DNA Polymerase III from *Saccharomyces cerevisiae*

II. INHIBITOR STUDIES AND COMPARISON WITH DNA POLYMERASES I AND II

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The newly identified yeast DNA polymerase III was compared to DNA polymerases I and II and the mitochondrial DNA polymerase. Inhibition by aphidicolin (I00) of DNA polymerases I, II, and III was 4, 6, and 0.8 μg/ml, respectively. The mitochondrial enzyme was insensitive to the drug. N2-(p-n-butylphenyl)-2'-deoxyguanosine 5'-triphosphate strongly inhibited DNA polymerase I (I50 = 0.3 μM), whereas DNA polymerase III was less sensitive (I50 = 80 μM). Conditions that allowed proteolysis to proceed during the preparation of extracts converted DNA polymerase II from a sensitive form (I50 = 2.4 μM) to a resistant form (I50 = 2 mm). The mitochondrial DNA polymerase is insensitive (I50 > 5 mm). With most other inhibitors tested (N-ethylmaleimide, heparin, salt) only small differences were observed between the three nuclear DNA polymerases.

Polyclonal antibodies to DNA polymerase III did not inhibit DNA polymerases I and II, nor were those polymerases recognized by Western blotting. Monoclonal antibodies to DNA polymerase I did not cross-react with DNA polymerases II and III.

The results show that DNA polymerase III is distinct from DNA polymerases I and II.

The rigorous prevention of proteolysis during yeast cell breakage in combination with the resolving power of high pressure liquid chromatography (HPLC) has allowed us to identify and purify a novel DNA polymerase activity from log phase cells of *Saccharomyces cerevisiae* (1). DNA polymerase III has an associated 3'-5' exonuclease activity, exonuclease III, with the capacity for proofreading during *in vivo* DNA replication. The biochemical properties of DNA polymerase III do not indicate a specific role for this enzyme during DNA replication or DNA repair. The interaction of DNA polymerase III with a second exonuclease, exonuclease IV, however, is suggestive of a role for this enzyme during the maturation of Okazaki fragments (1).

Recent experiments with the cloned DNA polymerase I gene have shown that this enzyme is required during the S-phase of the yeast cell (2, 3). DNA polymerase I has an associated DNA primase activity, encoded by a separate gene, but no associated 3'-5' exonuclease activity (4-7). In contrast, DNA polymerase II does have a proofreading exonuclease activity (5, 6). The enzyme has not been studied in detail. Its failure to elongate DNA primers in *vitro* argues against its involvement in Okazaki fragment synthesis in *vitro*, but no other role has been assigned to this enzyme (5, 6).

The most curious observation made during analytical and preparative HPLC separations of extracts prepared under varying conditions was that the major DNA polymerase activity consisted of either DNA polymerase I or DNA polymerase III (1). Two extreme examples are given in Fig. 1. Because these results indicated that DNA polymerase I and DNA polymerase III might be two different forms of the same enzyme, we carried out inhibitor and immune studies to compare both enzymes with each other and with the minor nuclear DNA polymerase II, as well as the mitochondrial enzyme. These studies are presented in this paper.

**MATERIALS AND METHODS**

DNA substrates and general DNA polymerase and exonuclease assays are as described (1). The regular DNA polymerase assay used activated calf thymus DNA as a substrate; the regular exonuclease assay used 3'-labeled single-stranded calf thymus DNA as a substrate (1). Monoclonal antibodies to yeast DNA polymerase I were a gift from Dr. L. M. S. Chang (Uniformed Health Services University) (8). These monoclonals were generated against the native DNA polymerase I, containing predominantly the 140-kDa polypeptide and its proteolytic 110-kDa fragment (7, 8). None of these antibodies inhibit enzyme activity directly, but their affinity for DNA polymerase I was measured by precipitation with secondary antibodies (8). The monoclonal antibodies do not bind to the denatured enzyme and they fail to give a signal on Western blots. Monoclonal antibody y-48 was used by Flevani et al. (25) to immunopurify the DNA polymerase I-primase complex. Of the six independent monoclonal antibodies provided, y-9, y-66, y-98, y-34, y-48, and y-60, the last three bound most strongly to our preparation of DNA polymerase I, whereas the first three were less active. A mixture of equal volumes of y-34 (IgG1), y-48 (IgG2b), and y-60 (IgG1) was used for enzyme binding studies. N2-(p-n-butylphenyl)-2'-deoxyguanosine-5'-triphosphate (BuPhdGTP) and N2-(p-n-butylphenyl)-2'-deoxyadenosine-3'-triphosphate (BuPhdATP) were generously provided by Dr. George Wright (University of Massachusetts Medical School). Aphidicolin was prepared from the culture supernatant of *Cephalosporium aphidicola* as described (9). All other chemicals were from Sigma.

