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Editorial

A special issue on DNA damage responses and genome maintenance

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There is nothing more fundamental than the genome for the existence and maintenance of all living beings. The importance of the genome is increasingly appreciated as recent discoveries have revealed that changes in the human genome, regardless of being inherited or induced, can result in diseases that either significantly shorten lives (as seen in cancer) or dramatically affect the quality of lives (often seen in neurodegenerative diseases). Therefore, maintaining genome integrity is critical for not only the continuation of a species in evolution (although mutations may be occasionally beneficial during evolution) but also for longevity and general health.

In this special issue, *Cell Research* presents a series of reviews covering cellular mechanisms that ensure the integrity of the genome. There are two classes of genome-maintenance systems, one responsible for accurately propagating the genetic information in DNA, and the other responsible for proper processing of DNA damage caused by various endogenous and exogenous agents.

Cells employ multiple mechanisms to ensure DNA replication accuracy. First, DNA replication fidelity is primarily maintained by the high selectivity and proofreading function of replicative DNA polymerases (see review by McCulloch and Kunkel). However, these replicative polymerases occasionally misincorporate deoxynucleotides, generating mispairs that can lead to mutations. In such a case, cells recruit the mismatch repair machinery to remove these mispaired bases (reviewed by Li). When replicative polymerases are unable to copy DNA containing bulky adducts induced during replication or left unrepaired, a polymerase-switch strategy is often employed. Specialized DNA polymerases (also called translesion synthesis polymerases) are employed to deal with the bulky DNA lesion followed by a switch back to the replicative polymerases to continue normal replication once the lesion is bypassed (see reviews by Andersen *et al.* and Gan *et al.*).

DNA damage processing can be divided into two categories: damage response and damage repair. Cells possess a signaling network to respond to all types of DNA damage. The function of this network is to help cells make a decision if the damage should be repaired or the cells should commit suicide. Articles by Huen & Chen and Jean Wang & colleagues provide mechanistic insights into this subject. The second category of DNA damage processing deals with damage repair. There are various types of DNA damage, including base modification and adduct formation, DNA strand breaks, and DNA strand cross-links. Distinct pathways have evolved to repair diverse damages. While Sankar Mitra & colleagues and Samuel Wilson & colleagues describe molecular details of how the cells use different base excision repair enzymes to remove DNA base lesions and repair single-strand breaks, John Turchi & colleagues and Maria Fousteri & Leon Mullenders describe global genome and transcription-coupled nucleotide excision repair mechanisms respectively for the repair of bulky base adducts in DNA. DNA double-strand breaks can be fixed by either the homologous recombination (HR) pathway (see Li & Heyer) or the non-homologous end joining (NHEJ) pathway (see Weterings & Chen and Lieber *et al.*). However, how do cells selectively choose between HR and NHEJ? The article by Jac Nickoloff and col-

leagues addresses this question.

It should be pointed out that the various repair pathways are interconnected and collaborative. Whereas a repair process is capable of repairing multiple DNA lesions, a particular DNA lesion/unusual structure can be processed by multiple repair pathways. For example, maintaining the stability of triplet repeat sequences in the genome requires collaborative efforts involving the replication machinery, base excision repair, and mismatch repair (see article by Kovtun and McMurray). From a structural and functional perspective, Wei Yang's article outlines fundamental molecular strategies that various genome maintenance systems use to cope with DNA damage.

While the aforementioned articles emphasize our current understanding of the genome maintenance systems, Errol Friedberg presents a brief history story appreciating how these systems were initially discovered.

It is our sincere hope that this special issue brings our readers enlightenment and offers sufficient introductory information to help them appreciate new breakthroughs in the field.

We wish the readers a happy and productive New Year!