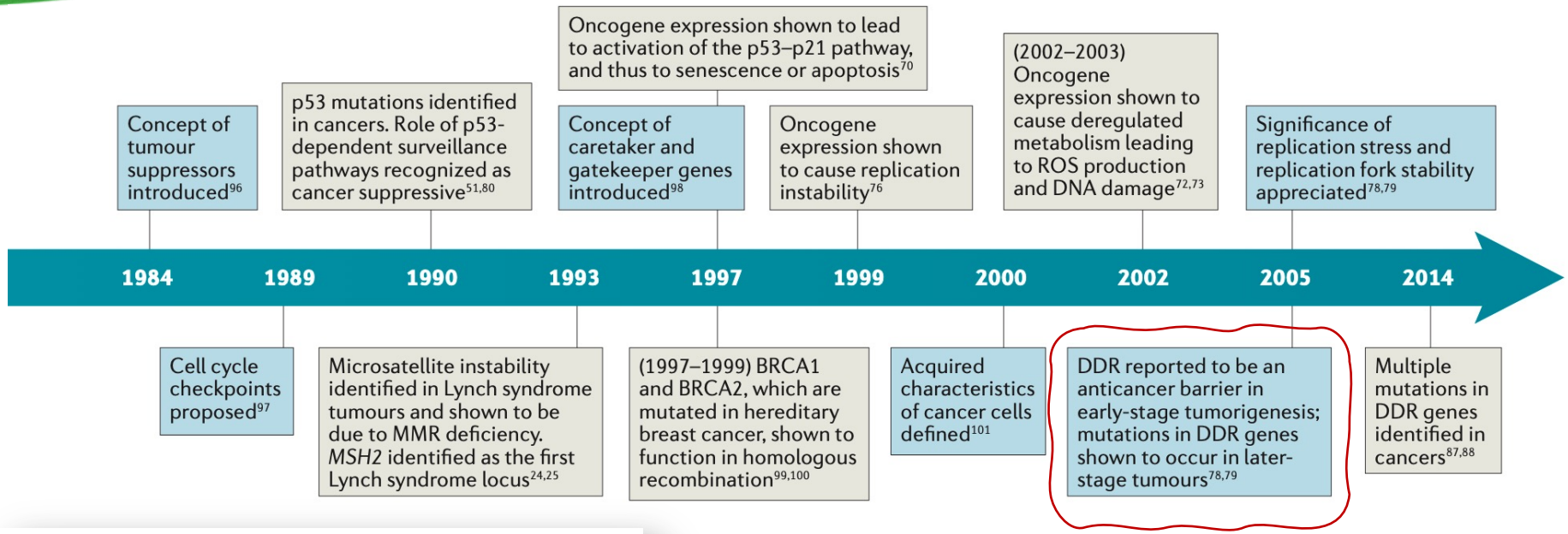
ATTIVAZIONE DELLA DDR NEI TUMORI

Instabilità genetica e danno al DNA



Activation of the DNA damage checkpoint and genomic instability in human precancerous lesions

Vassilis G. Gorgoulis[1]*, Leandros-Vassilios F. Vassiliou[1]*, Panagiotis Karakaidos[1], Panayotis Zacharatos[1], Athanassios Kotsinas[1], Triantafillos Liloglou[2], Monica Venere[3,4], Richard A. DiTullio Jr[3,4], Nikolaos G. Kastrinakis[1], Brynn Levy[6], Dimitris Kletsas[7], Akihiro Yoneta[3], Meenhard Herlyn[3], Christos Kittas[1] & Thanos D. Halazonetis[3,5]

DNA damage response as a candidate anti-cancer barrier in early human tumorigenesis

Jirina Bartkova[1], Zuzana Hořejší[1,5], Karen Koed[2], Alwin Krämer[1], Frederic Tort[1], Karsten Zieger[2], Per Guldberg[1], Maxwell Sehested[3], Jahn M. Nesland[4], Claudia Lukas[1], Torben Ørntoft[2], Jiri Lukas[1] & Jiri Bartek[1]

Jeggo et al., 2016;

Attivazione DDR nei tumori

Che cosa attiva DDR nel tumore?

