Chromatin Plasticity in the DNA Damage Response: a Key Player in Double-Strand Break Repair Pathway Choice

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1 INTRODUCTION

Cellular DNA suffers on average 10^5 lesions per day caused by both exogenous and endogenous factors that severely challenge genome integrity and cell viability. Numerous DNA repair mechanisms exist to cope with these lesions, which repair a 99,98% of them.

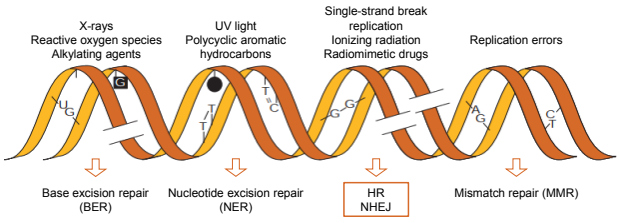
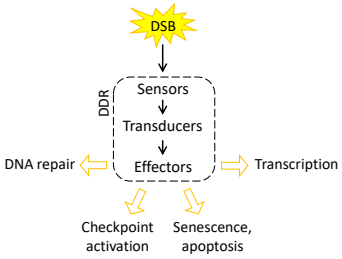


Figure 1. DNA damaging agents, lesions and associated repair mechaisms. Modified from reference (1).



The DNA damage response (DDR) coordinates double-strand break (DSB) repair process

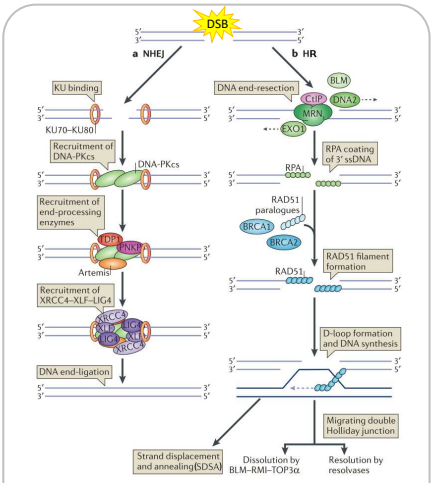


Figure 2. Schematic of the two main DNA DSB repair pathways: **a**) NHEJ and **b**) HR. Modified from reference (2).

2 AIMS

To analyse the active role of chromatin plasticity following a DNA double-strand break in the four major outcomes of the DDR:

1. Checkpoint activation
2. **DNA repair factor recruitment and DSB repair pathway choice**
3. Local chromatin structure alteration
4. Modulation of the gene expression profile

3 METHODOLOGY

- Literature search in the databases PubMed and Scopus
- **Keywords**: DNA damage response, DSB repair pathway choice, chromatin plasticity, 53BP1, BRCA1
- Selection of reviews and original articles based on abstract, publication date and number of citations
- Information integration and report writing

