Ageing Research Reviews xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Quality control mechanisms in cellular and systemic DNA damage responses

Q1 Maria A. Ermolaeva[a,b,*], Alexander Dakhovnik[a,b], Björn Schumacher[a,b]

[a] Institute for Genome Stability in Ageing and Disease, Medical Faculty, University of Cologne, Joseph-Stelzmann-Str. 26, 50931 Cologne, Germany
[b] Cologne Excellence Cluster for Cellular Stress Responses in Ageing-Associated Diseases (CECAD) and Systems Biology of Ageing Cologne, University of Cologne, Joseph-Stelzmann-Str. 26, 50931 Cologne, Germany

ARTICLE INFO

Article history:
Received 25 September 2014
Received in revised form
21 December 2014
Accepted 23 December 2014
Available online xxx

Keywords:
DNA damage
Ageing
Ubiquitin proteasome system
DNA repair
Progeroid syndromes
Genome stability

ABSTRACT

The maintenance of the genome is of pivotal importance for the functional integrity of cells and tissues. The gradual accumulation of DNA damage is thought to contribute to the functional decline of tissues and organs with ageing. Defects in multiple genome maintenance systems cause human disorders characterized by cancer susceptibility, developmental failure, and premature ageing. The complex pathological consequences of genome instability are insufficiently explained by cell-autonomous DNA damage responses (DDR) alone. Quality control pathways play an important role in DNA repair and cellular DDR pathways. Recent years have revealed non-cell autonomous effects of DNA damage that impact the physiological adaptations during ageing. We will discuss the role of quality assurance pathways in cell-autonomous and systemic responses to genome instability.

Contents

Abbreviations: ARF, adenosine diphosphate ribosylation factor; AT, ataxia telangiectasia; ATM, ataxia telangiectasia mutated; ATP, adenosine triphosphate; BER, base excision repair; CEP-1, *C. elegans* p53-like 1; COFS, cerebro-occulo-facio-skeletal syndrome; CPD, cyclobutane pyrimidine dimer; CS, cockayne syndrome; CSA and CSB, cockayne syndrome complementation group A and group B proteins; CUL4, Cullin 4; DDB2, DNA damage binding protein 2; DDR, DNA damage response; DSB, DNA double strand break; ERCC-1, excision repair cross-complementation group 1; ERK, extracellular signal regulated kinase; FA, Fanconi anaemia; FOXO, forkhead box protein class "O"; GDISR, germline DNA damage-induced systemic stress resistance; GH, growth hormone; HIF-1, hypoxia inducible factor 1; HR, homologous recombination; ICLs, inter-strand crosslinks; IGF-1, insulin like growth factor 1; IL, interleukin; JAK, Janus kinase; JNK, c-jun N-terminal kinase; K63, Lysine 63; MAPK, mitogen-activated protein kinase; MDM2, mouse double minute 2 homolog; MMS2, methylmethane sulphonate sensitive protein 2; MPK-1, mitogen-activated protein kinase 1; NER, nucleotide excision repair; NBS, Nijmegen breakage syndrome; NF-κB, nuclear factor kappa B; NHEJ, non-homologous end joining; PCNA, proliferating cell nuclear antigen; PMK-1, p38 MAP kinase family 1; RAD, radiation sensitive; RANKL, receptor activator of nuclear factor kappa B ligand; RNAPII, RNA polymerase II; ROS, reactive oxygen species; RPA, replication protein A; SASP, senescence associated secretory phenotype; Sirt6, Sirtuin 6; STAT, signal transducer and activator of transcription; TYR, tyrosinase; TLS, translesion synthesis; Ubc, ubiquitin conjugating protein; UPR, unfolded protein response; UPS, ubiquitin proteasome system; UV, ultraviolet light; XP, Xeroderma pigmentosum; XPC, Xeroderma pigmentosum complementation group C protein; 6-4PPs, pyrimidine (6–4) pyrimidone photoproducts.