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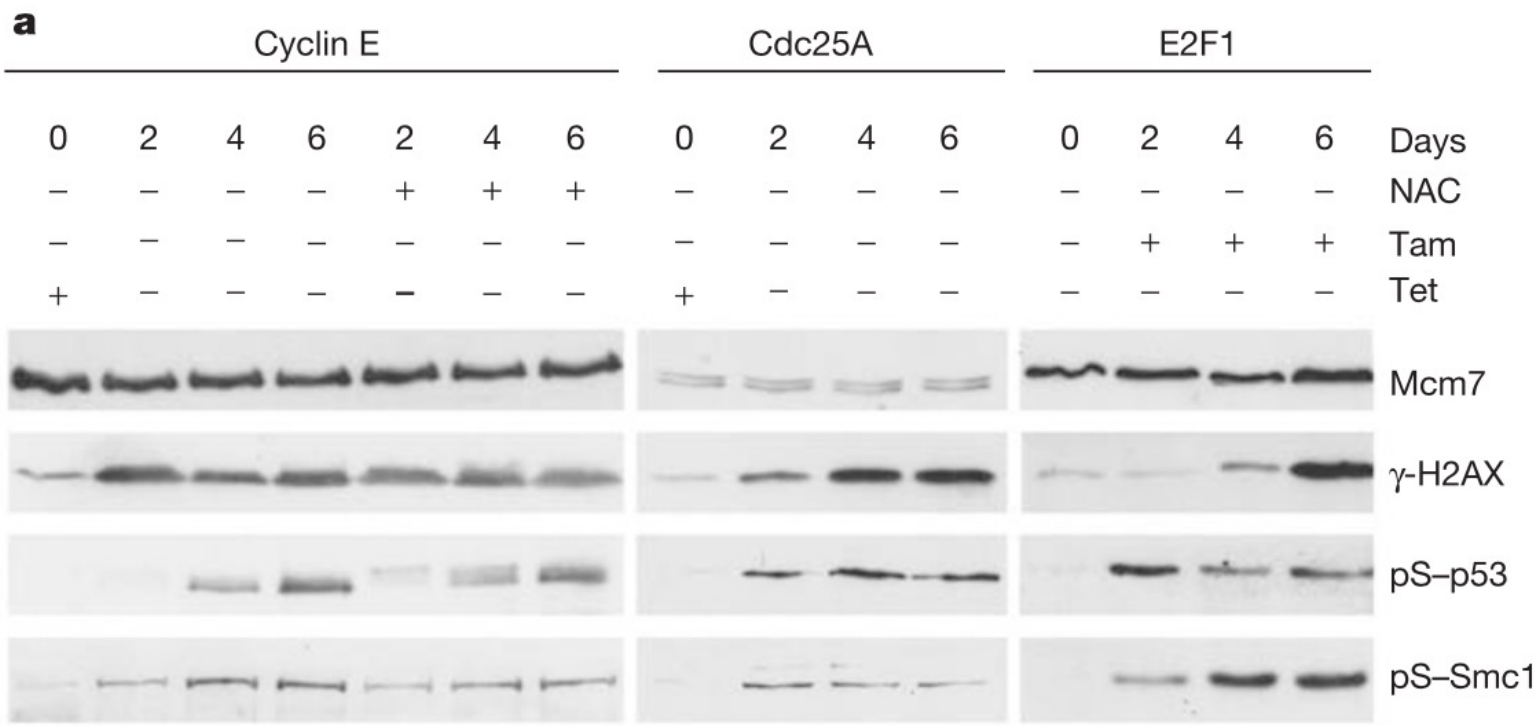

Gorgoulis et al., 2005

Attivazione DDR nei tumori

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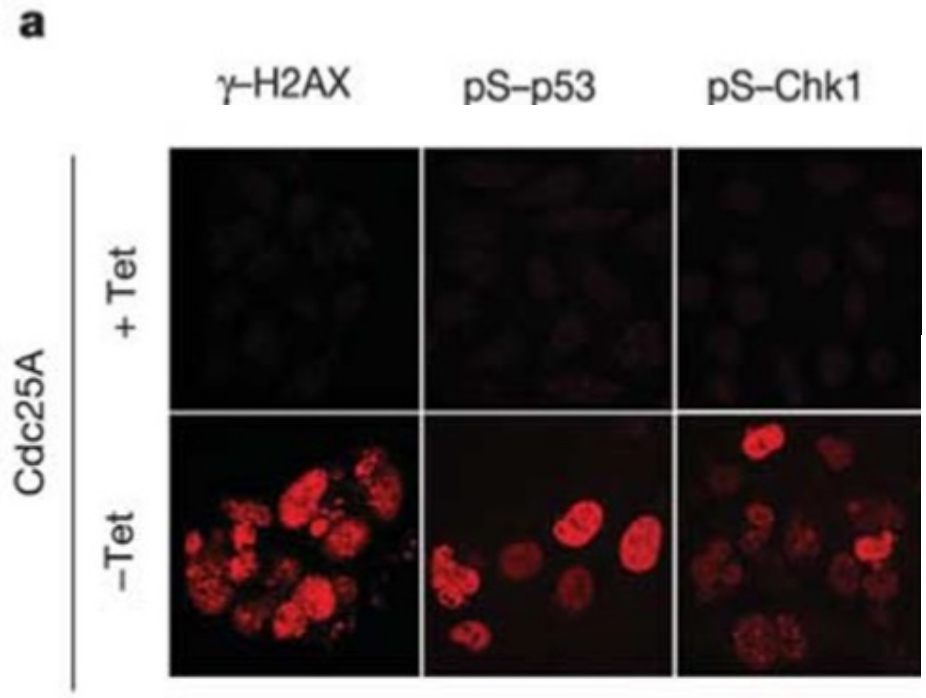
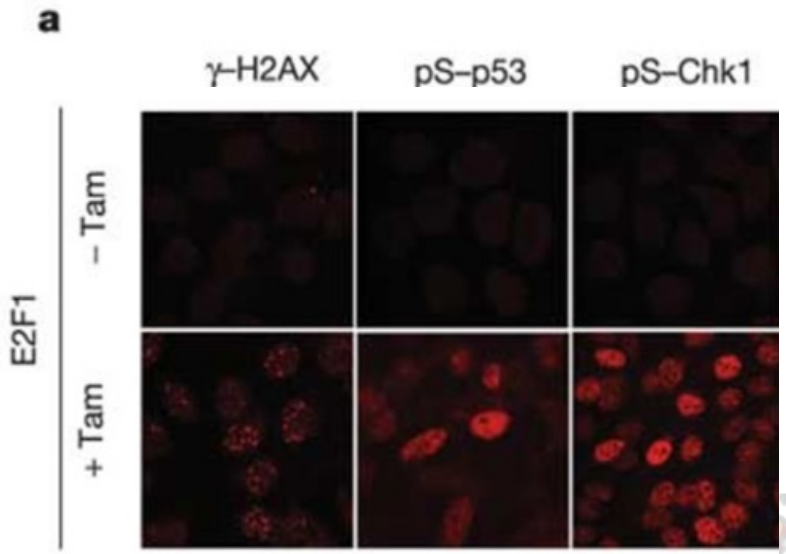
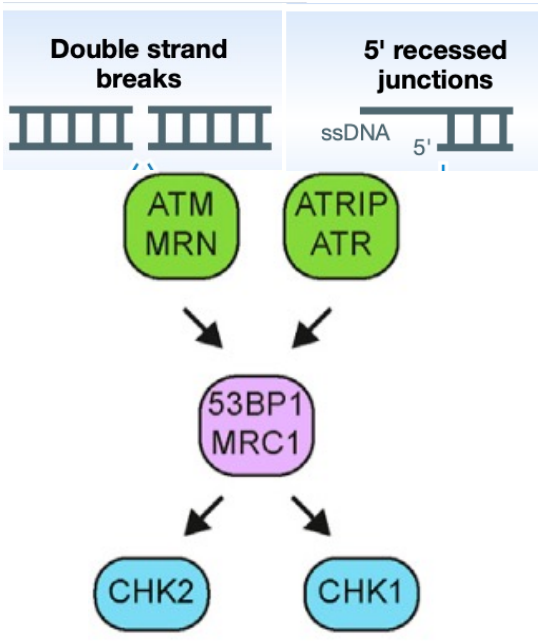


