Functional DNA repair assays with clinical and translational applications

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Abstract:
High-throughput RNA and DNA sequencing approaches continue to yield informative data that provides insights into genomic patterns and variations that influence disease susceptibility and therapy outcome in cancer. The field is currently in need of high-throughput functional assays to test the impact of genetic variations identified by these next generation genomic techniques. Such methods are essential to identify mutations and genetic patterns that drive cancer or impact response to treatment. Since a majority of diseases associated with genome instability are driven by dysfunctional DNA repair pathways, there is an urgent need for assays that can effectively characterize mutations in DNA repair genes. This review outlines salient DNA repair pathways and functional repair assays described in literature that have clinical applications.

Keywords: DNA repair, functional genomics, cancer, biomarkers, functional repair assays

Introduction

Genomic instability is the hallmark of various diseases including cancer and neurodegenerative disorders (1-4). Maintenance of genomic stability is primarily conducted by DNA repair mechanisms which have evolved into sophisticated pathways that can guard against multiple forms of damage to the genome including stress responses, aging, oxidative damage and environmental carcinogens (5-8). DNA repair is also involved in cellular resistance to chemotherapeutic agents that elicit tumor cell killing through DNA damage (9-12). This ubiquitous and vital role of DNA repair in preventing disease, maintaining genomic integrity and influencing response to therapy, makes it an extremely significant diagnostic and predictive determinant (12-16).

This review aims to first describe in brief the various DNA repair pathways that are known to play a role in disease susceptibility and therapy resistance and then discuss some of the salient functional DNA repair assays that have clinical applications.

DNA Repair Pathways

Mismatch Repair (MMR): MMR is a mechanism that detects and resolves mispaired bases resulting recombination or replication events that cause insertions or deletions (17,18). Defects in MMR are associated with increased microsatellite instability which is used a biomarker for certain cancers such as hereditary nonpolyposis colorectal cancer which results from MMR gene mutations (19-21).

Nucleotide Excision Repair (NER): NER detects bulky adducts that distort the DNA helix and removes single-stranded segments containing the lesion. It is particularly relevant towards repair of DNA adducts caused by environmental carcinogens such as UV light and polycyclic aromatic hydrocarbons (22-24). Transcription coupled repair (TCR) is considered a specialized sub-pathway of NER which repairs lesions encountered on an actively transcribing gene and thus protects against transcriptional mutagenesis (25-27). Defects in NER results in the Xeroderma Pigmentosum phenotype characterized by extreme sensitivity to UV light and cancer susceptibility. Defective TCR, on the other hand, causes accelerated aging and neurodevelopmental delays as seen in Cockayne Syndrome (28-32).

Base Excision Repair (BER): BER excises non-bulky DNA lesions that impede replication or result in incorrect DNA base pairing. The removal of the patch of single-stranded DNA is followed by DNA synthesis by DNA Polymerase β (Pol β) which is mutated in 30% of all human cancers (33-36). Since BER removes alkylated bases, it is an important mechanism in cellular resistance to alkylating chemotherapeutic agents (37-40).

Double Stranded Break Repair (Homologous Recombination & Non-Homologous End Joining): Homologous recombination (HR) and Non-homologous End Joining (NHEJ) are the two main pathways involved in the repair of double-stranded DNA breaks (DSBs) (41). DSBs are a particularly deleterious form of DNA damage since repair is not aided by the availability of an undamaged complementary strand. HR acts during the S and G2 phases of the cell cycle when a homologous sister chromatid is available as a template to repair the missing genetic code while various forms of NHEJ exist throughout the cell cycle to join the broken ends (42,43). While reduced HR is associated with elevated breast and ovarian cancer risk, increased HR rate has been observed in Bloom's' Syndrome as detected by the sister-chromatid exchange (SCE) assay which shows an increased frequency of SCEs (44). The two main familial breast cancer susceptibility genes, BRCA1 and 2, are major players in HR (45,46). Defective NHEJ is characterized by extreme radiosensitivity and immunodeficiency (47-49). Both HR and NHEJ are mechanisms of chemoresistance since a wide variety of anticancer therapies such as topoisomerase inhibitors, crosslinkers, alkylating agents and radiation, cause cell killing through DSBs (50-53). Polymorphisms in HR and NHEJ influence therapeutic outcome in various cancers and small molecule inhibitors that affect these pathways are being identified and explored as adjuvant agents to improve the efficacy of anticancer drugs (54).

Table 2.