Q2 * Corresponding author at: Cologne Excellence Cluster for Cellular Stress Responses in Ageing-Associated Diseases (CECAD) and Systems Biology of Ageing Cologne, University of Cologne, Joseph-Stelzmann-Str. 26, 50931 Cologne, Germany. Tel.: +49 2214701647.
E-mail addresses: ermolaem@uni-koeln.de (M.A. Ermolaeva), bjoern.schumacher@uni-koeln.de (B. Schumacher).

http://dx.doi.org/10.1016/j.arr.2014.12.009
1568-1637/

1. DNA repair machineries maintain genome integrity

The nuclear genome, with the exception of a few mitochondrial genes, harbours the entire genetic information of a cell. The genomic sequence, once altered or lost, cannot be replaced. However, the genome is constantly attacked by a large variety of genotoxic insults. It has been estimated that in each cell tens of thousands of damaging events occur on a daily basis (De Bont and van Larebeke, 2004). DNA damage can be inflicted by exogenous sources such as the UV irradiation of the sun, ionizing radiation, or chemicals. Also endogenous by-products of the cellular metabolism such as reactive oxygen species (ROS) attack the genome. The types of DNA lesions can vary widely. Single strand breaks are probably the most frequently occurring lesions, followed by spontaneous depurination, alkylations, various oxidative base modifications, and deamination. Even highly cytotoxic lesions such as double strand breaks and interstrand crosslinks that are induced during anti-tumour therapeutic interventions also occur endogenously (De Bont and van Larebeke, 2004; Schärer, 2005). Genotoxins have from the early steps of evolution threatened the maintenance and inheritance of the genetic material and thereby of life itself. Therefore, DNA repair systems are required to remove the damage and maintain genome integrity (Table 1). The first challenge of the DNA repair machinery is the recognition of the altered DNA structure. This might be rather obvious if a strand break occurs or a replication fork stalls at obstructive lesions. However, slight structural alterations require highly specialized recognition molecules that allow distinguishing the damaged DNA from normal structural alterations occurring e.g. during decondensation of the double helix as part of the DNA metabolism. The damage recognition is tightly linked with the most appropriate DNA repair mechanism. For instance, the frequently occurring oxidative lesions are effectively removed by base excision repair (BER) that uses glycosylases to excise the damaged base and short-patch or long-patch repair to refill the gap (Sung and Demple, 2006). Single strand break repair rapidly joins the frequently arising breaks in one of the DNA strands (Caldecott, 2008). UV-induced cyclobutane pyrimidine dimers (CPDs) lead to a slight helix distortion that requires highly sophisticated recognition systems before they are excised by nucleotide excision repair (NER) (Cleaver et al., 2009). Global genome (GG-) NER scans throughout the genome for helix-distorting lesions, while transcription-coupled (TC-) NER activates the repair once RNA polymerase II (RNAPII) stalls at a lesion. While transcription is a relatively slow process, replication forks need to move quickly through the genome to enable timely replication during quick cycles of cell divisions. Therefore, specialized DNA polymerases are able to read through damaged templates at the risk of incorporating a wrong nucleotide (Sale et al., 2012). Translesion synthesis (TLS) thus facilitates speedy replication fork progression at the cost of elevated error rates. DNA double strand breaks (DSBs) form a serious threat to the genomic integrity of the cell, as aneuploidy might result from aberrant chromosome segregation (Chapman et al., 2012). DSBs can be repaired quickly by non-homologous end joining (NHEJ) and yet again speed comes at the expense of accuracy as the break sites are resected prior to end joining. More laborious but error free, homologous recombination (HR) uses the undamaged template that is available during late S-phase and G2 phase. HR is also used to resolve replicative impediments that result in strand breaks. During replication, however, HR can lead to chromosomal aberrations demonstrating that DNA repair systems might also themselves become obstructive at times (Wolters et al., 2014).

Table 1
Overview of DNA repair pathways.