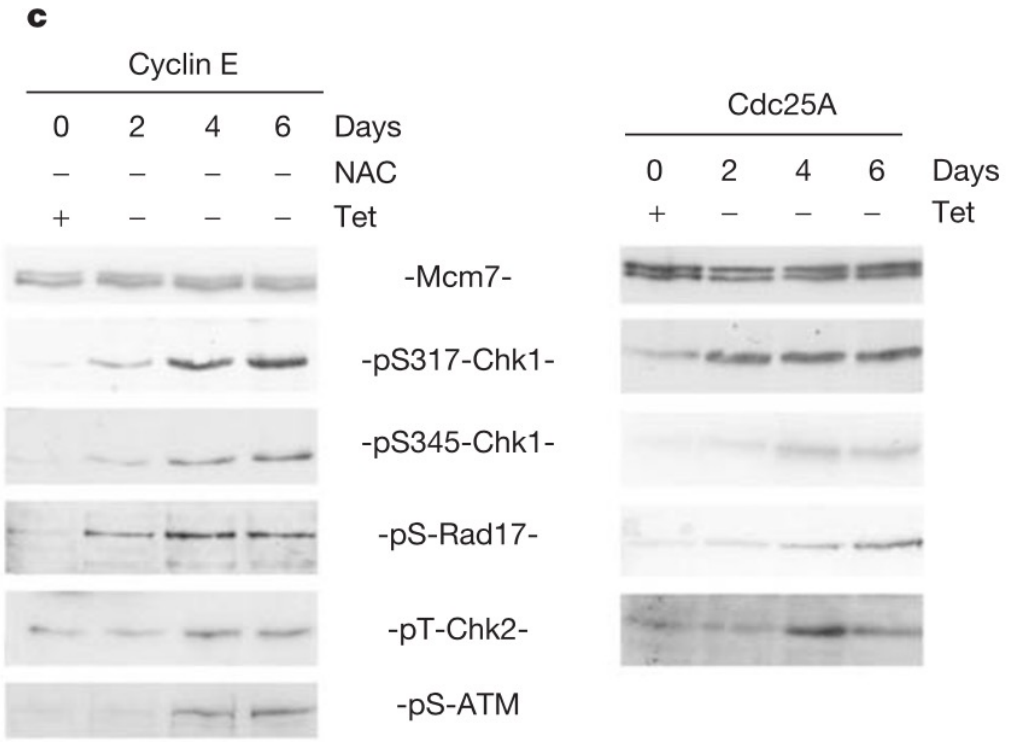


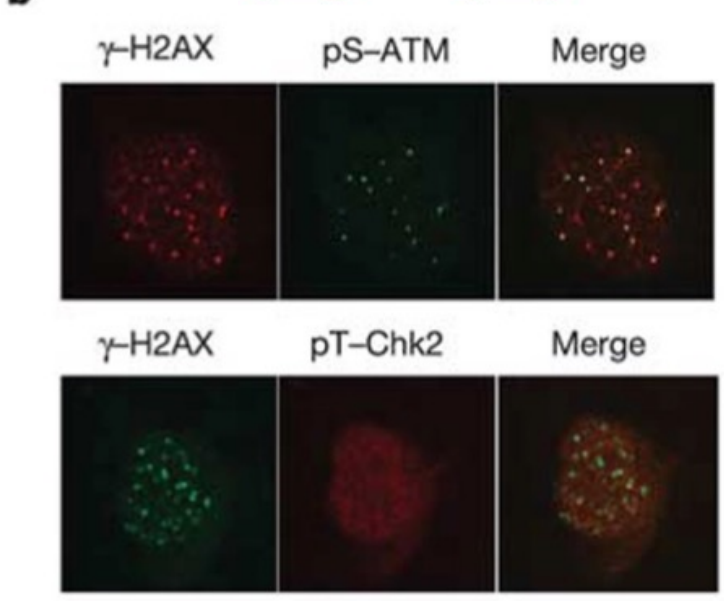
Gorgoulis et al., 2005

Attivazione DDR nei tumori

E' più attiva ATR o ATM?







