed a 2:2 cosegregation of cycloheximide resistance with the phenotype of poor growth on low iron, suggesting that both phenotypes are because of mutations in a single gene.

**The Low Iron Phenotype of MS35 Is Caused by a Mutation in PDR1**—Transcription of ABC genes is primarily controlled by two homologous transcription factors, Pdr1p (25) and Pdr3p (26, 27), which belong to a large family of zinc finger-containing transcription factors (28). Pdr1p and Pdr3p have an overlapping pattern of regulation in that they control many of the same genes (27). Semidominant gain of function point mutations in PDR1 and PDR3 have been characterized in yeast that, like MS35, are resistant to abnormally high concentrations of various drugs (29). In these mutants, as in MS35, levels of Pdr1p- and Pdr3p-regulated ABC genes are increased at least 2-fold (24).

Several experiments indicated that MS35 has a gain of function mutation in Pdr1p. First, expression of PDR1 or PDR3 from a high copy plasmid partially suppressed the low iron growth defect although the cycloheximide resistance phenotype was less affected (Fig. 3A), consistent with studies showing that expression of the normal allele reduces the phenotype of PDR gain of function alleles (10, 30). Second, deletion of PDR1 in MS35 confers growth on low iron medium and abrogates cycloheximide and oligomycin resistance (Fig. 3B).

Third, transformation of wild type cells with a genomic library derived from MS35 cells and cloned into single copy plasmids resulted in the identification of plasmids that conferred both cycloheximide resistance and the low iron growth phenotype. Sequence analysis of the genes encoded on two of...
the plasmids revealed a PDR1 gene with a mutation that resulted in the substitution of histidine for arginine at amino acid position 821 (referred to henceforth as PDR1(R821H)).

That PDR1(R821H) is mutated in the same region as other gain of function mutations (28) suggests that the mutation in MS35 is a gain of function allele of PDR1. Further support was provided when transformation of the gain of function allele PDR1–3 also conferred cycloheximide resistance and a low iron defect to wild type cells (Fig. 3C). Finally, transformation of PDR1(R821H) into wild type cells leads to a reduction in high affinity iron transport (Fig. 3D).

The PDR1(R821H) Allele Causes a Decrease in Cytosolic Iron—Whereas we hypothesized that the decrease in iron transport activity in MS35 cells or in cells transformed with PDR1(R821H) was not great enough to lead to the observed low iron growth defect, we devised a genetic experiment to test this hypothesis. If PDR1(R821H) causes a low iron growth defect by affecting iron uptake, we would not expect the growth defect to occur in cells with a deletion in a component of the high affinity iron transport system. Cells containing a deletion in FET3 and transformed with a PDR1(R821H) containing plasmid were found to have a decided growth disadvantage when plated on low iron medium (Fig. 4A). This result suggests that the low iron growth defect is independent of iron uptake activity.

We considered the possibility that the low iron growth defect results from export or sequestration of cytosolic iron through genetic manipulation of CCC1, which encodes a transporter that affects the transport of iron from cytosol to vacuole (7). Deletion of CCC1 produces sensitivity to high medium iron concentrations because of an inability to sequester excess iron in the vacuole. Transformation of PDR1(R821H) into Δccc1 cells suppressed this high iron sensitivity (Fig. 4B), suggesting that PDR1(R821H) affects iron efflux from the cell, sequestration of iron into cellular compartments, or a combination of these two effects.

We attempted to measure iron efflux through the use of 59Fe pulse-chase experiments. Neither wild type cells nor MS35...
cells, when incubated with $^{59}$Fe for 10 min, showed loss of radioactivity over a subsequent 5-h period (data not shown). These experiments were performed after cells had been incubated in low iron medium for 6 h, and under such conditions, it may not be possible to easily observe iron efflux because of low intracellular iron pools and/or the possible rapidity of the efflux process. We therefore examined the effect of PDR1 (R821H) on cells incubated in high iron medium. Initially, we measured the total cellular iron content in wild type and Δccl1 cells transformed with PDR1 (R821H) or a control vector. We observed that, when incubated in high iron medium, either wild type cells (Fig. 5A) or Δccl1 cells (Fig. 5B) transformed with PDR1 (R821H) had higher levels of iron than cells transformed with only the vector. Interestingly, we observed that in low iron medium the reverse was true: wild type or Δccl1 cells transformed with PDR1 (R821H) had less iron than vector-transformed cells. As mentioned previously, the sensitivity of Δccl1 cells to high iron is thought to be because of cytosolic iron accumulation. If PDR1 (R821H)-transformed Δccl1 cells have more total cellular iron but are less iron sensitive, then we might expect that the increased iron is not in the cytosol. In fact, vacuoles isolated from PDR1 (R821H) Δccl1 cells were found to have a higher iron content than vacuoles isolated from vector-transformed Δccl1 cells (Fig. 5C). This result suggests that the PDR1 (R821H) allele leads to increased iron storage.

