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News & Views

Linking, thinking & fixing: the story about the 2015 Chemistry Nobel Prize and the future of science

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Did you know there are roughly over 10,000 DNA damages in a cell per day? Do not be too alarmed though, thanks to various vital DNA repair mechanisms we are able to continue function normally as an organism and maintain our genome integrity. It is no wonder then why this year prestigious Chemistry Nobel Prize(s) went to Drs. Thomas Lindahl, Aziz Sancar, and Paul Modrich for their extensive research and breakthrough discoveries on DNA repair mechanisms (http://www.nobelprize.org).

So what is DNA repair and why should we care? DNA repair is a collection of dynamic processes to ensure stability but still allowing for evolutionary diversity. Take human cells for example, both endogenous damages (e.g., reactive oxygen species and replication errors) and exogenous damages (e.g., ultraviolet radiation, X-rays, gamma rays, thermal disruption, plant toxins, mutagenic chemicals, certain drugs, and viruses) can cause DNA damages, resulting in multiple molecular lesions in cells on a daily basis. In most cases, the damage can be repaired due to the powerful and robust DNA repair processes. However, when the repair fails, the damage may lead to harmful (even fatal) outcome, such as double-strand breaks and DNA cross-linkages, mitosis interference, and mutation-driven fatal diseases. At a molecular level, Drs. Tomas Lindahl, Aziz Sancar, and Paul Modrich's pioneering contribution is to interpret the fundamental biochemistry processes of how cells identify and repair damaged DNA, allowing the genetic information to be protected.

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1 The Nobel Prize in chemistry 2015

1.1 Tomas Lindahl and DNA decay

Inspired by the heat-induced RNA molecules' degradation, Dr. Tomas Lindahl began his study on DNA stability in the early 1970s, which demonstrate a slow but steady degradation of the DNA molecule, *a.k.a* DNA decay, including the mechanism of the base excision repair pathway for the removal of endogenous damage from cellular DNA at a molecular level [1]. These discoveries are part of the reason Dr. Lindahl won the Chemistry Nobel Prize in 2015. In fact, a set of milestone discoveries earmark Dr. Lindahl's important contribution in this field of the fundamental understanding of DNA repair mechanisms in cancer, genetic disorders, and ancient DNA [1]. This includes the quantitative measurements of DNA decay such as the rate and degree of base loss and cytosine deamination, which the latter led to the famous discovery of uracil-DNA glycosylase [1]. The deaminated cytosine residue (i.e., uracil), but not thymine, can be rapidly excised by the abundant and ubiquitous uracil-DNA glycosylase to generate a base-free site, which can be further efficiently and correctly refilled (Fig. 1a) [2]. This mechanism was used to interpret (1) uracil-DNA glycosylase-deficient bacteria strains which have a 10–20x higher spontaneous mutation rate due to the cytosine deamination and (2) inefficient repair of deaminated 5-methylcytosine (i.e., thymine) which leads to a spontaneous point mutation and inherited human disease [2]. Moreover, successful