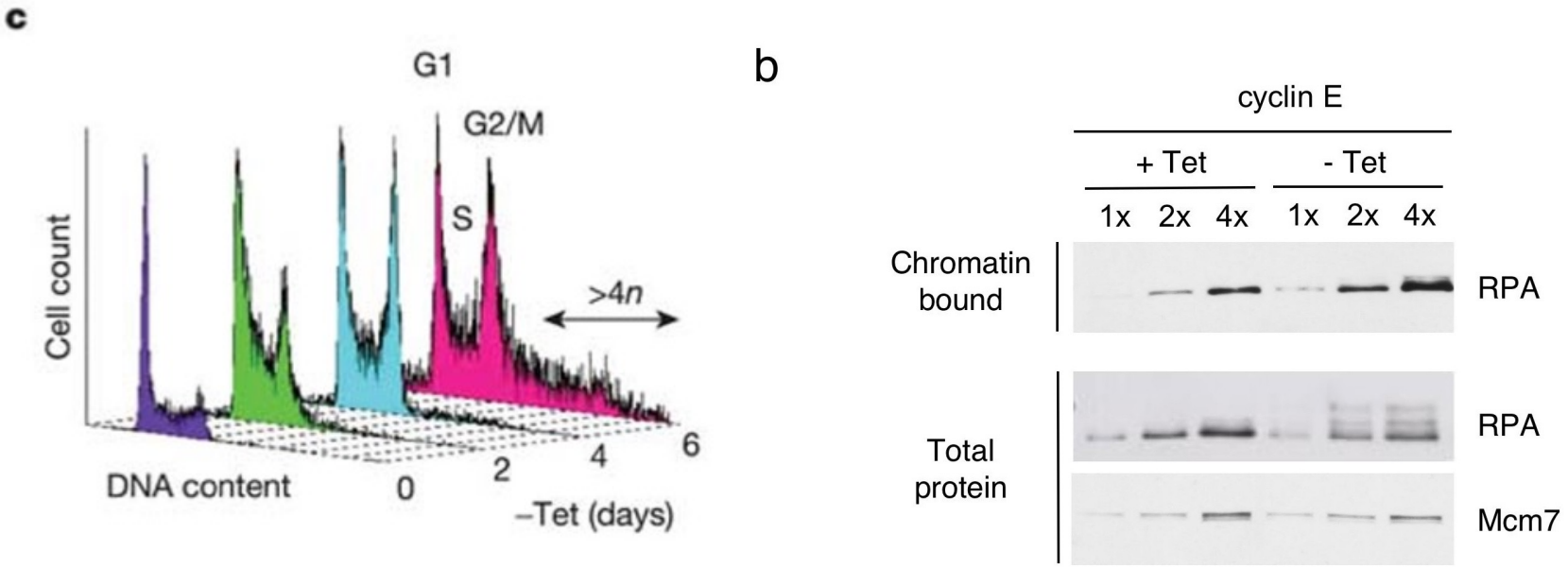
Gorgoulis et al., 2005

Attivazione DDR nei tumori

Attivazione oncogeni interferisce con la replicazione del DNA?

cyclin E overexpression in U-2-OS-derived cells

Replication tracts



Gorgoulis et al., 2005

Attivazione DDR nei tumori

Attivazione oncogeni interferisce con la replicazione del DNA in vivo?

cyclin E è overespressa in early tumor?

a

Tumour	Aberration	Tumour (%)
B(Ta)	RB loss	18
B(Ta)	FGFR3 mut	64
B(Ta)	High cyclin E	86
C (adenoma)	High cyclin E	52

Fragile sites detected by SNP analysis

e

Fragile site	LOH preference
8p23.1/8p21.3	3.1–11.5-fold
9q32	3.2–14.9-fold
11p15.1	4.4–13.2-fold

