FROM DOUBLE STRAND BREAK (DBS) SIGNALIZATION TO CHROMOSOME ABERRATION FORMATION

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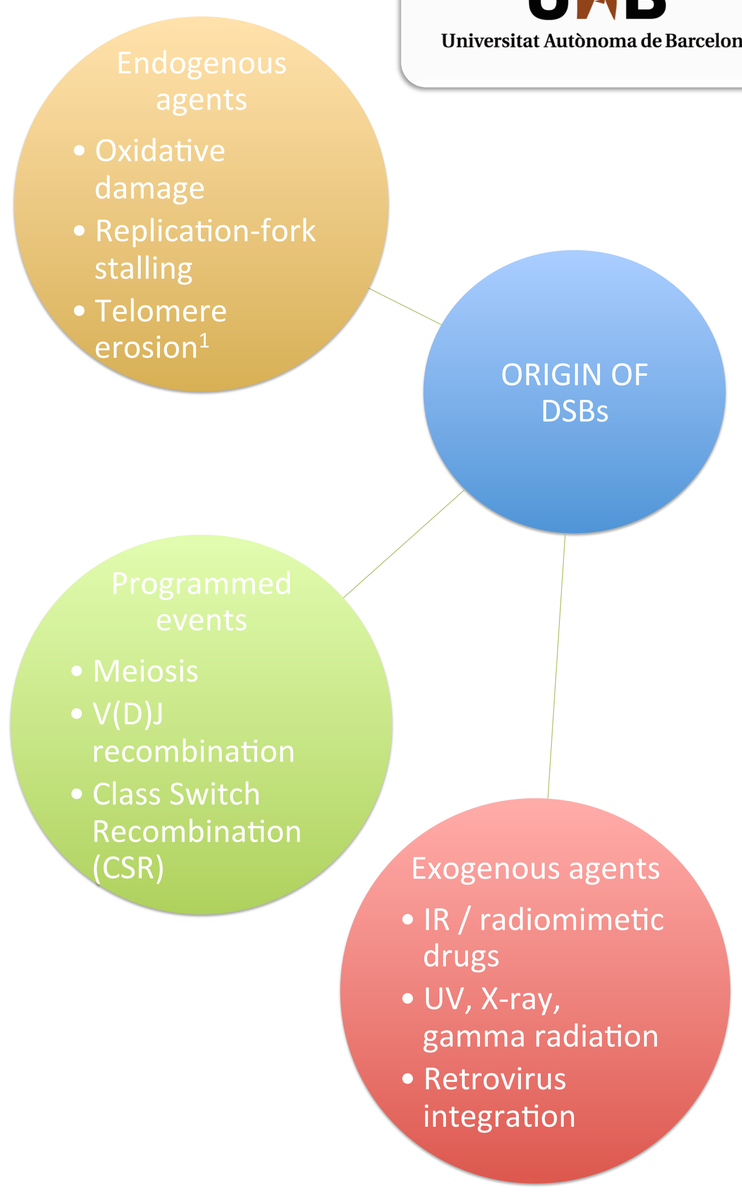
What is a DSB?

A DSB is a break in a DNA duplex in which both strands have been severed at the same place. It is the most deleterious form of DNA damage and inaccurate or lack of repair can lead to mutations or to larger-scale genomic instability (it can promote potentially lethal chromosomal rearrangements). Such genome changes have a tumorigenic potential (activation of oncogenes and/or the loss of tumor suppressors) and in other instances, DSBs can be sufficient to induce apoptosis. DSBs can be repaired by Homologous Recombination (HR) and Non-Homologous End-Joining (NHEJ).

Origin of DSBs:

DSBs are randomly generated by exogenous agents, endogenous events leading to accidental DSB and by cellular programmed events:



Damage DNA Response (DDR):

Sensor proteins recognize DNA damage, transducer proteins amplify and diversify it and a range of downstream effectors regulate several cellular functions.