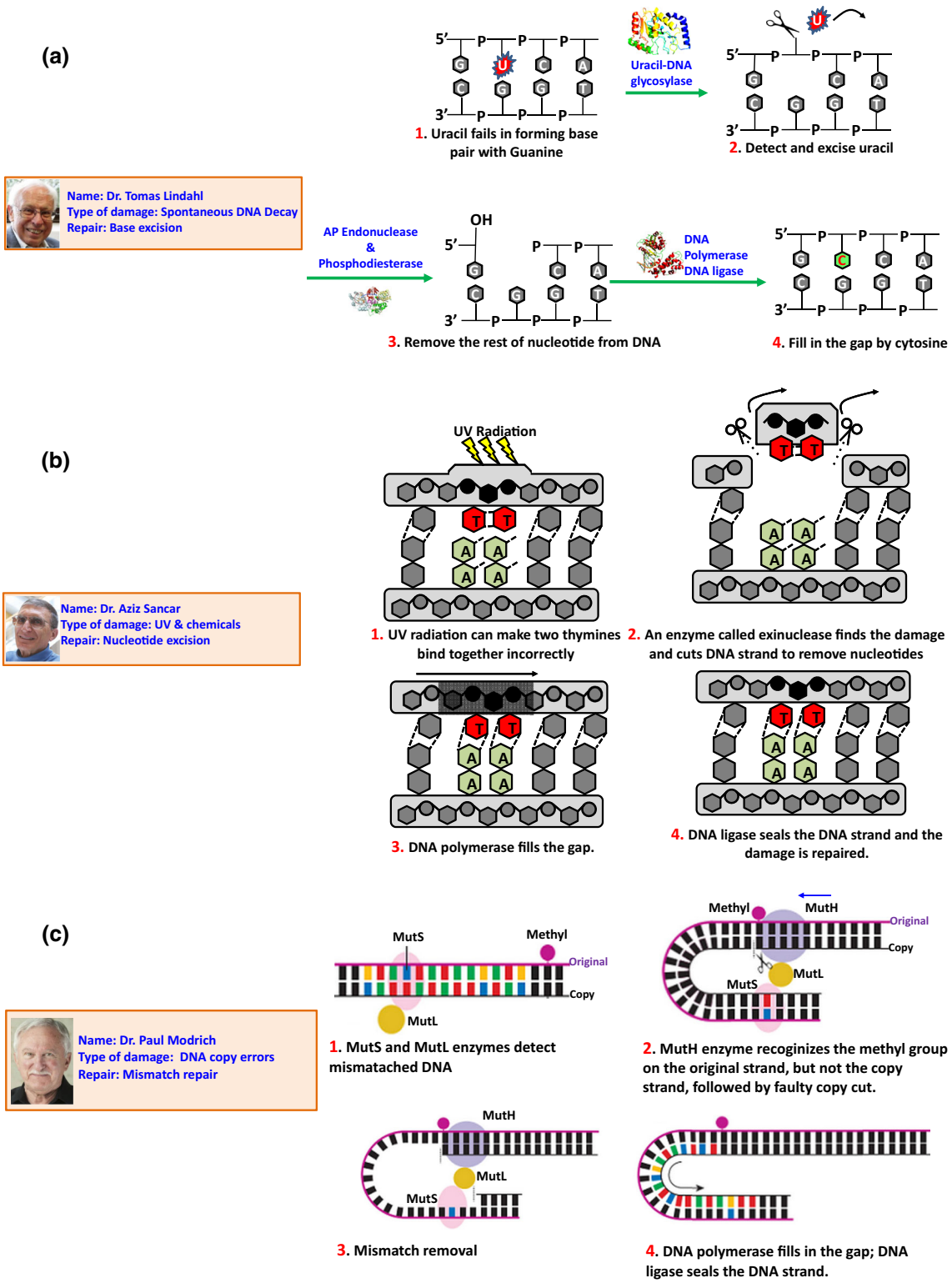

Fig. 1 (Color online) The 2015 Chemistry Nobel Prizes went to Drs. Thomas Lindahl, Aziz Sancar, and Paul Modrich for their significant contribution in the understanding of DNA repair mechanisms. **a** Dr. Tomas Lindahl demonstrated that DNA decay includes a molecular machinery mechanism and base excision repair efficiently repair the collapse of DNA molecule. **b** Dr. Aziz Sancar demonstrated a nucleotide excision repair mechanism by which cells use to repair DNA damage due to the UV radiation and mutagenic substance-induced lesions/defects. **c** Dr. Paul Modrich demonstrated a mismatch repair mechanism by which cells correct the mismatch errors during DNA replication in cell division. Panel c is modified based on a figure from Nobel Foundation. Credits for the photos of Nobel Prize laureates: http://www.wsj.com/

demonstration of cell-free analysis for mammalian DNA nucleotide excision repair was also reported. Dr. Lindahl discovered multiple distinct DNA ligases including the first use of genetic work on DNA ligases I, III, and IV [1]. He also discovered the mammalian exonuclease DNase III (TREX1), which was further shown to be involved in human autoimmune diseases. Additional impressive DNA repair discoveries include mutagenic DNA adduct O^6-methylguanine (O^6mG) and the action of AlkB enzyme [1].

