Base excision: evolving complexities of a crucial pathway for epigenetic control and DNA repair

T. Roldán Arjona[1,2,3*]

[1] *Maimónides Biomedical Research Institute of Córdoba (IMIBIC), Córdoba, Spain*
[2] *Department of Genetics, University of Córdoba, Córdoba, Spain*
[3] *Reina Sofía University Hospital, Córdoba, Spain*
* ge2roarm@uco.es

Base Excision Repair (BER) is a key pathway that preserves genome integrity by removing damaged, mispaired, or non-canonical bases. In plants, BER fulfills both canonical DNA repair functions and specialized epigenetic roles, notably the active replacement of 5-methylcytosine (5-meC) with cytosine to shape DNA methylation landscapes. Plant active DNA demethylation is mediated by plant 5-meC DNA glycosylases typified by *Arabidopsis* REPRESSOR OF SILENCING 1 (ROS1). The C-terminal domain of ROS1 mediates interaction with the N-terminal tail of histone H3, and this interaction is specifically disrupted by phosphorylation at H3S28 indicating sensitivity to chromatin state. Conserved residues within the C-terminal domain are required for histone interaction, efficient DNA binding, and catalytic activity. Thus, the ROS1 C-terminal domain functions as a histone reader module that links chromatin marks to targeted DNA demethylation.

Following base excision, downstream BER steps depend on the coordinated action of additional repair enzymes. AP endonucleases incise abasic sites generated by glycosylases, producing strand breaks with 5′-deoxyribose phosphate (5′-dRP) termini that must be further processed to complete repair. In contrast to mammals, which use DNA polymerase β (Pol β) for 5′-dRP removal and gap filling, plants encode a single X-family polymerase, Pol λ. *Arabidopsis* Pol λ exhibits intrinsic dRP lyase activity and is required for efficient BER, establishing it as a functional Pol β analog in plants.

Divergence between plant and animal BER is also evident at the level of AP endonuclease specificity. In contrast to APE1, the major human AP endonuclease, its *Arabidopsis* ortholog ARP displays orphan base-dependent cleavage and limited activity on single-stranded DNA (ssDNA). Differences in two key DNA-intercalating residues determine such substrate divergence. Notably, the residue governing ssDNA activity in APE1 is essential for mammalian antibody diversification, suggesting an evolutionary adaptation in metazoans. Collectively, these observations reveal the evolving molecular complexity of BER at the intersection of genome maintenance, chromatin signaling, and epigenetic regulation.

Funding: Ministerio de Ciencia e Innovación (MICINN), Spain, [PID2019-109967 GB-I00, PID2022-140458NB-I00].