The abbreviations used are: HPLC, high pressure liquid chromatography; BuPhdGTP, N2-(p-n-butylphenyl)-2'-deoxyguanosine-5'-triphosphate; BuPhdATP, N2-(p-n-butylphenyl)-2'-deoxyadenosine-3'-triphosphate.

* This work was supported in part by Public Health Service Grant GM 32451 from the National Institutes of Health, by Award 33086 from the Mallinckrodt Foundation, by Award 83-A-405 from the Chicago Community Trust/Searle Scholars Program (to P. M. J. Burgers) and by a National Research Service Award S-T32-GM-07067 from the National Institutes of Health (to G. A. Bauer).

2 Established Investigator of the American Heart Association (860129).

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* Dr. L. M. S. Chang, personal communication.
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DNA polymerase III (Fraction Vla) was purified for most studies. Fraction IV was generally used for immunological studies (1). Mitochondrial DNA polymerase was partially purified through DEAE-cellulose chromatography as described (10). Measurements of specific activities and comparison with literature values from Refs. 5, 8, and 10 for DNA polymerases I, II, and the mitochondrial enzyme, respectively, showed that these enzymes were pure for about 3, 10, and 5%, respectively. They were, however, not cross-contaminated.

Immunological Techniques—Rabbit anti-DNA polymerase III or control serum was incubated with enzyme (30 units) with buffer IPB added to adjust the total volume to 50 μl. After 2 h at 0 °C, 50 μl of protein A-agarose beads (Sigma; 4.2 mg of extracellular protein A/ml of gel; resuspended in buffer IPB and washed with volumes of IPB) were added and, after agitation at 0 °C for 1 h, the beads were spun down and 10–20 μl of the supernatant used for an assay. Inhibition by anti-DNA polymerase III serum was measured as percent activity of that with control serum. The control serum did not inhibit the activity of any of the four DNA polymerases. In fact, addition of large amounts of control serum slightly (10–20%) stimulated enzyme activity.

Culture supernatants to mouse myeloma cell lines secreting monoclonal antibodies to DNA polymerase I (a mixture of γ-34, γ-48, and γ-60, each at about 5 μg/ml) or control supernatants were incubated with enzyme (30 units) with buffer IPB added to adjust the total volume to 50 μl. After 2 h at 0 °C, carrier mouse IgG (75 ng) was added, followed by excess rabbit anti-mouse IgG (1 μg). After another 1 h at 0 °C, the samples were spun for 15 min in a microcentrifuge and 5–10 μl of the supernatant was used for an activity assay. Inhibition of the monoclonal antibodies was measured as percent activity of that with control supernatant. The control supernatant did not inhibit nor stimulate enzyme activity.

RESULTS

Inhibition by Aphidicolin—Both the polymerase and exonuclease activities of the DNA polymerase III-exonuclease III complex were strongly inhibited by the tetracyclic diterpenoid aphidicolin (for a review see Ref. 11). Inhibition of the exonuclease activity by aphidicolin was dependent upon the substrate concentration. At 1.5 μg/ml of single-stranded DNA, the apparent Ki exonuclease activity was inhibited for 50% at 50 μg/ml of aphidicolin. At a saturating DNA concentration of 8 μg/ml, 50% inhibition was at 10 μg/ml of aphidicolin (Fig. 2). Similarly, inhibition of the polymerase activity was most potent at saturating template DNA concentrations. Plevani et al. (12) have observed a similar template dependent inhibitory effect for yeast DNA polymerases I and II. For comparative purposes inhibition of DNA polymerases I and II were measured under identical conditions. Both were about an order of magnitude less sensitive to aphidicolin. The mitochondrial enzyme was insensitive to the drug (Fig. 2, Table I).