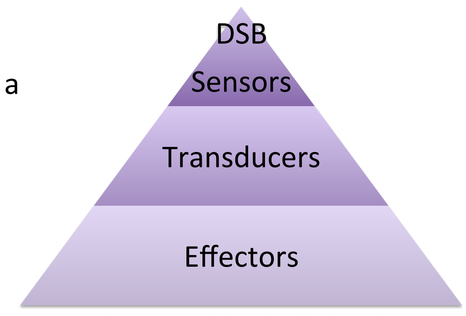


Figure 1. Classical signal-transduction cascades[2]

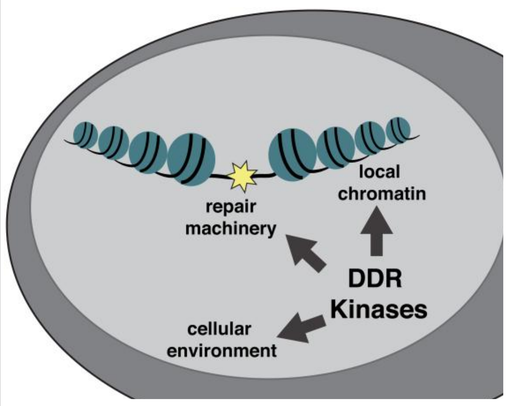


Figure 2. DDR kinases regulation[3]

When a DSB is detected, the DDR leads the signalization pathways to induce cell cycle arrest (or delay the progression) in order to give time to the repairing machinery to repair the damaged DNA. Transcription, chromatin remodeling and apoptosis pathways are also induced by DDR.

DDR kinase signaling cascades include Ataxia Telangiectasia-Mutated (ATM), Ataxia Telangiectasia Rad3-related (ATR) and DNA-dependent Protein Kinase Catalytic Subunit (DNA-PKcs).