Expression of at Least Six Genes Is Required for the Low Iron Phenotype—As determined by microarray analysis, the effect of the PDR1 (R821H) allele is to increase transcription of at least 20 different genes. To address which of these genes is responsible for the low iron phenotype, we took advantage of the collection of homozygous diploid deletion strains purchased from Research Genetics. This collection consists of 4,600 yeast strains, each of which has a targeted deletion in a specific gene. We transformed PDR1-3 or PDR1 (R821H) into strains carrying a single deletion in 15 of the genes that were identified as overexpressed by microarray analysis. The strains that were not tested were not included in the deletion collection. Transformation of either of these PDR1 alleles into wild type diploids (BY4743) reproduced the mutant phenotype of reduced growth on low iron medium and increased cycloheximide resistance (Fig. 6A). A Δpdr5 strain transformed with PDR1 (R821H) was cycloheximide-sensitive but still showed decreased growth on low iron medium (Fig. 6B). This result confirmed previous studies indicating that Pdr5p is responsible for cycloheximide resistance (31), and showed that Pdr5p is not involved in the low iron phenotype conferred by PDR1 (R821H).

We found that deletion of any of six of the top 19 genes shown to be up-regulated by microarray analysis resulted in the loss of the low iron growth defect while still retaining cycloheximide resistance. An example of the phenotype of transformed deletions and their phenotypes is given in Fig. 6C and the names or designations of the relevant genes are listed in Table II. These results suggested that all six genes must be overexpressed for the low iron phenotype, as loss of...
any of the six was sufficient to complement expression of PDR1(R821H).

PDR1(R821H) Confers Resistance to Copper and Manganese but Increased Sensitivity to Cobalt—The observation that PDR1(R821H) can protect cells from high iron toxicity led us to examine whether this allele provides protection from toxicity of other transition metals. Wild type diploid (BY4743) or diploid strains homozygous for deletions in specific genes were transformed with a control plasmid, PDR1-3, or PDR1(R821H) on a high copy plasmid. Serial dilutions of the transformed cells were plated on low iron and cycloheximide containing plates. A, wild type diploid results are shown. B, deletion of PDR5 leads to loss of multidrug resistance but has no affect on the low iron growth phenotype. C, deletion of YOR1 does not affect multidrug resistance but does result in the loss of the low iron growth defect.

**Table II**

| Genes required for low iron sensitivity | Genes required for copper resistance |
|----------------------------------------|--------------------------------------|
| YOR1                                  | ICT1                                 |
| SNQ 2                                 | SNQ2                                 |
| TPO1                                  | YLR346C                              |
| CTP1                                  | YCR061W                              |
| YGR095C                               | YKL071W                              |
| YMR102C                               | PDR5                                 |

The increased resistance to Cu$^{2+}$ was associated with decreased accumulation of Cu$^{2+}$ as measured by atomic absorption spectroscopy (Fig. 7B). We did not observe a statistically significant difference in Mn$^{2+}$ content between vector-transformed and PDR1(R821H)-transformed cells (Fig. 7C).

We took advantage of the homozygous deletion collection to ask whether the same genes that were responsible for iron sensitivity were responsible for copper resistance. As shown in Fig. 8 at least five genes are required to show the copper phenotype. These genes, however, are different from those that lead to the iron sensitivity (Table II). Thus, transition metal response because of PDR1(R821H) is a multigenic trait.
Most previously characterized yeast mutants unable to grow in low iron are because of either defects in iron transport or mutations in iron-requiring proteins. Invariably, these mutants are recessive. MS35 is extraordinary in that it is semidominant, has a low iron growth defect, and yet has no defect in the assembly of the iron transport system. Identification of the mutant gene in MS35 revealed that it is a gain of function allele of PDR1, a transcription factor that regulates genes involved in multidrug resistance. The mutated amino acid in PDR1(R821H) is near the mutation in the gain of function PDR1–3 allele, which has a phenylalanine to serine substitution at position 815 (28). The mechanism of the PDR1(R821H) and PDR1–3 gain of function mutations is unclear, as the altered amino acids lie neither in the inhibitory domain nor in the activation domain of Pdr1p (32). It has been postulated that this region, when mutated, could affect binding of the “major inhibitory effector.”

