

Under the scanner: Scientists unravel the inner workings of DNA repair enzymes

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Minding the Gap: Interplay of Enzymes in DNA Repair

DNA suffers routine damage from UV light, Inflammation, Air pollution, Metabolism, Ionizing radiation, and Smoking.

Cells contain enzymes like AP endonucleases (ExoIII and APE1) that recognize and repair DNA damage through a process called base excision repair.

Dynamic observation of gap creation by ExoIII using single-molecule fluorescence resonance energy transfer

- AP site (missing purine/pyrimidine base)
- Gap creation by ExoIII is apurinic/aprimidinic (AP) site-dependent
- AP site binding causes the distributive ExoIII to change to processive ExoIII
- ExoIII creates a gap and a transient single-stranded DNA (ssDNA) loop
- Gap size limited to maintain genomic stability

Mechanism of DNA repair

ExoIII binds to AP site → Processive ExoIII works by anchoring at the AP site → Distributive ExoIII Vs. Processive Pol I → Distributive ExoIII Vs. Processive Pol I → Pol I fills the gap and removes the AP site → DNA ligase seals the nick

The findings provide novel insights into how DNA damage signals regulate the functions of repair enzymes

The mechanism of gap creation by a multifunctional nuclease during base excision repair
 Yoo et al. (2021)
 Science Advances | 10.1126/sciadv.abg0076

GIST Gwangju Institute of Science and Technology

The mechanism of gap creation by a multifunctional nuclease during base excision repair. Credit: Gwangju Institute of Science and Technology

DNA is the instruction manual for every living organism, guiding the development and functioning of all biological processes. In essence, it is a molecule with a double helix structure with each unit of a helix containing what are known as "DNA bases."

Maintenance of DNA is extremely important for smooth operation of all bodily functions. DNA may be damaged by cellular metabolism byproducts, such as reactive oxygen species, and ionizing radiation (UV and gamma rays). In such a scenario, a set of enzymes (proteins that act as catalysts for biochemical reactions) are activated to repair the damage. The sequence of processes undertaken by the enzymes to fix DNA damage is known as "base excision repair" (BER).

BER is mainly carried out by the exonuclease III (ExoIII) and polymerase I (Pol I) enzymes. Despite the importance of the functions of these enzymes, the mechanism underlying their coordination has not been elucidated in previous studies.

Now, scientists led by Dr. Gwangrog Lee from the Gwangju Institute of Science and Technology (GIST) in Korea have utilized the latest [technology](#) in single molecule detection to study enzymatic interactions and observe the mechanism of BER, filling the gap in our understanding of this coordination mechanism.

In their paper published in *Science Advances*, the scientists reported that ExoIII has an affinity for apurinic/aprimidinic (AP) sites—spots on the DNA double helix where a DNA base is missing—in damaged DNA. It attaches itself to the AP site in damaged DNA and cleaves the double strand of DNA into a single strand by digesting a selective number of bases from the other strand. Because ExoIII is highly responsive to salt concentration, the number of bases digested and the resulting gap size depends on the physiological salt conditions. Thereafter, Pol I attaches itself to the 3' (3 prime end) of the digested DNA strand and fills the gap.

Dr. Lee highlights the crux of the study, saying, "Interestingly, there is perfect temporal and spatial regulation between the gap creation activity of ExoIII and the gap filling activity of Pol I, such that genomic stability

is always maintained."

Understanding the role of ExoIII in BER has opened several doors for future research. For instance, the expression of AP endonucleases in [cancer cells](#) is significantly higher than in [normal cells](#), allowing AP endonucleases (e.g., ExoIII and APE1) to be used as a biomarker for cancer diagnosis. "This study provides insights for investigation of operational mechanisms of other enzymes involved in DNA repair. Further research in this area could lead to technologies for targeted gene repair and [drug development](#)," concludes Dr. Lee.

More information: Jungmin Yoo et al, The mechanism of gap creation by a multifunctional nuclease during base excision repair, *Science Advances* (2021). [DOI: 10.1126/sciadv.abg0076](https://doi.org/10.1126/sciadv.abg0076)

Provided by GIST (Gwangju Institute of Science and Technology)

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