1.2 Aziz Sancar and nucleotide excision repair

As mentioned previously, DNA is being constantly subjected to cellular alterations by exogenous agents. Essentially, DNA damage can alter the quasi-equilibrium and even alter biochemical pathways that regulate cellular growth [3]. DNA damages happen regularly, and these damages can lead to degenerative diseases and cancer to name a few, Dr. Sancar saw the need and how potentially this mechanism could prolong lives. In the 1970s, while at North Carolina Chapel Hill Dr. Sancar published a paper elucidating some of the DNA repair mechanisms in bacteria and suggested some of the mechanisms in humans [3]. After years of extensive research, he then further continued publishing into the research of enzymes involved in DNA repair mechanisms in organisms. In 2004, he published a paper elaborating profoundly the DNA repair mechanism pathways in humans including extensive research on nucleotide repair [4].

So where does nucleotide repair fit in all this? As humans, one of the DNA damages comes from environmental factors. We are exposed to daily UV radiation (some of us more than others). UV radiation can cause two thymines to bind together incorrectly. Dr. Sancar demonstrated the process by which cells repair UV-induced lesion by excising an entire nucleotide, rather than just the base. In this case, an enzyme called excinuclease cuts out the damage in DNA strand (Fig. 1b) and multiple lesions in the nucleotides in question from the DNA strand. DNA polymerase (an enzyme that assembles nucleotides) then comes along and fills the gap followed by DNA ligase which finally seals the DNA strand and the damage is repaired.

1.3 Paul Modrich and mismatch repair

With trillions of cells in the body and 3 billion base pairs in a strand of human DNA, there are considerable chances for a mismatch error in the process of transcription, which sometimes the outcome could be serious, i.e., cause cancer. In order to ensure the precision during chromosome replication and genetic recombination, a sophisticated but efficient mechanism—for repairing transcription mismatches [5]—has been revealed by a study led by the Nobel Prize laureate: Dr. Paul Modrich [6]. As shown in Fig. 1c, a 95-kD enzyme, called MutS, moves along the strand of DNA to bind to the mismatches, and a homodimer of a 68-kD enzyme MutL binds to this complex via an ATP-dependent fashion. MutS-MutL interaction with the heteroduplex further activates a 25-kD enzyme MutH, which is capable of cleaving a copy strand without a methyl marker, a marker only appears in the original strand [5]. MutH enzyme removes the mismatched section in the copy strand, followed by the addition of correct section under the assistance of DNA polymerase and ligase [5]. This was in agreement with the discovery in bacteria in which the *E. coli* mutants of high rate spontaneous mutation exhibited inactivation of mutation avoidance systems, such as MutH, MutL, and MutS [6]. The role of this highly cooperative fidelity device can be demonstrated in the inactivation of the corresponding human pathway which is the primary cause of certain carcinoma disease [6].

2 Potential applications behind the understanding on DNA repair mechanisms

The advantageous outcomes are commercially successful and scientifically fruitful, as well as socially beneficial. With 2015 marking a milestone in DNA repair, this opens up new horizons in many fields and applications including targeted therapy for cancer treatments, commercial anti-aging, and a much-needed fundamental understanding in neurodegenerative diseases (Fig. 2). It has been shown that approximately 25 % of the variation in human life span is governed by genetic information including the fact that candidate longevity genes encode proteins involved in DNA repair. In essence, this discovery opens up doors into longevity research and the prevention of disease, i.e., lower the risk of cancer melanoma gene instability.

