We used to think cells could get by with just a few DNA polymerases. One processive polymerase in *Escherichia coli* [polymerase III (Pol III)] was needed to make the long trip around the genome, and another one (Pol I) was needed to replace Okazaki fragment primers or damaged nucleotides. This view changed radically after 2 seminal studies by Nelson, Lawrence, and Hinkle (1, 2) in which 2 yeast enzymes, Rev1 and Rev3-Rev7, were found to incorporate nucleosides or polymerize past template sites with missing or damaged bases. These new polymerases helped explain a rich history of mutational phenomena and led to the realization that organisms have several of these specialized DNA polymerases; *E. coli* has 3 (Pol II, Pol IV, and Pol V). Yeast have 5. Humans have 3 (Pol II, Pol IV, and Pol V).

The concept that translesion polymerases function during replication in the presence of DNA damage (Fig. 1) is biologically relevant, as part of the SOS regulon (6). The replicational-slowing model is the observation that Rev-1, a central regulator of translesion synthesis after DNA damage with kinetics very similar to that for wild-type cells (9). A checkpoint function that slows replication and allows more time for repair might be predicted to provide a more general protective effect against a broad spectrum of DNA damage.

Curiously, although the effect of translesion polymerases on viability is relatively minor, their effect on mutagenesis can be comparatively dramatic. Pol V mutants were originally isolated based on their mutational effects after DNA damage (10). Similarly, the presence or absence of Pol II or Pol IV can alter the mutation frequency after DNA damage, even when survival is unaffected (3). Analogously in humans, patients with the variant form of xeroderma pigmentosum (XP) lack a polymerase, Pol η, that efficiently bypasses UV-induced lesions. These patients are at risk of developing cancer and appear clinically similar to those XP patients who are defective in repairing UV-induced damage (11). Remarkably, however, unlike cells from any of the repair-deficient forms of XP, viability is not significantly compromised in XP variant cells exposed to UV (11).

The distinction between the mutational phenotype and the lethal phenotype has led other investigators to propose alternative models, in which the translesion polymerases function to fill in gaps left at damaged sites after replication, somewhat like touching up the missed spots after painting a room (Fig. 1B). This type of model is based on observations that the presence or absence of these polymerases does not alter the rate at which replication recovers after DNA damage in *E. coli* or the ability of cells to complete replication in yeast (9, 12, 13). Also consistent with this type of model is the observation that Rev-1, a central regulator of translesion synthesis in yeast, is up-regulated after S phase and just before the G2–M transition in the cell cycle (13).

In addition to the novelty of the model suggested, the Indiani et al. study (4) contributes to an emerging view that replication is a far more dynamic process.
cess than previously appreciated. The dynamics appear to center around the ability of multiple polymerases to interact with the replication machinery’s processivity clamp, a protein complex that encircles the DNA to keep the polymerase tethered to its template (14–16). The plasticity of these interactions is highlighted in the Indiani et al. study by their observation that Pol II or Pol IV can gain access to the processivity clamp within an active replisome, engage the primed template, and then continue to extend the nascent strand without interruption. Impressively, all of this occurs without disrupting either the processivity clamp or the helicase operating at the replication fork.

Other recent studies from this group have revealed additional plasticity within the replisome. In addition to exchanging polymerases, the polymerase in the replisome is able to release and reengage with a different primer during elongation (17). As with the polymerase exchange, the primer exchange also occurs without disrupting the clamp or helicase of the replisome. Potentially extending the dynamics of replication even further is their observation that the replication holoenzyme can accommodate 3 core polymerases, rather than 2 (18). Although the biological significance of these observations remains to be established, they are exciting and challenge us to rethink some fundamental aspects of how the genome is copied.

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