4 RESULTS

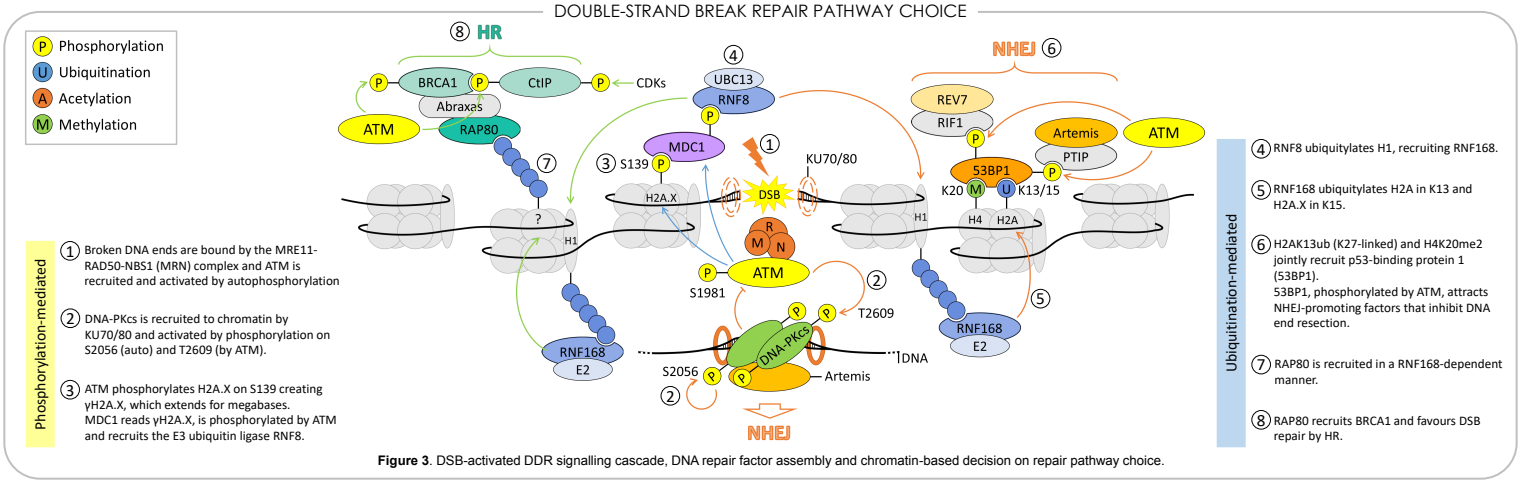


Figure 3. DSB-activated DDR signalling cascade, DNA repair factor assembly and chromatin-based decision on repair pathway choice.

CHECKPOINT ACTIVATION

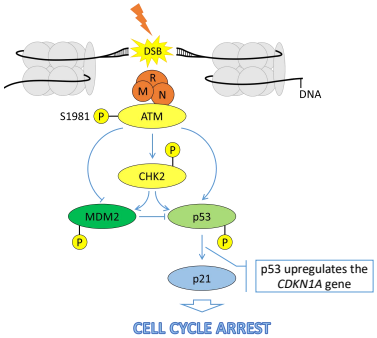


Figure 4. ATM-CHK2 checkpoint activation, p53 stabilization and cell cycle arrest at G1, senescence or apoptosis.

LOCAL CHROMATIN STRUCTURE ALTERATION

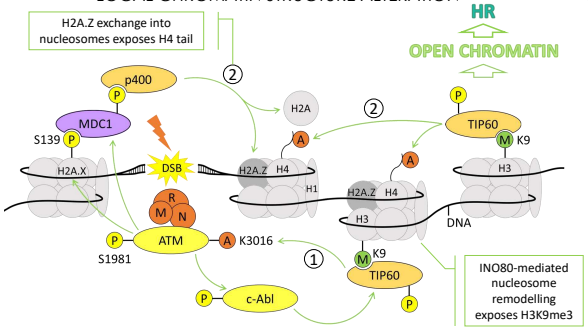


Figure 5. **1**) Chromatin structure-dependent activation of ATM and **2**) NuA4 complex-mediated chromatin decompaction in response to a DSB. p400 and TIP60, along other molecules like TRRAP, form the NuA4 complex. They have been represented separately for simplicity.

TRANSCRIPTION MODULATION

In order to avoid the collision between the transcription and the repair machineries, transcription at DSB sites is repressed and most genes are downregulated.

RNF8/RNF168 E3 ubiquitin ligases
↓
H2A monoubiquitination
↓
RNA polymerase II elongation

Genes encoding DNA repair proteins, histones and nucleotide-synthesizing enzymes are instead upregulated to restore chromatin.

5 CONCLUSIONS

1. The DDR activated by cells in response to DSBs leads to 1) cell cycle arrest, 2) damage signalling, 3) recruitment of DNA repair proteins and damage repair, and 4) modulation of gene expression.
2. Chromatin plasticity actively contributes to the four aforementioned consequences.
3. NHEJ and HR are the two major DSB repair pathways and the choice between them depends on 1) cell cycle phase and 2) the equilibrium between DNA end resection, i.e. BRCA1 recruitment, and DNA end protection, i.e. 53BP1 recruitment, by ATM-activated chromatin-based signalling cascade.
4. Open chromatin domains created at DSB sites to enable the access of the repair machinery promote DSB repair by HR.
5. Strategies to promote the use of HR over NHEJ could facilitate precise DNA modification by gene editing.

6 REFERENCES

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