Inhibition of BuPhdGTP and BuPhdATP—BuPhdGTP is a potent inhibitor of the mammalian DNA polymerase α (13). Much higher concentrations of this dGTP analog are required to inhibit DNA polymerase β (14). DNA polymerases β and γ are insensitive (13). Yeast DNA polymerase I was very sensitive to BuPhdGTP. Under the assay conditions used, 50% inhibition was observed at 0.3 μM BuPhdGTP. In contrast, DNA polymerase III was only weakly inhibited by BuPhdGTP with Ib2 = 80 μM (Fig. 3A, Table I). To ensure that the low sensitivity of DNA polymerase III to BuPhdGTP was not due to some kind of inactivation of the inhibitor (e.g. hydrolysis),

![Figure 1](image1.png)

**Fig. 1.** DEAE-silica gel HPLC chromatograms of extracts of wild-type cells, prepared without protease inhibitors (A) and of protease-deficient cells prepared with protease inhibitors (B). Data taken from Ref. 1, Fig. 1.

![Figure 2](image2.png)

**Fig. 2.** Inhibition by aphidicolin. The regular DNA polymerase assay was used, except that the dCTP concentration was lowered to 8 μg/ml.

| Table I | Comparison of the yeast DNA polymerases |
|---------|----------------------------------------|
|         | Polymerase | I | II | III |
| dNTPs (Km, μM) |                   | 4.6 | 5.2 | 7.1 |
| Mg2+ (Ib2, mM) |                   | 24 | 39 | 16 |
| KCl (Ib2, M)  |                   | 0.13 | 0.20 | 0.12 | 0.31 |
| BuPhdGTP (Ib2, μM) |                   | 0.3 | 2.4 | 80 | >5000' |
| BuPhdATP (Ib2, μM) |                   | 1.2 | 6 | 250 | >5000' |
| N-ethylmaleimide (Ib2) |                   | >5000' |
| Aphidicolin (Ib2, μg/ml) |                   | 4 | 6 | 0.6 | >1000' |
| Heparin (Ib2, μg/ml) |                   | 1.2 | 1.8 | 1.3 | 300 |

* See Ref. 1 for method of determination.

a In comparison to the optimum Mg2+ concentration.

b KCl or heparin was added to the regular DNA polymerase assay.

c BuPhdGTP was lowered to 10 μM in the regular assay.

d Estimated from extrapolation of the curves (see Figs. 2 and 3).

e BuPhdATP was lowered to 10 μM.

f Complete assays minus dithiothreitol and template DNA were incubated with N-ethylmaleimide (1 mM) for various times at 0 °C. Dithiothreitol and activated calf thymus DNA were then added to 10 μM and 150 μg/ml, respectively, and, after another 5 min at 0 °C, the reactions were incubated at 37 °C for 30 min.

h dCTP was lowered to 10 μM in the regular assay.
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Inhibitors of Yeast DNA Polymerase III—The $K_a$ values for dNTPs were measured for the four yeast polymerases (Table I). No large differences were observed that could be used to differentiate between the yeast DNA polymerases. The $K_a$ value for DNA polymerase I (4.6 $\mu$m/nucleotide) is in agreement with those determined by Badaracco et al. (7) (0.66, 1.0, 1.7, and 1.9 $\mu$m for dGTP, dATP, dTTP, and dCTP, respectively) if one takes into consideration that the apparent $K_a$ value for a single dNTP with the other three dNTPs at saturation is several fold lower than when all four dNTP concentrations are subsaturating (15).