We discovered that overexpression of PDR1-regulated genes results in a decrease in cytosolic iron, as shown by reduced growth of PDR1(R821H) expressing cells in low iron medium and increased survival of PDR1(R821H) transformed Δccc1 cells in high iron medium. Whereas there is a decrease in the activity of the high affinity iron transport system in PDR1(R821H) expressing cells, the decreased low iron growth is not because of a defect in iron transport. This point is suggested by the fact that PDR1(R821H) expressing cells that lack a component of the high affinity iron transport system (Δfet3Δ) are more sensitive to low iron than Δfet3 cells transformed with a control vector. Whereas we were not able to directly demonstrate increased iron efflux caused by PDR1(R821H), we did find that expression of PDR1(R821H) led to increased resistance to high iron medium in Δccc1 cells. We observed that, whereas expression of PDR1(R821H) led to decreased cellular iron when either wild type or Δccc1 cells were grown in low iron medium, there was an increase in cellular iron when the same cells were grown in high iron medium. This observation suggests that there is a difference in the mechanism(s) leading to low iron growth sensitivity and high iron resistance conferred by PDR1(R821H). As high iron conditions down-regulate most of the known iron transporters, PDR1(R821H) is unlikely to affect changes in iron uptake. Rather, we observed that vacuoles from PDR1(R821H)-transformed cells have higher levels of iron than those from vector-transformed cells. As CCC1 encodes the major, if not the only, vacuolar iron transporter, PDR1(R821H) expression must lead to an increase in vacuolar iron accumulation.

These results suggest that PDR1 targets, depending on iron concentration, may affect both iron efflux and sequestration. The hypothesis that both efflux and sequestration occur is strengthened by the identification of the genes that are required to produce the low iron phenotype (see Table II). Some of the known genes encode ABC transporters present on the vacuole (TP01) or plasma membrane (YOR1 and SNQ2). There is some limited data on the role of multidrug resistance genes in transition metal metabolism. A double deletion of SNQ2 and PDR1 were shown to effect Mn2+ and Ni2+ resistance (33), as wild type cells were shown to export Mn2+ at a greater rate than Δsnq2Δpdr1 cells. It was not clear, however, whether the loss of these genes directly affected Mn2+ efflux or whether this effect was a downstream consequence of the gene deletions. It is known that many transporters that recognize Mn2+ also recognize Fe2+, suggesting that Snq2p could also modulate iron export (7). However, the formal possibility remains that expression of Snq2p somehow modulates plasma membrane permeability rather than mediating active transport of metal ions.

Expression of the PDR1(R821H) allele resulted in an increase in transcription of at least 19 different genes. We took advantage of a homozygous deletion collection to determine which of those genes were involved in transition metal metabolism by transforming the PDR1(R821H) allele into strains that have a deletion in a single gene and examining their phenotype on low iron and on cycloheximide containing medium. We observed that deletion of a single gene, PDR5, abrogated cycloheximide resistance but did not eliminate the low iron phenotype. This result confirms previous studies that show that PDR5 is responsible for cycloheximide resistance. In contrast, we discovered that at least six genes were required for the low iron phenotype. That multiple genes are required to fully express a multidrug resistance phenotype is not unprecedented (for review see Ref. 23). It is of interest that whereas both Snq2p and Pdr5p were shown to be required for resistance to Mn2+ and Li+, we observed that deletion of PDR5 did not affect the low iron growth phenotype (33).

We further demonstrated that PDR1(R821H) provided resistance to copper and manganese but rendered cells more sensitive to cobalt. The increased cobalt sensitivity may result from the affect on cytosolic iron on the allele of the PDR1(R821H). A recent study demonstrated that reduced cytosolic iron levels lead to increased cobalt sensitivity, whereas increased cytosolic iron protected against cobalt toxicity (34). The finding that expression of PDR1(R821H) results in low cytosol iron is consistent with the expectation that such cells might be cobalt-sensitive. Expression of PDR1(R821H) also led to increased resistance to copper and manganese. Measurement of cellular copper indicates that resistance is because of lowered cellular levels. Interestingly, the genes required for resistance to copper with one exception (SNQ2) are different from those required for the iron sensitivity. In both cases simultaneous expression of multiple genes are required to develop the phenotype. Our biochemical experiments suggest that copper resistance may be because of metal export. The high level of media copper should result in the down-regulation of copper transporters, suggesting that decreased cellular copper may be because of increased copper efflux. Experiments are currently in progress to determine whether the same genes
that are required for copper resistance are also required to rescue Δαcc1 cells from high iron.