Gorgoulis et al., 2005

Attivazione DDR nei tumori

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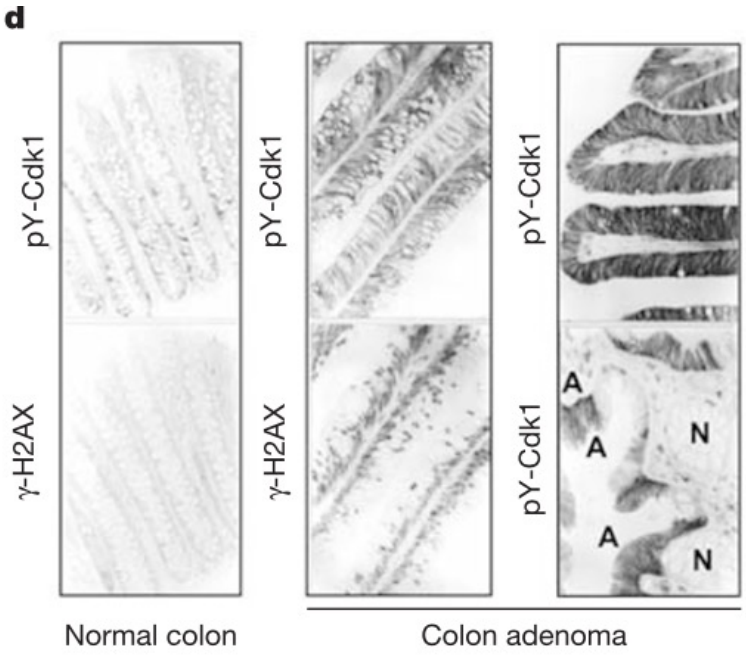
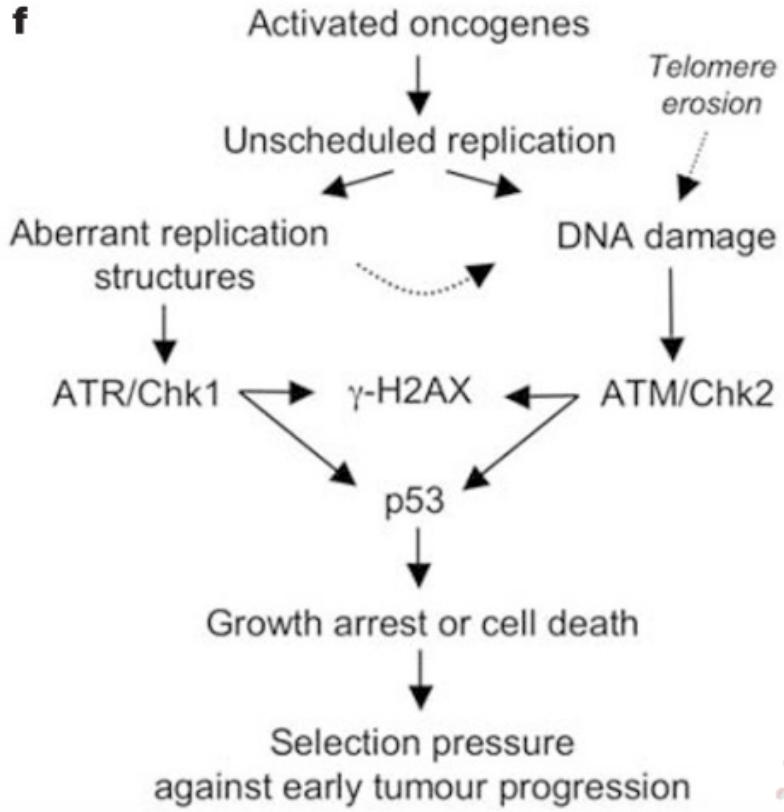