Other inhibitors than aphidicolin or BuPhdGTP were less informative about the yeast DNA polymerases. Thus, rates of inactivation by N-ethylmaleimide of the three nuclear DNA polymerases were almost identical, whereas the mitochondrial enzyme was much more sensitive. Similarly, inhibition by heparin served to distinguish the mitochondrial enzyme from the three nuclear enzymes but did not differentiate among these (Table I). Salt ($K^+$) inhibition paralleled Mg$^{2+}$ inhibition (Fig. 3B, Table I). Similar results were obtained with the dATP analog BuPhdATP (Table I). Except for the inhibition by these inhibitors, DNA polymerase Ila (sensitive) and DNA polymerase Iib (insensitive) were identical within experimental error with regard to all other criteria. This includes sensitivity to aphidicolin (7 $\mu$m for Ila, 6 $\mu$m for Iib), N-ethylmaleimide ($t_{50} = 3.1$ min for Ila, 2.4 min for Iib), salt ($I_{50} = 0.20 M$ KCl for Ila and Iib), high levels of Mg$^{2+}$ ($I_{50} = 38$ mM for Ila, 40 mM for Iib), and heparin ($I_{50} = 2.0 \mu g/ml$ for Ila, 1.5 $\mu g/ml$ for Iib). Furthermore, the apparent $K_a$ values for dNTPs were virtually identical (5.5 $\mu$m for Ila, 4.9 $\mu$m for Iib). In addition, neither enzyme Ila nor enzyme Iib were inhibited by antibodies to DNA polymerase I or III (see below). The average values of enzymes Ila and Iib for all inhibitors except BuPhdGTP and BuPhdATP are given in Table I. Both enzyme Ila and Iib consistently eluted as sharp peaks at identical salt concentrations from an analytical DEAE-silica gel column (Fig. 1).

Further Characterization of Yeast DNA Polymerases—The $K_a$ values for dNTPs were measured for the four yeast polymerases (Table I). No large differences were observed that could be used to differentiate between the yeast DNA polymerases. The $K_a$ value for DNA polymerase I (4.6 $\mu$m/nucleotide) is in agreement with those determined by Badaracco et al. (7) (0.66, 1.0, 1.7, and 1.9 $\mu$m for dGTP, dATP, dTTP, and dCTP, respectively) if one takes into consideration that the apparent $K_a$ value for a single dNTP with the other three dNTPs at saturation is several fold lower than when all four dNTP concentrations are subsaturating (15).

Other inhibitors than aphidicolin or BuPhdGTP were less informative about the yeast DNA polymerases. Thus, rates of inactivation by N-ethylmaleimide of the three nuclear DNA polymerases were almost identical, whereas the mitochondrial enzyme was much more sensitive. Similarly, inhibition by heparin served to distinguish the mitochondrial enzyme from the three nuclear enzymes but did not differentiate among these (Table I). Salt ($K^+$) inhibition paralleled Mg$^{2+}$ inhibition with DNA polymerases I and III as the most sensitive enzymes, followed by enzyme I. The mitochondrial enzyme is most active at 60 mM Mg$^{2+}$ and much higher concentrations were needed to inhibit this enzyme by 50% (Table I, 10).

Antigenic Determinants of the Nuclear DNA Polymerases—More than the use of inhibitors antibodies should be useful in defining and distinguishing the three nuclear DNA polymerases. A mixture of three monoclonal antibodies to DNA polymerase I (see "Materials and Methods") was tested for binding to the other two enzymes. Neither enzyme II, nor enzyme III, were inhibited by these antibodies (Fig. 4).

The polyclonal serum to DNA polymerase III inhibited both DNA polymerase III and exonuclease III activities to the same extent (Fig. 5; data not shown for exonuclease III). DNA polymerases I and II were refractory to this antiserum (Fig. 5). In addition, Western blots with the polyclonal serum of fractions from a DEAE-HPLC separation of the three nuclear DNA polymerases showed prominent bands in the DNA polymerase III region (Fig. 6, lane 1). No cross-reactive bands, except a 70-kDa band, were seen in the DNA polymerase I and II regions (lanes 2 and 3). This band is due to a 70-kDa polymerase-unrelated polypeptide which streaks across the entire gradient and is also present in fractions that do not contain any DNA polymerase activity. The 70-kDa protein is probably one of a family of heat shock proteins because the same band is also visualized with antibodies to the major

