

domains is 'N-out, C-in', as expected, with the NG-domain exposed towards the cytoplasm. Although these sequence-based suggestions have not yet been tested experimentally, the existence of a very hydrophobic N-terminal segment supports the notion that membrane targeting of these FtsY homologues might occur co-translationally, as with the eukaryotic receptor¹¹. The question of how the *E. coli* FtsY and most of the bacterial homologues are targeted to and associated with the membrane in the absence of a transmembrane segment (Fig. 1), and an SR- β homologue, remains to be elucidated.

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A unified nomenclature for the subunits of eukaryotic DNA polymerase δ

DNA polymerase δ (Pol δ) plays a central role in eukaryotic chromosomal DNA replication, repair and recombination¹. Highly purified preparations of mammalian Pol δ typically comprise a heterodimer of 125-kDa and 50–60-kDa proteins². The 125-kDa protein is the catalytic subunit of the enzyme, a family B DNA polymerase; the smaller 50–60-kDa protein has been designated the B-subunit. However, recent studies in the yeasts *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*, and now also in mammals, have identified additional Pol δ subunits. To simplify future discussion of the roles of these new subunits in Pol δ function, we propose to extend the existing subunit nomenclature system to designate specific C- and D-subunits (see Table 1, Fig. 1). Widespread adoption of this nomenclature will greatly aid discussion of the function of these proteins.

Highly purified Pol δ from the fission yeast *S. pombe* is a dimer of heterotetramers of the Pol3, Cdc1, Cdc27 and Cdm1 proteins^{3,4} (see Table 1; Fig. 1). The Pol3 protein is the catalytic subunit, comprising both polymerase and 3'→5' proofreading exonuclease domains. Pol3 interacts directly with Cdc1, which, in turn, interacts directly with Cdc27 (Ref. 5). These three proteins are essential for the completion of S-phase in *S. pombe*. Cdc27 is required for dimerization of the heterotetramer (although the actual function of the dimeric form of the enzyme is unclear) and also for maximal enzyme processivity⁴ (see Fig. 1). Recently,

Cdc27 was shown to interact directly with the conserved polymerase processivity factor, the sliding clamp PCNA (for 'proliferating cell nuclear antigen') via a conserved PCNA-binding motif located at its extreme C terminus⁶. This interaction is essential for Cdc27 *in vivo*. The fourth subunit, the Cdm1 protein, associates with Pol3 and/or Cdc1, even in the absence of Cdc27, and appears to play a role in stabilizing the complex⁴. However, in contrast to Pol3, Cdc1 or Cdc27, Cdm1 is nonessential *in vivo*⁷.

In budding yeast *S. cerevisiae*, Pol δ purifies as a dimer of heterotrimers, comprising homologues of *S. pombe* Pol3, Cdc1 and Cdc27, named Pol3p, Pol31p/Hys2p and Pol32p, respectively (see Table 1)^{8–11}. In contrast to the situation in *S. pombe*, the Cdc27 homologue Pol32p is nonessential for growth and division¹⁰, although *pol32 Δ* cells display growth defects consistent with impaired DNA replication. Like Cdc27, Pol32p also interacts directly with the budding yeast PCNA homologue Pol30p (Ref. 8). Although at present there is no evidence for a homologue of *S. pombe* Cdm1p in *S. cerevisiae*, this does not preclude the possibility that such a protein will be identified at a later date.

As noted above, purification of mammalian Pol δ by conventional methods suggested that this enzyme was dimeric in structure, comprising the catalytic subunit and the B-subunit, a protein in the 50–60-kDa range. The mammalian B-subunit protein was later shown to be closely related to the *S. pombe* Cdc1 and *S. cerevisiae* Pol31/Hys2 proteins^{5,10–12}. Related proteins are found as subunits of eukaryotic DNA polymerases α and ϵ and archaeal DNA polymerase II (Ref. 13). Recently, several reports have appeared indicating that the subunit structure of the mammalian enzyme has

Table 1. Pol δ subunit designations

Subunit designation	<i>S. pombe</i>	<i>S. cerevisiae</i>	Mammals	Comments
A	Pol3	Pol3p	p125	Catalytic subunit; interacts with B-subunit
B	Cdc1	Pol31p/Hys2p	p50/p55	Interacts with catalytic subunit and C-subunit
C	Cdc27	Pol32p	p66/KIAA0039	Interacts with B-subunit and with PCNA
D	Cdm1	–	p12/THC112256	Interacts with A- and/or B-subunit

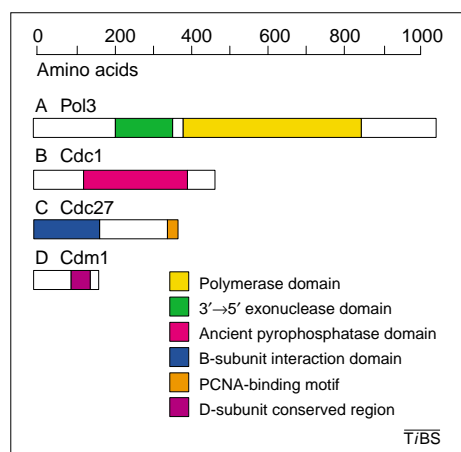


Fig. 1. Subunit structure with proposed nomenclature. The four subunits of *Schizosaccharomyces pombe* Pol δ are shown schematically, with protein domains coloured (see key).

more in common with its (fission) yeast counterpart than was hitherto suspected. First, a mammalian Cdc27 homologue was identified as a component of a protein complex, isolated using PCNA-affinity chromatography, that showed PCNA-stimulated Pol δ activity¹⁴. This protein, termed p66/KIAA0039, shares ~20% identity with *S. pombe* Cdc27, and, like Cdc27 and Pol32p, has a PCNA-binding site at its extreme C terminus (Fig. 1). In addition to p66/KIAA0039, a purified form of Pol δ containing a protein with significant similarity to a short region of *S. pombe* Cdm1 has also been identified¹⁵; this protein has been designated p12/THC112256. Although both the p66/KIAA0039 and p12/THC112256 proteins share only a low level of sequence similarity with their *S. pombe* counterparts, their identification as Cdc27 and Cdm1 homologues, respectively, is not in doubt. Database searching reveals further members of the Cdc27 and Cdm1 families in a wide range of eukaryotic species (S.A. MacNeill, unpublished).

Further studies of these conserved proteins, both in mammalian and yeast systems, will be required to determine precisely their function within the Pol δ holoenzyme (most probably a dimer of the heterotetrameric Pol δ , the heteropentameric replication factor C and the homotrimeric PCNA). However, we believe that the discussion of the functions of these subunits will be hampered by the lack of a uniform system of nomenclature for them. Therefore, we propose to extend the existing nomenclature system for the subunits of Pol δ by designating the *S. pombe* Cdc27 and Cdm1 proteins, and their homologues in other species, as the Pol δ C- and D-subunits, respectively (Table 1). Thus, the *S. pombe* enzyme (and presumably its mammalian counterparts) would have the subunit composition [ABCD]₂, whereas the *S. cerevisiae* enzyme would be represented as [ABC]₂. Widespread adoption of this nomenclature will greatly simplify discussion of the roles of these subunits in Pol δ function.

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