In addition to the longevity application, understanding the fundamental biology of DNA repair mechanisms has provided new therapeutic target(s) for multiple diseases, such as cancer [7]. For example, the combination of chemotherapeutic reagent with one or multiple inhibitors of DNA repair pathways can bring additional or synergistic outcomes for cancer inhibition [7]. Another example is to target the alterations in the DNA repair pathways in the process of tumor development, i.e., DNA perturbation and high genetic instability. This allows the use of a medicinal chemistry designed inhibitor to act as monotherapy to attack lethal interactions between a tumor defect and DNA repair pathway [7]. Moreover, scientists already envisage that DNA repair inhibitors could be used to amplify tumor-specific replication lesions due to oncogene activation or the tumor microenvironment to kill cancer cells with high specificity [8]. These new strategies have led to promising results preclinically and currently tested in several clinical trials for breast and ovarian cancer treatment [7].

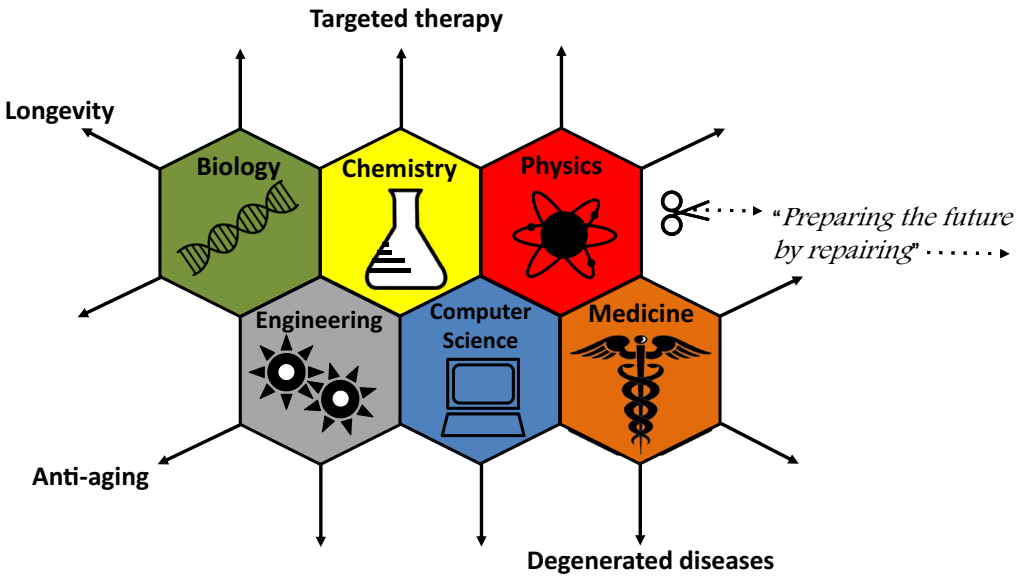

Fig. 2 (Color online) A diagram to represent the different areas of interdisciplinary potential for the future following the discovery of DNA repair mechanisms

Understanding DNA damage can also positively impact the treatment for neurological disease [8]. It has been revealed that the nervous system could be profoundly involved DNA repair deficiency, leading to neurodegeneration disease (Alzheimer's and Parkinson's disease), microcephaly, and glioma [8]. An efficient DNA repair mechanism is required at both the rapid cellular proliferation (*a.k.a* developmental) stage and after replication (*a.k.a* maturation) stages in the brain. The high brain oxidative load as well as the oxidative oxygen stress species generation can result in various DNA damage, such as single-/double-strand breaks, base modifications, helix-distorting lesions, or cross-links of DNA strands, similar to other cell types [8]. Blocked base excision repair pathway or nucleotide excision repair pathway can lead to human neurological disease, with the different neuropathological outcome that relates to the type of damage and the stage at which it occurs. While efficient treatment for DNA repair deficiency in brain is not a trivial task, one thing is crystal clear at this stage is that a rational medicinal design of such drug and therapeutic approach requires the fundamental understanding of neuro-biochemistry (including DNA repair) at a molecular level.