Repair system	Type of lesions	Accuracy
Base Excision Repair (BER)	Oxidative lesions	Error free
Nucleotide Excision Repair (NER)	Helix-distorting lesions	Error free
Translesion synthesis	Various lesions	Error prone
Miss Match Repair (MMR)	Replication errors	Error free
Single Stand Break Repair (SSBR)	Single strand breaks	Error free
Homologous Recombination (HR)	Double-strand breaks	Mostly error free
Non-Homologous End Joining (NHEJ)	Double-strand breaks	Mostly error prone
DNA Interstrand Crosslink Repair Pathway	Interstrand crosslinks	Largely error free

The importance of DNA repair systems for human health has become particularly apparent in a wide variety of rare congenital syndromes that are caused by mutations in genome maintenance genes (Schumacher et al., 2008a). Importantly, DNA repair deficiency syndromes precipitate in three major disease components namely developmental impairment, cancer susceptibility, and accelerated ageing (Wolters and Schumacher, 2013). The most severe types already impair early development. For example, while several glycosylases redundantly excise oxidized bases, a complete lack of BER lead to embryonic lethality in mice (Ludwig et al., 1998). Mutations in NER genes can also give rise to growth and mental retardation. Particularly, mutations in the TC-NER specific components *CSA* and *CSB* usually give rise to Cockayne syndrome (CS) that leads to postnatal growth defects, mental retardation, and eventually many signs of premature ageing (Marteijn et al., 2014). Other mutations in the same genes can lead to cerebro-occulo-facio-skeletal syndrome (COFS) with patients developing abnormalities already prenatally (Laugel et al., 2010). Strikingly, other mutations in NER genes lead to skin cancer predisposition and pigmentation abnormalities on sun-exposed areas of the skin in Xeroderma pigmentosum (XP) patients (Cleaver et al., 2009). Depending on the specific mutation in NER, XP patients also suffer from mental retardation. However, the clearest link to cancer predisposition is evident when specifically the damage recognition by GG-NER is impaired leading to elevated mutation rates that then fuel the malignant transformation of the damaged cells. In contrast, the TC-NER deficient CS cells are confronted with persistent stalling of the RNA polymerase II (RNAPII) eventually leading to cell death thus fuelling cell loss and tissue degeneration. TC-NER and GG-NER defects have helped to clarify the distinct contributions of unrepaired DNA lesions to cancer development and accelerated ageing. Most patients suffering from premature ageing, however, also show enhanced susceptibility to develop cancer. For example defects in responding to DSBs in ataxia telangiectasia (AT) or Nijmegen breakage syndrome (NBS) patients confers premature ageing as well as highly elevated lymphoma risk (Shiloh, 1997).

The consequences of DNA damage largely depend on the action of the DDR. It has first been recognized in yeast, that cells respond to DNA damage not only by activating the respective repair machinery, but also by halting cell cycle activity until the damage is repaired (Hartwell and Weinert, 1989; Rowley et al., 1992). The DNA damage checkpoints are conserved from yeast to mammals and are important for preventing damaged cells to transforming into cancer cells (Bartek and Lukas, 2007). The most frequent mutations found in human cancers alter the function of the tumour suppressor p53 (Reinhardt and Schumacher, 2012). The p53 gene has evolved during metazoan evolution and orchestrates the checkpoint response. In the simple nematode *Caenorhabditis elegans* p53 controls the apoptotic demise of germ cells that carry unrepaired DSBs in late stages of meiotic pachytene (Derry et al., 2001; Schumacher et al., 2001). The meiotic DNA damage checkpoint exemplifies the significance of apoptosis as additional outcome of the DDR as it allows the removal of genomically compromised germ cells before maternal resources are deposited into growing oocytes

Please cite this article in press as: Ermolaeva, M.A., et al., Quality control mechanisms in cellular and systemic DNA damage responses. Ageing Res. Rev. (2015), http://dx.doi.org/10.1016/j.arr.2014.12.009