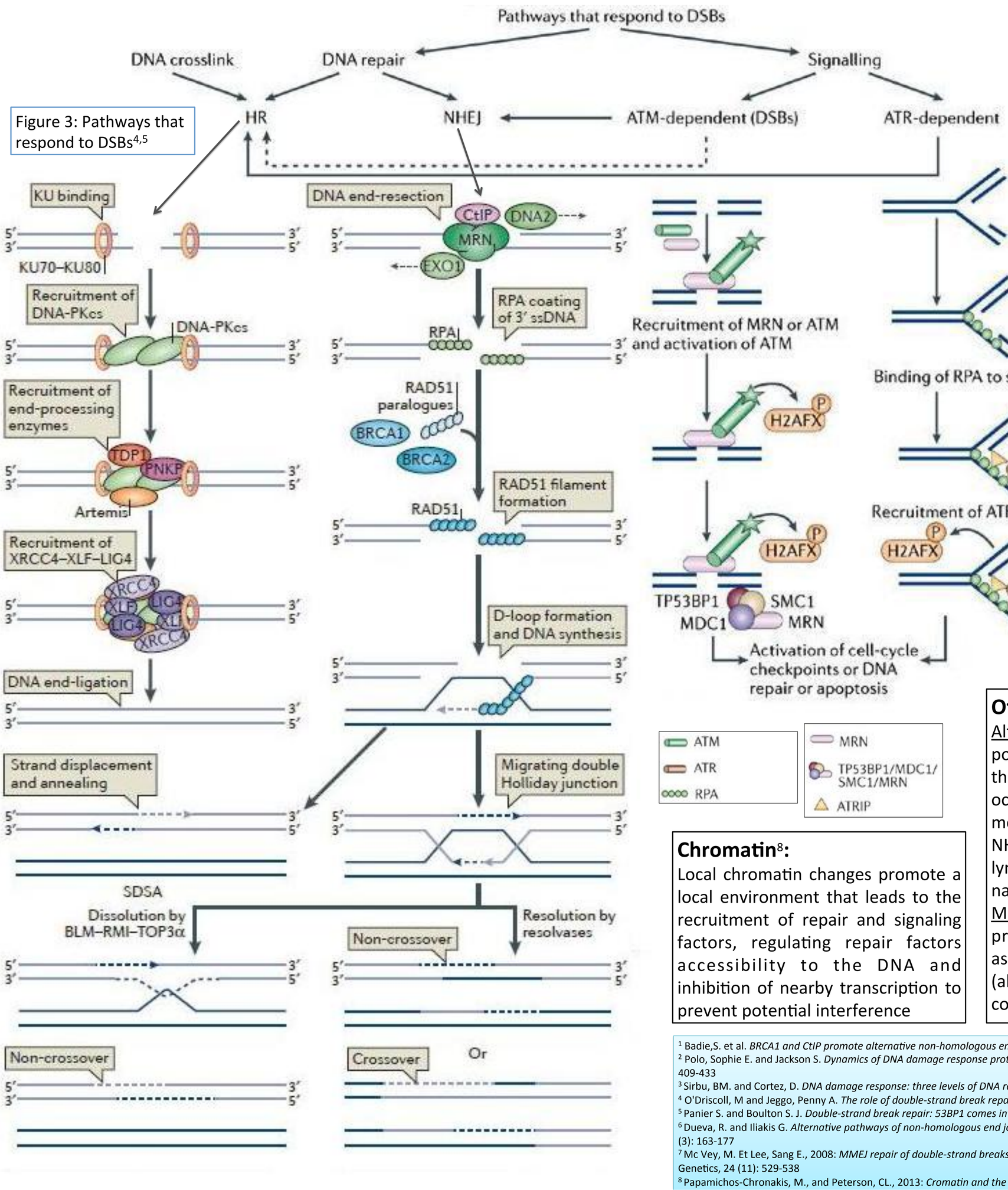


Figure 3: Pathways that respond to DSBs[4,5]

The two main DSB repair pathways in eukaryotic cells:

HR utilizes an undamaged homologous sequence as a repair template (preferably sister chromatid) and this type of repair is conservative and non-mutagenic. As sister chromatids don't exist in G1 phase of the cell cycle, HR occurs specifically in late S and G2 phases.

In G1, the main repair pathway is NHEJ although it functions throughout the whole cell cycle. Its kinetics are faster than HR's. It involves the ligation of DNA ends with minimal processing that may include cleavage and gap filling prior to ligation. NHEJ is error-prone since it is associated with sequence alterations (insertions and deletions of several base at the junction or random exchanges of nucleotides) and can in principle join any DNA ends irrespective of molecular origin and cause chromosomal translocation.

Both pathways collaborate and compete in order to ensure genomic integrity.

Chromatin[8]:

Local chromatin changes promote a local environment that leads to the recruitment of repair and signaling factors, regulating repair factors accessibility to the DNA and inhibition of nearby transcription to prevent potential interference

Other pathways[6,7]:

Alternative NHEJ (alt-NHEJ/A-EJ): suppressed by NHEJ and possibly by HR, is considered a backup pathway when these two fail (however, recent studies indicate that it occurs even in cells proficient for NHEJ). A-EJ relies on more extensive processing and sequence deletion than NHEJ: evidences show it is implicated in leukemia and lymphoma. A-EJ may be preferentially functional on naturally shortened telomeres.

Microhomology-Mediated End Joining (MMEJ): is error-prone and requires short patches (5-25bp). It is associated with chromosome abnormalities: deletions (always), translocations (often), inversions and other complex rearrangements.

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[4] O'Driscoll, M and Jeggo, Penny A. *The role of double-strand break repair — insights from human genetics*. Nature Reviews Genetics (2006) 7, 45-54
[5] Panier S. and Boulton S. J. *Double-strand break repair: 53BP1 comes into focus*. Nature Reviews, Molecular cell biology (2014), 15
[6] Dueva, R. and Iliakis G. *Alternative pathways of non-homologous end joining (NHEJ) in genomic instability and cancer*. Review in Tanslational Cancer Research (2013) 2 (3): 163-177
[7] Mc Vey, M. Et Lee, Sang E., 2008: *MMEJ repair of double-strand breaks (director's cut): deleted sequences and alternative endings*. Cell Press Review, Trends in Genetics, 24 (11): 529-538
[8] Papamichos-Chronakis, M., and Peterson, CL., 2013: *Cromatin and the genome integrity network*. Nature Reviews, Genetics (2013), 14