3 The future of science: an interdisciplinary effort

While there are different options on given the Chemistry Nobel Prize in the field of non-classic (or pure) chemistry topic, over the last decade, this award has often gone to biochemistry, which this year is no an exception. As a result of multidisciplinary research, the borders of classic disciplines are becoming almost blurry, and a more integrative/mutualistic symbiosis is taking place, thus creating a much more profound well-rounded investigation. The results are, in our opinion, definitely more fruitful as given is some examples below.

In addition to DNA repair, one impressive example is nano-/bioresearch, which intrinsically requires a multidisciplinary science approach (Fig. 3a). With the nanoindustry exponentially growing, there is a need for hazard assessment, sustainability, and research on potential safe implementation of nanotechnology in different fields (e.g., nanomanufacture and nanomedicine). As illustrated in Fig. 3a, a multidisciplinary approach is needed to cover all these necessary areas through knowledge acquisition, research, and policy making.

The similar impact can be also illustrated in the emerging technology, such as an incremental concept like eHealth (Fig. 3b). Scientists and engineers proposed the concepts, i.e., the idea of eHealth (computers/health/monitoring) was initiated a while ago. However, it is only recently in the last couple of years that we have seen the phenotype, e.g., Misfit® and Fitbit®, emerge into commercialism to monitor and measure things such as calories, blood pressure, pulse, and glucose. The success of this phenotype, which requires integration of a variety of expertise domains, illustrates a perfect example of multidisciplinary research and innovation.