REFERENCES
1. Eide, D. J. (2000) Adv. Microb. Physiol. 43, 1–38
2. Askwith, C., and Kaplan, J. (1998) Trends Biochem. Sci. 23, 135–138
3. Askwith, C., Eide, D., Van Ho, A., Bernard, P. S., Li, L., Davis-Kaplan, S., Sipe, D. M., and Kaplan, J. (1994) Cell 76, 403–410
4. Yamaguchi-Iwai, Y., Dancis, A., and Klausner, R. D. (1995) EMBO J. 14, 1231–1239
5. Stearman, R., Yuan, D. S., Yamaguchi-Iwai, Y., Klausner, R. D., and Dancis, A. (1996) Science 271, 1552–1557
6. Radisky, D. C., Snyder, W. B., Emr, S. D., and Kaplan, J. (1997) Proc. Natl. Acad. Sci. U. S. A. 94, 5662–5666
7. Li, L., Chen, O. S., Ward, D. M., and Kaplan, J. (2001) J. Biol. Chem. 276, 29515–29519
8. Miller, J. (1972) Experiments in Molecular Genetics, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY
9. Sherman, F., Fink, G. R., and Lawrence, C. W. (1989) Methods in Yeast Genetics, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY
10. Meyers, S., Schauer, W., Balzi, E., Wagner, M., Goffeau, A., and Gelin, J. (1992) Curr. Genet. 21, 431–436
11. Katzmann, D. J., Burnett, P. E., Golin, J., Mahe, Y., and Moyle-Rowley, W. S. (1994) Mol. Cell. Biol. 14, 4653–4661
12. Eide, D., and Guarente, L. (1992) J. Gen. Microbiol. 138, 347–354
13. Amberg, D. C., Botstein, D., and Beasley, E. M. (1995) Yeast 11, 1275–1280
14. Eide, D., Davis-Kaplan, S., Jordan, I., Sipe, D., and Kaplan, J. (1992) J. Biol. Chem. 267, 20774–20781
15. Ausubel, F. M. (1995) Current Protocols in Molecular Biology, Wiley, New York
16. Sambrook, J., Fritisch, E. F., and Maniatis, T. (1989) Molecular Cloning: A Laboratory Manual, 2nd Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY
17. Dower, W. J., Miller, J. F., and Ragsdale, C. W. (1988) Nucleic Acids Res. 16, 6127–6145
18. Calvin, N. M., and Hanawalt, P. C. (1988) J. Bacteriol. 170, 2796–2801
19. Li, L., and Kaplan, J. (1998) J. Biol. Chem. 273, 22181–22187
20. Yuan, D. S., Stearman, R., Dancis, A., Dunn, T., Beeler, T., and Klausner, R. D. (1995) Proc. Natl. Acad. Sci. U. S. A. 92, 2632–2636
21. Davis-Kaplan, S. R., Askwith, C. C., Bengtzen, A. C., Radisky, D., and Kaplan, J. (1998) Proc. Natl. Acad. Sci. U. S. A. 95, 13641–13645
22. Askwith, C. C., and Kaplan, J. (1998) J. Biol. Chem. 273, 22415–22419
23. Bayer, R. E., Woller, H., and Kuchler, K. (1999) Biochim. Biophys. Acta 1461, 217–236
24. DeMayo, J., van den Hazel, B., Balzi, E., Brown, P., Jacq, C., and Goffeau, A. (1997) Gene 186, 16871–16879
25. Balzi, E., Chen, W., Ulaszewski, S., Capieux, E., and Goffeau, A. (1986) J. Biol. Chem. 261, 29515–29519
26. Delaveau, T., Delahodde, A., Carvajal, E., Subik, J., and Jacq, C. (1994) Mol. Gen. Genet. 244, 501–511
27. Carvajal, E., van den Hazel, H. B., Cybulski-Kolaczkowska, A., Balzi, E., and Goffeau, A. (1997) Mol. Gen. Genet. 256, 496–415
28. Nourani, A., Papajova, D., Delahodde, A., Jacq, C., and Subik, J. (1997) Mol. Gen. Genet. 256, 397–405
29. Mahe, Y., Neuvrilli, A., Lampschwell, A., Lamprecht, A., and Kuchler, K. (1996) Mol. Microbiol. 20, 199–217
30. Leppert, G., McDevitt, R., Fial, S. C., Van Dyk, T. K., Ficke, M. B., and Golin, J. (1990) Genetics 125, 13–20
31. Kolaczkowska, A., Kolaczkowski, M., Delahodde, A., and Goffeau, A. (2002) Mol. Genet. Genomics 267, 96–106
32. Miyahara, K., Mizunuma, M., Hirata, D., Tsujiya, E., and Miyakawa, T. (1996) FEBS Lett. 399, 317–320
33. Starkey, J. A., Schaye, R. J. (2002) J. Biol. Chem. 277, 39649–39654
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