Assay Type	**Assay subtype**	**Damage type measured**
Enzymatic or biochemical assays	Nuclear/ protein extracts	BER (55), HR (56), NHEJ (57), NER (58),
	Site-specific DNA lesions (in-vitro assay using cell extracts)	Multiple DNA repair assays (test the effect of DNA lesion on replication, transcription) (59-62)
DNA damage response/ challenge assays	Direct DNA repair markers (foci, comet assay)	HR (63,64), NHEJ (65), NER (66-69),
	Response to pharmacological agents	HR, NHEJ, NER, BER
	Indirect markers: microsatellite instability, sister chromatid exchanges, micronucleus assay, anaphase bridges.	MMR (70-72), HR (73), generic DNA repair integrity/ genome instability assays (74,75)
Plasmid Reactivation Assays	non-specific lesions, site-specific lesions, enzyme induced lesions (DSBs)	HR, NHEJ, NER, TCR (76-84)

Single Stranded Break Repair Assays:

1. Enzymatic repair assays: These assays that measure the activity of specific BER and NER DNA repair enzymes using substrates and have broad clinical applicability as they can be conducted using extracts from human cells and tissue samples. In 1973, RJ Wilkins (85) refurbished an assay originally employed by Strauss et al. (86) in bacteria to evaluate DNA repair capacities using an enzymatic assay, sensitively and rapidly in human cells. The assay principle was based on the changes in DNA molecular weight dependent on endonuclease sensitive sites caused by DNA breaks. Since single stranded breaks are intermediates of NER, this assay measured excision repair capacity. This brief study, using the radioactive profile of UV-treated DNA reported that while normal human fibroblasts reduced the UV-induced endonuclease sensitive sites in DNA over time, cells derived from NER-deficient xeroderma pigmentosum (XP) patients did not, indicating a defect in repair capacity in the XP cells. Livneh et al. described an epidemiology-grade assay to measure the enzymatic activity of the DNA repair enzyme 8-oxoguanine DNA glycosylase (OGG) in protein extracts from human blood cells (87). This assay was based on the removal of the oxidative lesion 8-oxoG from DNA by OGG and can measure damage/ repair of lesions caused by agents such as cigarette smoke, intracellular metabolism and ionizing radiation. This assay is particularly useful in measuring exposure to environmental carcinogens that cause oxidative damage and oxidative stress caused due to aging. Moreover, the OGG assay established a link a between reduced BER activity and increased non-small cell lung cancer risk. More recently, this group also developed an assay to measure the activity of methylpurine DNA glycosylase (MPG), a key enzyme in BER which identifies the damaged base, excises it from DNA, creating an abasic site, which is removed and replaced using information from the complementary strand. This radioactive assay measured the excision of a site-specific lesion by protein extracts derived from patient blood cells. The resultant nick at the site of the lesion was quantitated by polyacrylamide gel electrophoresis. Due to the broad specificity of the MPG enzyme, this assay can be used to measure repair capacity in response to oxidative metabolites of environmental carcinogens as well as chemotherapeutic agents. A major limitation of the enzymatic assays is its narrow application towards specific enzyme substrates. The unscheduled DNA synthesis (UDS) assay measures cellular NER capacity by measuring the amount of radioactive thymidine incorporated into DNA during repair synthesis after UV damage. This assay has been used to specifically detect the repair of photoproducts and pyrimidine dimers following UVC damage to the whole genome and has been used to measure the NER capacities of clinically derived samples (88).
2. DNA damage response assays: Development of the comet assay offers a non-radioactive and sensitive technique for quantification of DNA strand breaks generated as intermediates during both BER and NER. In 1984, Ostling and Johanson described a method for measuring DNA damage by lysing cells embedded in agarose gel followed by electrophoresis and fluorescent staining to visualize the migration of broken

DNA which resembles a comet-like structure (89). As described by Olive et al. in various publications, the length and structure of the "comet" is proportional to the amount and type of damage and neutral versus alkaline conditions during lysis of the cells can be used to distinguish between double versus single stranded breaks. Inclusion of lesion-specific endonucleases following lysis can further add to the specificity of the comet assay (90). The mini-gel format which accommodates more samples has been used to increase the throughput of the comet assay and apply this method to evaluate DNA repair activity as a biomarker in cancer biopsies (91).