Gorgoulis et al., 2005

Stress replicativo

Replication stress and cancer

Hélène Gaillard, Tatiana García-Muse and Andrés Aguilera

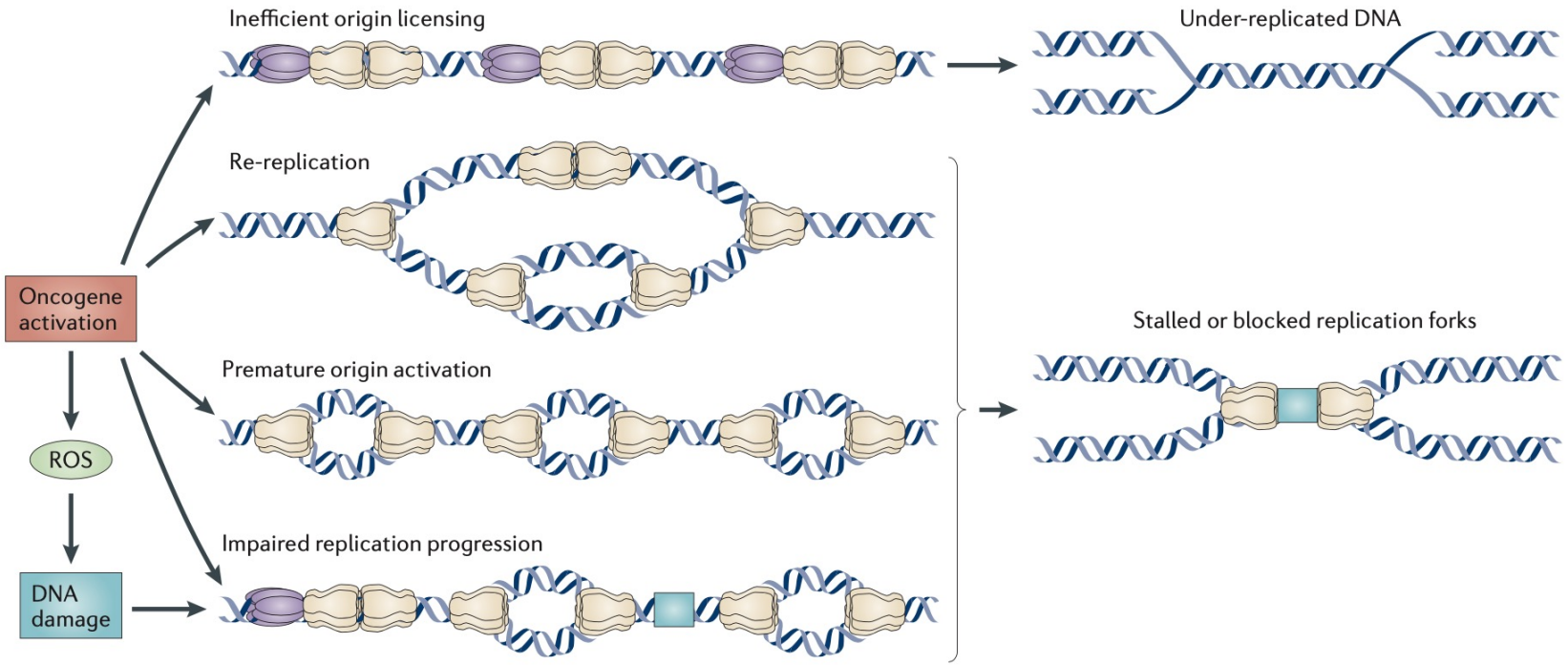


Figure 1 | **Oncogene-induced replication stress.** There are different ways by which oncogene activation can deregulate replication: a decrease in the number of licensed replication origins (as seen upon cyclin E overexpression[35]) reduces the number of active origins, leading to under-replicated DNA; whereas, unscheduled replication initiation causes re-replication and/or premature origin activation (as seen upon expression of cyclin E, cyclin D2 and MYC oncogenes[4,41,45,46]), which could result in replication fork stalling. Alternatively, replication fork stalling induced by oncogenes can be mediated by a direct effect of the oncogenes on replication fork progression (for example, the BCL-2 oncogene[50]) or by an accumulation of reactive oxygen species (ROS) leading to DNA damage with the potential to impair replication (as seen upon MYC overexpression[173]).

Gaillard et al., 2015

Stress replicativo

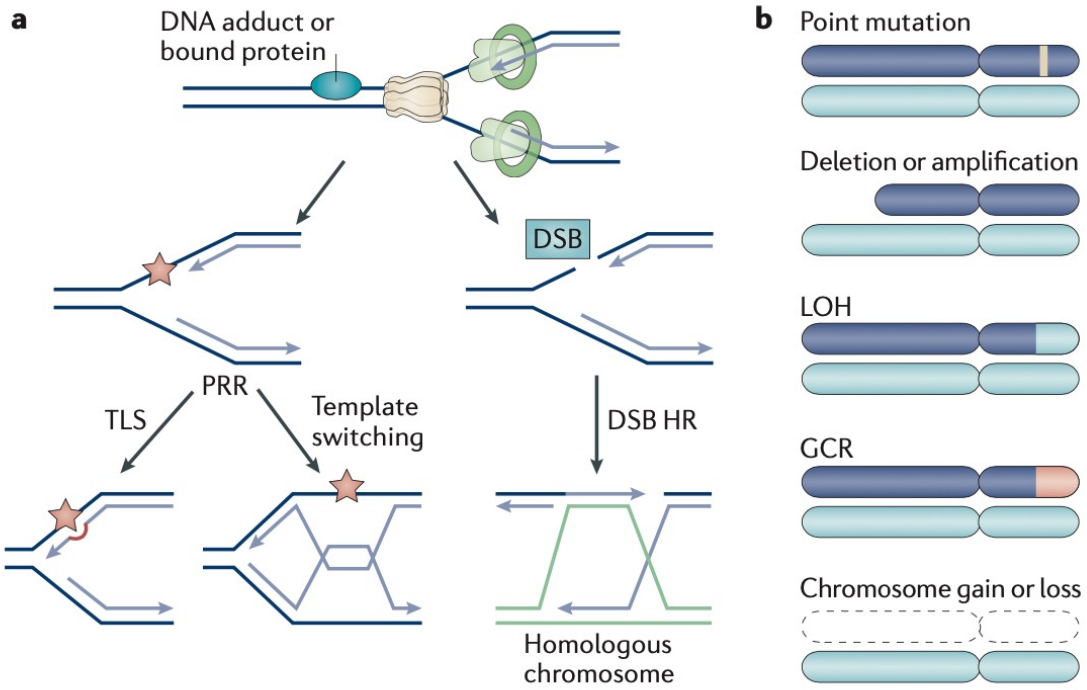


Figure 4 | **Genomic instability resulting from replication stress.** **a** | DNA adducts — DNA sequences covalently bound to a mutagenic chemical residue (blue oval) — or tightly DNA-bound proteins similar to yeast replication fork blocking protein Fob1 can block replication fork progression leading to single-stranded DNA (ssDNA) or double-strand breaks (DSBs) that activate the checkpoint. During replication, base lesions (orange star) can be bypassed via post-replicative repair (PRR) by translesion DNA synthesis (TLS) or by template switching with the sister chromatid using a homologous recombination (HR)-dependent process. Instead, DSBs are repaired by HR primarily using the sister chromatid, although this can also occur with the homologous chromosome (as shown). **b** | A defective response to replication stress by failure in PRR or HR can lead to genome instability, which can be observed as high levels of point mutations, deletions and amplifications, loss of heterozygosity (LOH), gross chromosomal rearrangements (GCRs) and chromosome gain or loss that presumably involve pathways or events such as error-prone DNA synthesis, non-homologous end joining (NHEJ), breakage–fusion–bridge, anaphase bridges, and so on.