Fig. 3. Inhibition by BuPhdGTP. The regular DNA polymerase assay was used, except that the dGTP concentration was lowered to 10 $\mu$m. A, inhibition of DNA polymerase I ( , 6 units), DNA polymerase III ( , 6 units), or DNA polymerase I plus III ( , 3 units each). The dotted curve (- - - -) was calculated from the separate DNA polymerase I and III curves assuming no interaction between the two enzymes or inactivation of BuPhdGTP. B, inhibition of mitochondrial DNA polymerase (DNA polymerase Ila ( , isolated from a protease-deficient strain), and DNA polymerase Iib ( , isolated from wild-type cells).

a mixing experiment was carried out. Equal units of DNA polymerase I and III were measured together in BuPhdGTP inhibition studies. The experimental points virtually coincided with the calculated data points indicating that no inactivation of the inhibitor occurred (Fig. 3A). Inhibition of DNA polymerases I and III by BuPhdGTP was also independent of the source of the enzyme (i.e., from wild-type or protease-deficient yeast), or the degree of purity of the enzyme, this is in contrast to DNA polymerase II (see below). The mitochondrial DNA polymerase was insensitive to the action of BuPhdGTP (Fig. 3B).

Inhibition of DNA polymerase II by BuPhdGTP was more complex and depended on the source of this enzyme. DNA polymerase II partially purified from a protease-deficient strain (PEP4) in the presence of protease inhibitors showed a biphasic response to BuPhdGTP with 60–80% of the enzyme being very sensitive to the inhibitor and 20–40% relatively insensitive (five independent extracts and DEAE-HPLC separations). A similar biphasic response was observed with DNA polymerase II partially purified from wild-type cells (PV4) without protease inhibitors. The sensitive component, however, only contributed 5–30% and the insensitive component 70–95% of the total DNA polymerase II activity (three independent extracts and DEAE-HPLC separations). An example of two extreme DNA polymerase II preparations is given in Fig. 3B. Enzyme Ila contains 76% sensitive component and 24% insensitive component, whereas enzyme Iib contains 95% insensitive component. $I_{50}$ values for the sensitive and insensitive components are 2.4 $\mu$m and 2 mM, respectively (Fig. 3B, Table I). Similar results were obtained with the dATP analog BuPhdATP (Table I). Exception for the inhibition by these inhibitors, DNA polymerase Ila (sensitive) and DNA polymerase Iib (insensitive) were identical within experimental error with regard to all other criteria. This includes sensitivity to aphidicolin (7 $\mu$m for Ila, 6 $\mu$m for Iib), N-ethylmaleimide ($t_{50} = 3.1$ min for Ila, 2.4 min for Iib), salt ($I_{50} = 0.20 M$ KCl for Ila and Iib), high levels of Mg$^{2+}$ ($I_{50} = 38$ mM for Ila, 40 mM for Iib), and heparin ($I_{50} = 2.0 \mu g/ml$ for Ila, 1.5 $\mu g/ml$ for Iib). Furthermore, the apparent $K_a$ values for dNTPs were virtually identical (5.5 $\mu$m for Ila, 4.9 $\mu$m for Iib). In addition, neither enzyme Ila nor enzyme Iib were inhibited by antibodies to DNA polymerase I or III (see below). The average values of enzymes Ila and Iib for all inhibitors except BuPhdGTP and BuPhdATP are given in Table I. Both enzyme Ila and Iib consistently eluted as sharp peaks at identical salt concentrations from an analytical DEAE-silica gel column (Fig. 1).
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**Fig. 4.** Inhibition by monoclonal antibodies to DNA polymerase I (see “Experimental Procedures” for details).

**Fig. 5.** Inhibition by antiserum to DNA polymerase III (see “Experimental Procedures” for details).

**Fig. 6.** Western blot of fractions from a DEAE-silica gel separation. Separation 1C (Fig. 1, Ref. 1) was used; Lane 1, DNA polymerase III (Fraction 10, 13 units); Lane 2, DNA polymerase I (Fraction 20, 22 units); Lane 3, DNA polymerase II (Fraction 28, 11 units).

chicken heat shock protein (results not shown) (16).