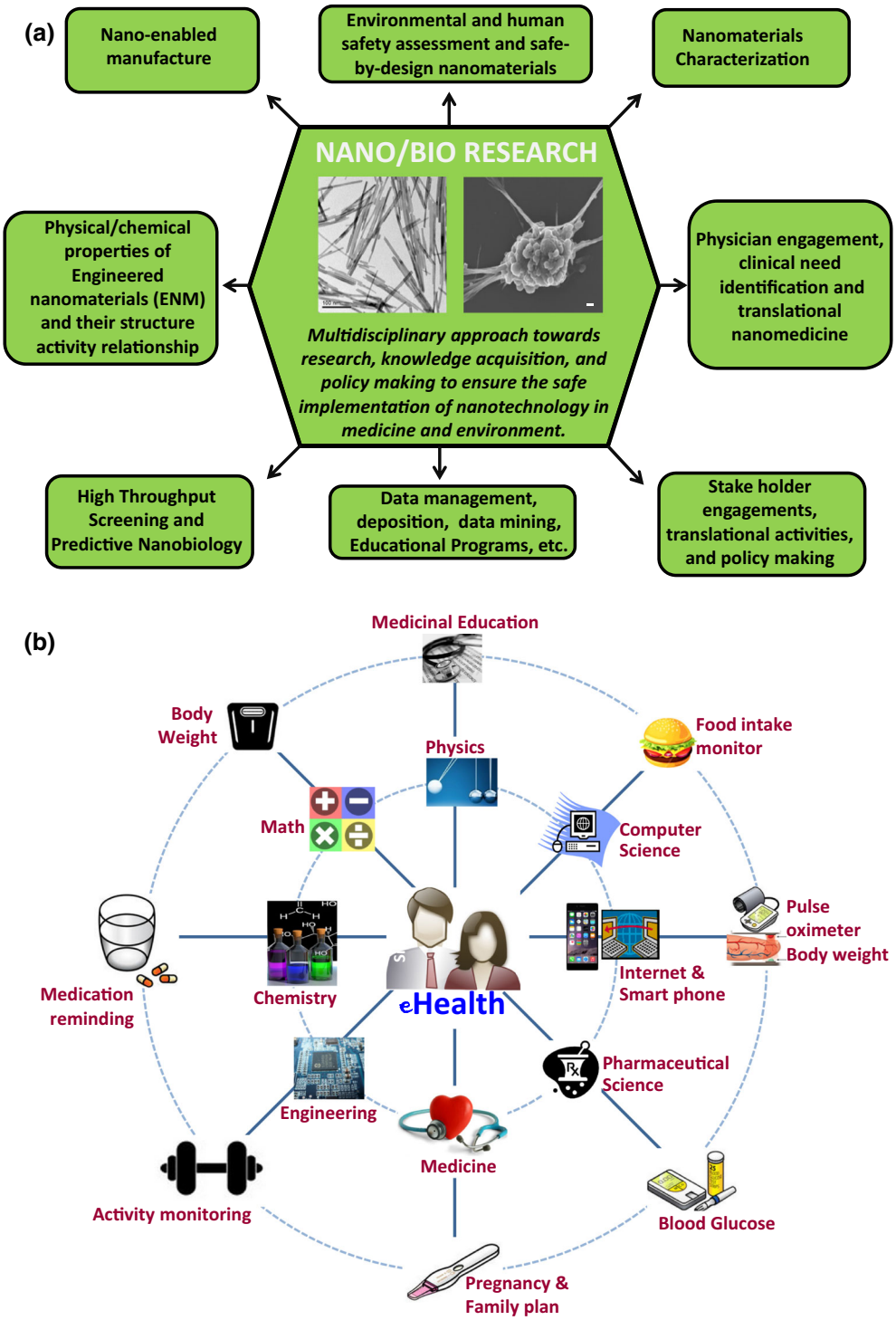

Fig. 3 (Color online) Diagrams to illustrate the perspective on the impact of multidisciplinary science approach in the 21st century. **a** Nano-/biointerface study serves as an example to illustrate how the multidisciplinary research significantly advances the sustainable implementation of nanotechnology including the development of more efficacious and safer nanomedicine. This requires the strategic integration of various expertise domains, including the establishment of nanomaterial libraries, physicochemical characterization, high throughput screening safety assessment, computer-aided data deposition and data mining, physician-engaged nanomedicine development/test, and required regulatory policy making facilitating translation. **b** Another multidisciplinary science development example of eHealth. The concept of eHealth is based on using various technologies/knowledge to improve the quality of current state-of-the-art health care. Various eHealth prototypes have emerged. Although the "e" in these first-generation eHealth products represents the "electronic", we envisage the scope and definition should be largely expanded with a view to impact broader spectrum of human health care

This is just the beginning for the interdisciplinary development in science and one thing is for certain; the future of science requires a more dynamic, sophisticated seamless integration (like the continuous buildup of a honeycomb network in Fig. 2), which allows and promotes us to make more and even bigger breakthroughs.

References

1. Lindahl T (2013) My journey to DNA repair. Genomics Proteomics Bioinformatics 11:2–7
2. Lindahl T (1993) Instability and decay of the primary structure of DNA. Nature 362:709–715
3. Sancar A (1996) DNA excision repair. Annu Rev Biochem 65:43–81
4. Sancar A, Lindsey-Boltz LA, Ünsal-Kaçmaz K et al (2004) Molecular mechanisms of mammalian DNA repair and the DNA damage checkpoints. Annu Rev Biochem 73:39–85
5. Modrich P, Lahue R (1996) Mismatch repair in replication fidelity, genetic recombination, and cancer biology. Annu Rev Biochem 65:101–133
6. Modrich P (1994) Mismatch repair, genetic stability, and cancer. Science 266:1959–1960
7. Helleday T, Petermann E, Lundin C et al (2008) DNA repair pathways as targets for cancer therapy. Nat Rev Cancer 8:193–204
8. McKinnon PJ (2009) DNA repair deficiency and neurological disease. Nat Rev Neurosci 10:100–112