Gaillard et al., 2015

Instabilità genetica e danno al DNA

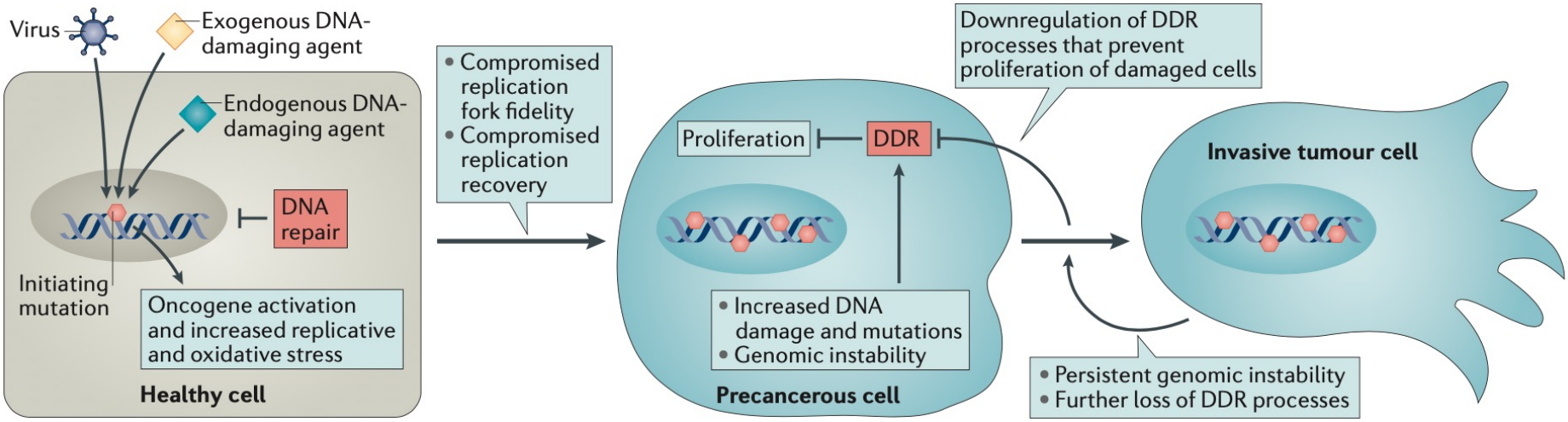


Figure 2 | **How the DNA damage response pathways influence steps leading to cancer.** The figure shows how changes in the DNA damage response (DDR) pathways promote critical steps in the aetiology of carcinogenesis. A healthy cell has a plethora of DDR processes to protect its DNA from exogenous and endogenously arising DNA-damaging agents, and respond to viral infections. Nonetheless, the processes are not perfect, and an early step in the aetiology of cancer is the generation of one or more mutational changes. This may directly or indirectly result in oncogene activation, which leads to replicative and/or oxidative stress. Genetic predisposition to cancer can arise when one of these DNA repair processes is compromised. However, although enhanced replication stress increases the level of DNA breakage, mutation or rearrangement, a range of responses — for example, the ability to accurately recover replication, the activation of checkpoint arrest or other p53-dependent responses — can prevent the proliferation of damaged cells. Progression from this precancerous state to ongoing proliferation requires the downregulation of these DDR processes, thereby facilitating persistent genomic instability. For clarity, these steps have been depicted to arise in a linear fashion, which may not be the case.

