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Review

Phenotyping for DNA repair capacity

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ABSTRACT

The ability to repair DNA damage is strongly associated with the risk of cancer and other human diseases as it is essential for maintenance of genome stability. Moreover, DNA repair capacity is an important factor contributing to the inter-individual variability in mutagen exposure, cancer development and treatment through an individualized adjusted therapy. In addition to genotypes, functional phenotypic assays which integrate the different pathways provide useful tools to explore the role of DNA repair in cancer susceptibility.

This review compares the presently available cellular DNA repair phenotype assays based on their characteristics, and discusses their advantages and limitations. Assays for assessment of DNA repair phenotype should be well characterized in terms of reliability, validity, sensitivity, inter- and intra-individual variability, and cancer predictivity.

Our comparison reveals that the G_1 and G_2 challenge assays, although labour-intensive, can be considered as very useful assays to investigate DNA repair phenotype. They have been successfully applied to investigate repair capacity of both cancer patients and environmentally exposed populations, and can detect deficiencies in different repair pathways. Moreover, these assays allow to predict the cancer therapy responses and to investigate the cancer prognosis.

Nevertheless, the choice of the assay depends on the scientific question addressed and on the objective of its application and more prospective studies are needed since the phenotype could reflect the pathophysiological alterations in the patient secondary to the disease.

Contents

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1. Introduction

The ability to repair DNA damage is strongly associated with the risk of cancer and other human diseases such as neurodegenerative and inflammatory disorders and aging (for review [1]) as it is an ubiquitous defence mechanism that plays an essential role in cell survival and the maintenance of genome stability.

DNA repair capacity is an important factor contributing to the inter-individual variability in response to mutagen exposure and cancer susceptibility [2]. Assessing this inter-individual variability in repair capacity is crucial in providing biomarkers not only for primary cancer prevention and early diagnosis but also for cancer treatment through individual adjusted radio- or chemotherapy. The discovery of millions of genetic polymorphisms in the human genome has sparked the hope that these variations in DNA sequences are the basis for inter-individual variations and will be useful for risk assessment and treatment of diseases, including cancer. One might consider that all genotypes of an individual can technically be described and, starting from this knowledge, extrapolate the potential functional activity also known as the phenotype. However, many factors can modulate this genotype–phenotype extrapolation including alternative splicing, gene silencing, post-transcriptional regulation, protein–protein interactions, and the fact that transcription of the genes is tissue and age dependent. Furthermore, environmental factors can modify both the DNA sequence (mutation) and/or regulation of transcription (epigenetic changes). If we consider a simple case, it is technically feasible to assess the functional activity of the protein corresponding to a given DNA sequence, as far as its function and target are known, this is a phenotype at molecular level. When the studied endpoint (e.g. repair of DNA strand breaks) is controlled by different gene products regulating a given pathway or different pathways, the complexity of the interactions is difficult to extrapolate from the knowledge of the individual molecular phenotypes, and a cellular phenotype integrating the interplay of the different enzymes and pathways might be a very useful information. Moreover it would allow to compare, for a same genotypic configuration, the efficiency of the functional activity of the gene product between different populations, e.g. between adults and newborns [3]. Ultimately, combination of the cellular phenotypes of different tissues would provide a realistic approach of the individual physiology and response to environmental changes.

The cell has developed a network of DNA repair mechanisms, to ensure that the large variety of DNA lesions induced by exogenous and endogenous sources are effectively dealt with. In the human genome more than 130 genes have been found to be involved in these DNA repair systems. At least four, partly overlapping, main repair pathways operate in the removal of DNA lesions: base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR) and double-strand break repair (DSBR) [1,4] (Fig. 1).

BER is the primary DNA repair pathway responsible for the correction of base lesions resulting from oxidative damage, alkylation, deamination and depurination/depyrimidination, as well as DNA single-strand breaks, two principal mechanisms are used: non-homologous end-joining (NHEJ) and homologous recombination (HR) (for review [5,6]). NER corrects a wide variety of DNA lesions, including chemically induced bulky adducts, intra- and interstrand cross-links, UV-induced pyrimidine dimers and photoproducts. In addition, NER can also recognize oxidative damage that poses a special challenge for BER: cyclopurines (for review [6,7]). This repair pathway consists of two branches: global genome repair (GGR), which probes the genome for strand distortions, and transcription-coupled repair (TCR), which removes distorting lesions that block elongating RNA polymerases. DSBR performs the repair of DNA double-strand breaks induced by endogenous and exogenous attacks on the DNA backbone, as well as by the conversion of single-strand breaks into double-strand breaks during DNA replication (for review [6,8]). DNA damage that blocks the regular replication machinery involving DNA polymerase δ/ε (e.g., breaks and cross-links) can be repaired, bypassed by homologous recombination, which involves template switching and strand displacement, or bypassed by translesional synthesis (TLS), a specialized, relatively error-free (but still somewhat mutagenic) means of bypassing a specific subgroup of lesions (for review [6]). The MMR system is responsible for the removal of base

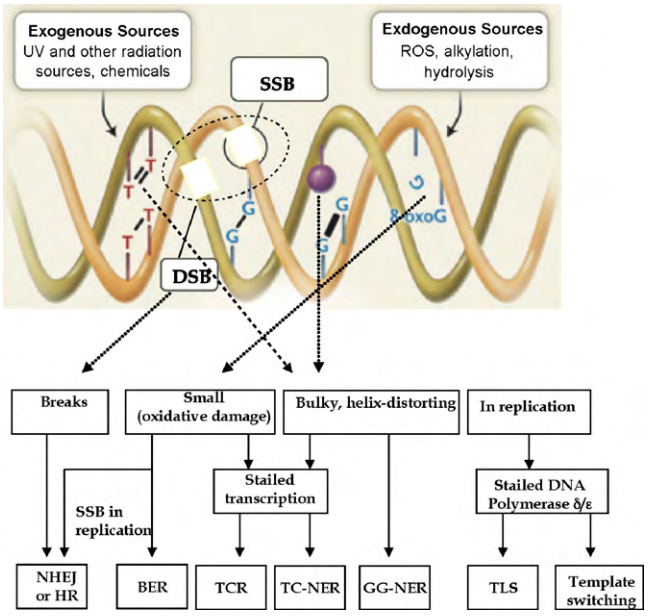

Fig. 1. Overview of the different DNA lesions and their DNA repair systems (Adapted from Hoeijmakers et al. [6]), abbreviations: see text.