Quantitation of DNA Polymerases I and III in Various Extracts—A major consideration in estimating the relative levels of DNA polymerases I and II is the possibility that preferential inactivation of one of these enzymes might occur during DEAE-silica gel chromatography. Attempts to quantitate these enzymes prior to DEAE-silica gel chromatography with the use of the mono- and/or polyclonal antibodies failed, presumably because the extracts were too crude to allow reproducible binding of the antibodies. However, because DNA polymerase I is very sensitive to BuPhdGTP and DNA polymerase III relatively insensitive, and, in addition, DNA polymerase II constitutes only a minor activity (20–30%), this inhibitor can be used to estimate the ratio of DNA polymerase III/DNA polymerase I in crude extracts prior to separation of the enzymes by DEAE-HPLC. At 2 μM BuPhdGTP, DNA polymerase I activity was inhibited by 92% and DNA polymerase III activity by 6% (Fig. 3A). Addition of 2 μM BuPhdGTP to assays of extracts (Fraction II) prepared from wild-type cells in the absence of protease inhibitors inhibited total DNA polymerase activity 61–73% (three independent extracts), indicating that DNA polymerase I was the major activity in these extracts. Extracts from protease-deficient cells made in the presence of protease inhibitors gave 14–37% inhibition of total DNA polymerase activity when 2 μM BuPhdGTP was added (five extracts), indicating that now DNA polymerase III was the major activity. Interestingly, when extracts (Fraction II) were prepared with protease inhibitors present, from protease-deficient cells which had been frozen in liquid nitrogen and then thawed prior to breakage, inhibition by 2 μM BuPhdGTP was 34–51% (three extracts). Analytical DEAE-silica gel chromatography of one of such extracts yielded DNA polymerase III and DNA polymerase I in the ratio 1.8:1 (results not shown). This is much lower than the ratio obtained (DNA polymerase III/DNA polymerase I is 4–5 in several experiments) when cells were not frozen prior to breakage. Thus, the inhibition data in crude extracts roughly correlate with the actual ratio of DNA polymerase III/DNA polymerase I obtained after DEAE-silica gel chromatography (Fig. 1). These results show that: (i) dialyzed ammonium sulfate preparations (Fraction II) from protease-deficient cells contain mostly DNA polymerase III; (ii) the amount of DNA polymerase I was increased (or DNA polymerase III decreased) when these cells were frozen and thawed prior to breakage; (iii) extracts (Fraction II) from wild-type cells broken in the absence of protease inhibitors contain mostly DNA polymerase I; (iv) because the degree of inhibition observed in crude extracts agrees well with the relative activities of DNA polymerases III and I observed after DEAE-silica gel HPLC chromatography, we conclude that none of the activities is preferentially inactivated during chromatography of this column.

**DISCUSSION**

Since the first report in 1970 on the separation of yeast DNA polymerases I and II (17), numerous studies have appeared on these two enzymes (5, 6, 12, 18, 19). DNA polymerase I, the major enzyme activity, has been most extensively studied. The enzyme elutes early from a DEAE-cellulose column, has a tightly associated primase activity but no associated 3′-5′ exonuclease activity (4–8, 20). DNA polymerase II constitutes about 10–30% of the total DNA polymerase activity. It elutes late from a DEAE-cellulose column and has an associated 3′-5′ exonuclease activity (5, 6).

To reconcile recent results reported in this and the preceding paper with the work cited above, we need to address three
Acknowlegdments—We are indebted to Dr. Lucy Chang for the generous gift of monoclonal antibodies to DNA polymerase I, as well as advice on immunological techniques. We thank Dr. G. Wright for supplying us with BuPhdGTP and BuPhdATP, Dr. Milton Schlesinger for antibodies to the chicken major heat shock protein, Heidi Heller for technical assistance, and Dr. John Majors for critical reading of the manuscript.

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