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Editorial

Guardians of the Genome: DNA Damage and Repair

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Abstract
This collection of reviews aims to summarise our current understanding on a fundamental question: how do we deal with DNA damage? After identifying key players that are important for this process, we are now starting to reveal the dynamic organization of detecting and repairing DNA damage. Reviews in this issue provide exciting research progress that are happening now in this field and also initiate discussion about future challenge and direction we are heading to.

Maintaining the genome stability is a challenge but essential task for cells. DNA damage, caused by both endogenous and exogenous sources, triggers the DNA damage response (DDR), a highly regulated signalling network. Acting as guardians of the genome, the DDR orchestrates various cellular pathways to detect, signal and repair different types of DNA damage. The exact spatial and temporal mechanisms of these pathways are still not fully understood, particularly when DNA repair coincides with other cellular processes, such as replication and transcription.

Failure to respond and repair DNA damage has severe consequences, such as cell death and genome instability, one of the hallmarks of cancer. The complexity and importance of maintaining genome stability motivated the organization of this issue, comprising a collection of 12 reviews from world leading research groups. This issue aims to summarise the latest research outcomes from many key aspects of DDR studies which further our understanding of its mechanism and regulation against DNA damage. Additionally, this issue highlights exciting achievements and possibilities, as discussed in each review, regarding to the current therapeutic applications and drug discovery potentials that can be translated from DDR research. I have grouped these 12 reviews into five themes, covering topics from molecular studies exploring the role of modifications at the DNA level to research at the cellular level exploring how the DDR can be exploited in treatment of disease.

1) **DNA modification and the chromatin environment**.

Sriraman et al. focused on how DNA methylation as a reversible epigenetic mark impacts gene integrity through DNA repair, replication, transcription and mutations (1). Tan and Huen summarised the relationship between chromatin environment during transcription and the repair of highly toxic DNA double-strand breaks (DSBs) (2).

2) **Emerging regulators/mediators for DNA damage response**.

The functions of RNA especially non-coding RNA (ncRNA) and RNA modifications in DSB repair were discussed in the review by Ketley and Gullerova (3). Da Costa and Schmidt reviewed the latest research progress on a group of ubiquitin-like proteins (UBLs) (ISG15, UBL5, FAT10 and UFM1) as co-regulators for DDR, gene splicing and telomere maintenance (4). MacDonald et al. explained current evidences for the

formation of micronuclei as a mediator that can stimulate the immune system in response to DNA damage and genome instability (5).

3) **Repair of double-strand breaks (DSBs).**

Xu and Xu discussed the pathway choice for DSBs based on DNA end condition, which is antagonistically controlled by BRCA1 and 53BP1, and other regulatory factors such as cell cycle and chromatin environment (6). Kawale and Sung focused on the proteins and mechanistic function of the homologous recombination (HR) pathway, describing four major stages: DNA end resection, presynaptic filament assembly, DNA strand invasion and repair DNA synthesis (7). Stavridi et al. explained the general mechanism of non-homologues end joining (NHEJ) pathway with focus specifically on druggable binding sites, available small molecule compounds and potential future candidates targeting protein-protein interaction interfaces among key NHEJ protein complexes (8).

4) **Structural insights for key DNA repair scaffold proteins and enzymes.**

Fanconi anemia (FA) pathway functions in DNA damage that blocks DNA replication, such as interstrand cross-links. Li et al. summarised currently available structures in FA pathway including latest cryo-electron microscopy (cryo-EM) structures of monoubiquitinated FANCI-FANCD2 and FA core complex with interpretations of the structural mechanism of FA pathway (9). RecQ family helicases function in multiple pathways involved in maintaining genome stability. Newman and Gileadi reviewed the whole family of helicase core structures and when they are in complex with DNA; Helicase and RNAse D C-terminal (HRDC) domains and the importance of oligomeric status for the function of RecQ helicases (Reference).

5) **DNA damage response for cancer treatments and neurodegenerative disease**.

Grundy and Parsons focused on the base excision repair (BER) pathway and summarised available inhibitors (including PARP inhibitors) developed to target various BER enzymes with the aim of improving the efficacy of radiotherapy and/or chemotherapy in cancer cells (10). The final review of this issue is from Yu et al. with a discussion of the latest studies that explore the role of the DNA damage response and its therapeutic potential in Amyotrophic Lateral Sclerosis (ALS), a rapidly disabling and fatal neurodegenerative disease (reference).

I believe that these selected reviews in this issue provide valuable knowledge of key topics in DNA damage response and also an overview of current research progress in this very active field. They also indicate an exciting future and challenge ahead for new therapeutic opportunities which enable us to enhance treatment outcome for cancer patients.

Competing interests

This author has declared no competing interests.

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Reference

1. Sriraman A, Debnath TK, Xhemalce B, Miller KM. Making it or breaking it: DNA methylation and genome integrity. Essays Biochem [Internet]. 2020 Aug 18; Available from: https://doi.org/10.1042/EBC20200009
2. Tan XY, Huen MSY. Perfecting DNA double-strand break repair on transcribed chromatin. Essays Biochem [Internet]. 2020 Apr 20; Available from: https://doi.org/10.1042/EBC20190094
3. Ketley RF, Gullerova M. Jack of all trades? The versatility of RNA in DNA double-strand break repair. Essays Biochem [Internet]. 2020 Jul 3; Available from: https://doi.org/10.1042/EBC20200008
4. Da Costa IC, Schmidt CK. Ubiquitin-like proteins in the DNA damage response: the next generation. Essays Biochem [Internet]. 2020 May 26; Available from: https://doi.org/10.1042/EBC20190095
5. MacDonald KM, Benguerfi S, Harding SM. Alerting the immune system to DNA damage: micronuclei as mediators. Essays Biochem [Internet]. 2020 Aug 26; Available from: https://doi.org/10.1042/EBC20200016
6. Xu Y, Xu D. Repair pathway choice for double-strand breaks. Essays Biochem [Internet]. 2020 Jul 10; Available from: https://doi.org/10.1042/EBC20200007
7. Kawale AS, Sung P. Mechanism and significance of chromosome damage repair by homologous recombination. Essays Biochem [Internet]. 2020 Aug 5; Available from: https://doi.org/10.1042/EBC20190093
8. Kefala Stavridi A, Appleby R, Liang S, Blundell TL, Chaplin AK. Druggable binding sites in the multicomponent assemblies that characterise DNA double-strand-break repair through non-homologous end joining. Essays Biochem [Internet]. 2020 Jun 24; Available from: https://doi.org/10.1042/EBC20190092
9. Li L, Tan W, Deans AJ. Structural insight into FANCI–FANCD2 monoubiquitination. Essays Biochem [Internet]. 2020 Jul 29; Available from: https://doi.org/10.1042/EBC20200001
10. Grundy GJ, Parsons JL. Base excision repair and its implications to cancer therapy. Essays Biochem [Internet]. 2020 Jul 10; Available from: https://doi.org/10.1042/EBC20200013