3. Plasmid reactivation assays: The plasmid reactivation or host-cell reactivation assays provide a direct measure the repair capacity of cells using a plasmid containing the lesion and a reporter gene to monitor repair (92,93). These assays have been widely used to measure the effects of polymorphisms in NER genes on repair capacity (94). The reporter genes include chloramphenicol acetyltransferase (CAT) and luciferase genes. The plasmid DNA is first damaged by subjecting it to UV-light and then transfected into respective cells lines to evaluate repair and reactivation of reporter gene by the host cell. A more specialized version of this assay includes an oligonucleotide containing a site-specific lesion incorporated into the reporter gene in a plasmid. This assay has been used by Scicchitano et al. to study transcriptional mutagenesis and transcript elongation past specific lesions. Initially, linear DNA templates containing a single, site-specific DNA lesion were constructed using biotin-avidin interactions and paramagnetic particles to purify the final product. This assay was used to evaluate the effects of several DNA lesions including DNA adducts derived from tobacco carcinogens on transcription elongation and to study the impact of stalled transcription complexes on DNA repair. An advanced and specialized form of this assay was then developed by Scicchitano et al. to study the effects of site-specific lesions in cells using a plasmid constructed using the gapped-duplex method with an oligo containing the lesion in the fluorescent reporter gene. Repair of the lesion results in activation of fluorescence measured by flow cytometric analysis of cells transfected with the reporter plasmid. Using this strategy, the group reported that the O6-methylguanine lesion induces transcriptional mutagenesis in human cells. The non-radioactive and high-throughput nature of the plasmid/ host cell reactivation assays give it several advantages over enzymatic and comet assays with transfection efficiency being a limiting factor which in turn is dependant on the cell lines being used.

Double-strand break Repair (DSBR) Assays: Homologous recombination (HR) and non-homologous end joining (NHEJ) are the two major DSBR pathways.

1. Enzymatic/ Protein extract assays: The ability of proteins extracts to support HR and NHEJ has been used to measure and compare repair proficiencies of cells and tissue samples by measuring recombination repair or rejoining of DSBs in reporter genes thus combining the enzymatic approach with plasmid/ reporter gene activation to provide a quantitative output of repair capacity.
2. Foci: DNA damage induced foci and localization of repair proteins have been used as a marker of DSBs and repair kinetics (65). Various proteins form

punctate foci at the site of DSBs and removal of the foci coincide with repair of the DSB lesions. Gamma-H2AX foci in particular have been widely used as a biomarker for exposure to DSB causing agents and also to study the effects of mutations on repair capacity (63,64). This marker has been used by clinical studies to measure the effects of therapy or cancer progression on DSB formation (95-98). Several studies have also documented the use of flow cytometric quantitation of gamma-H2AX foci based on a method optimized by Olive et al.(99-101).

3. Plasmid reactivation assay: Host cell reactivation assays have been commonly used in measuring HR capacity of human cells (102,103). A particularly high-throughput and effective assay based on plasmid reactivation was designed and executed first by Maria Jasin's group and later by the Gorbunova group (104-107). In the initial version of this assay, the I-SceI endonuclease is used to generate site-specific DSBs in a reporter gene. Cells are transfected with the reporter plasmid and output is measured by fluorescent analysis. Gorbunova et al. improved upon this methodology by using alternate orientations of the I-SceI recognition sites which could result in either incompatible or compatible sites which were substrates for either HR or NHEJ and allowed for direct comparisons between HR and NHEJ capacities/ frequencies in cells. Using this method, Gorbunova et al. reported that HR and not NHEJ is elevated in breast cancer cells. This method has wide clinical applicability especially in the area of personalized medicine in aiding selection of small molecule DNA repair inhibitors as adjuvant therapy to improve chemotherapeutic outcome. This approach can also be used to study factors influencing choice of DSBR pathway specifically during the emergence of chemoresistance or cross resistance to DSB causing anticancer agents.

Conclusion & remarks:

Current focus within the field is on obtaining global gene expression data which reveals new mutations, differentially expressed transcripts and provides a valuable snapshot of the cell's transcriptome (108-114). This approach has to led to some extremely informative studies including an exhaustive analysis comparing the genome of normal and oral cancer tissues (115,116) and a dissection of transcriptomic differences between post-mortem tissue samples from Alzheimer's and healthy brains (117-120). However, two major challenges of this approach remain the cost and the downstream interpretation of the large volumes of data. Validation through functional analysis is required especially in dissecting the role of specific gene expression patterns or pathway such that they can be used to further identify molecular targets for therapy. Tailoring assays described in this review for high-throughput use can assist in evaluating the impact of genetic defects in clinical samples and provide a functional tool to determine treatment approach and predict therapeutic outcome.

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