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Non mutagenic and mutagenic DNA damage tolerance

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Damage to DNA poses a serious impediment to replication and can cause genomic instability. To combat insults to the DNA, cells enact a checkpoint response to delay cell cycle progression late during the G2/M phase. This checkpoint ensures adequate time for the damage to the DNA to be repaired or tolerated by various cellular mechanisms. One of the DNA damage tolerance (DDT) mechanisms involves restoring the damaged DNA to its original form by engaging the recombinational apparatus (Homology Directed Repair or HDR), while another utilizes Translesion DNA synthesis (TLS), the process by which adducts and gaps in the DNA are replicated via the action of specialized TLS DNA polymerases.[1] TLS is frequently highly error-prone and is required for the vast majority of eukaryotic mutagenesis.[1] The error-prone branch of TLS is carried out by the TLS polymerases Rev1 and Polζ (Rev3/Rev7), whose genes were originally identified in genetic screens for non mutability.[2] The discovery that the *REV1, 3* and *7* gene products encode TLS polymerases led to speculation that their action occurs during the S phase of the cell cycle. Several observations challenging this notion prompted Callegari and Kelly[3] to investigate whether cells temporally partition accurate and error-prone modes of DNA damage tolerance and whether mutagenic TLS occurs during a specific phase of the cell cycle. These include evidence that the role of mutagenic TLS may be limited to a subset of daughter-strand gaps produced late during S phase,[4] the large increase in Rev1 expression during late S phase in budding yeast[5] and the increase in Polζ late in the cell cycle in human cells.[6] The authors use live-cell imaging to observe the response of individual fission yeast *Schizosaccharomyces pombe* cells to UV irradiation. Although the *S. pombe* cell cycle is similar to that of most eukaryotes, it differs in the respect that cells cleave soon after S phase rather than immediately after mitosis. Taking advantage of this property of the *S. pombe* cell cycle, Callegari and Kelly assessed the cleavage time to determine the stage at which cells incur DNA damage and to examine the contributions of the non-mutagenic and mutagenic DDT pathways after UV treatment. Surprisingly, they find that *S. pombe* employs primarily non-mutagenic DDT pathways prior to the G2/M checkpoint to repair the damaged DNA. One of the genes in this pathway, the Rad51 recombinase, elicits error-free repair via HDR prior to the G2/M checkpoint. These findings are significant because they provide the first evidence that repair of daughter-strand gaps occurs in a predominantly error-free manner, confining the action of the mutagenic polymerases Rev1 and Polζ to after the G2/M checkpoint. DNA Pol η, a TLS polymerase that can replicate quite accurately over UV-induced cyclobutane pyrimidine dimers, also predominantly acts prior to the G2/M checkpoint. This temporal separation of non-mutagenic and mutagenic pathways in the cell cycle suggests a sequential order of events, which ensures that most of the filling in of residual gaps in the DNA occurs accurately and limits mutagenesis to a small window of time. Prior studies have highlighted the importance of PCNA monoubiquitination, which occurs when replication is blocked by DNA damage, in controlling the action of TLS polymerases. These studies suggest a role for Rad51 in preventing mutagenesis while error-free methods of DDT are in play, providing a new cellular strategy to limit mutagenesis. An important future direction will be to elucidate the mechanism by which this process occurs and the types of mutations that persist after the G2/M checkpoint in response to various DNA-damaging agents including UV. Coming on the heels of the 2015 Lasker Awards to Evelyn M. Witkin and Stephen J. Elledge for their discoveries of the DNA damage response,[7] these crucial observations represent a major advance in our understanding of how cells maximize their survival after DNA damage while minimizing their mutational load.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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