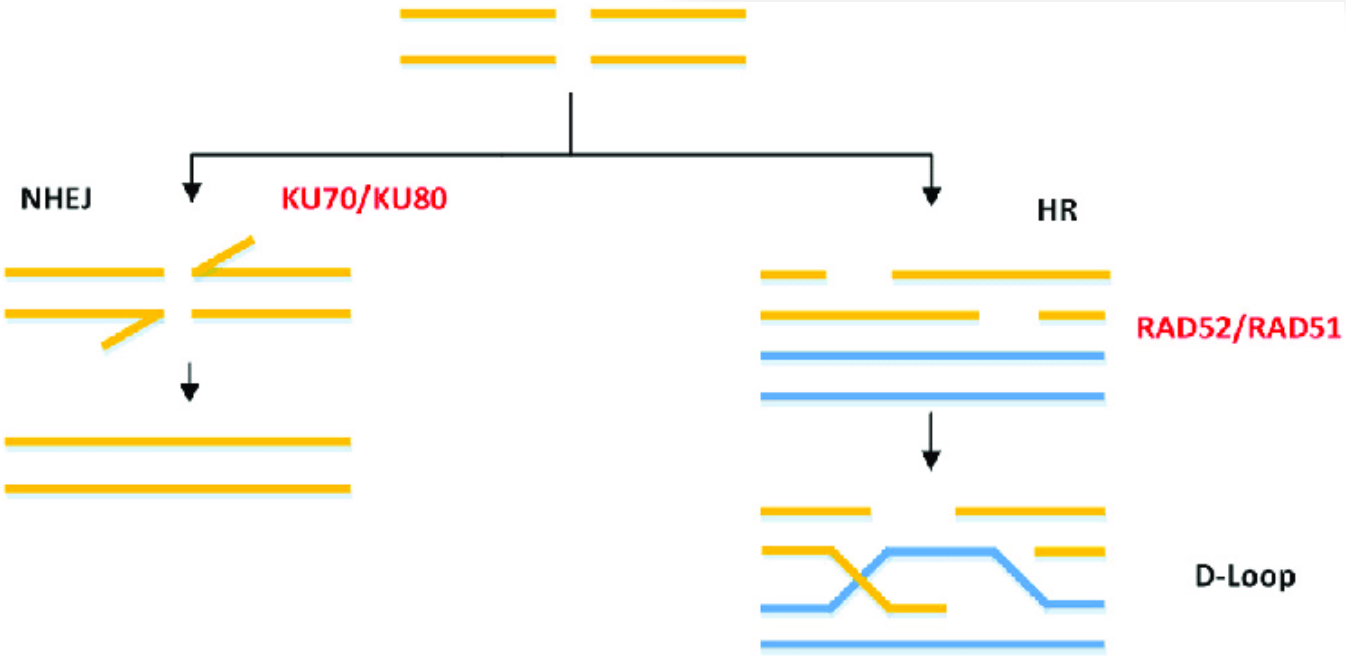
Jeggo et al., 2016

La riparazione dei danni a doppio filamento del DNA (DSB)

DNA DAMAGE

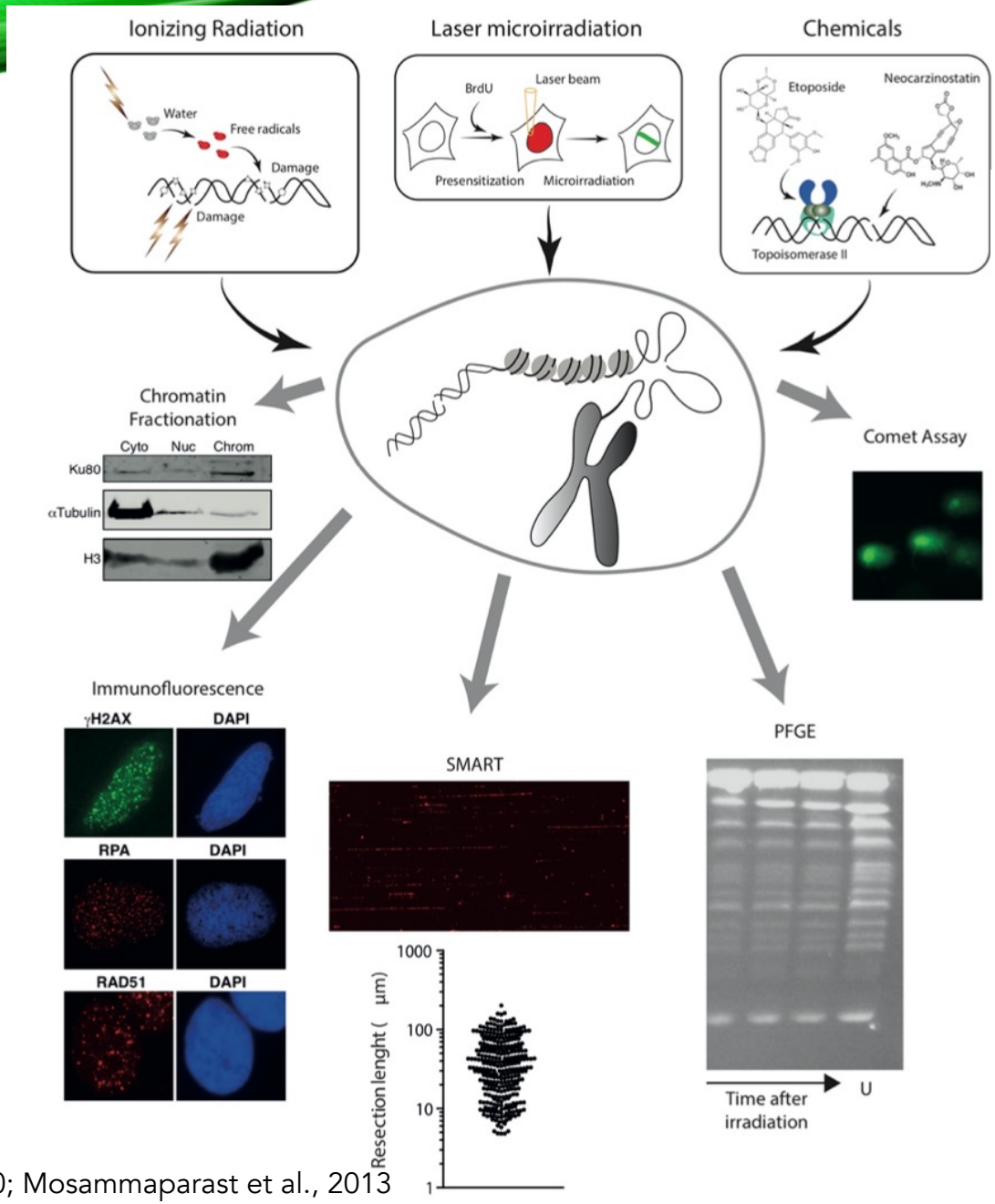
DNA double-strand break repair-pathway choice in somatic mammalian cells

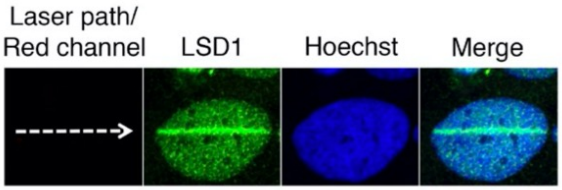
Ralph Scully, Arvind Panday, Rajula Elango and Nicholas A. Willis**



Scully et al., 2019

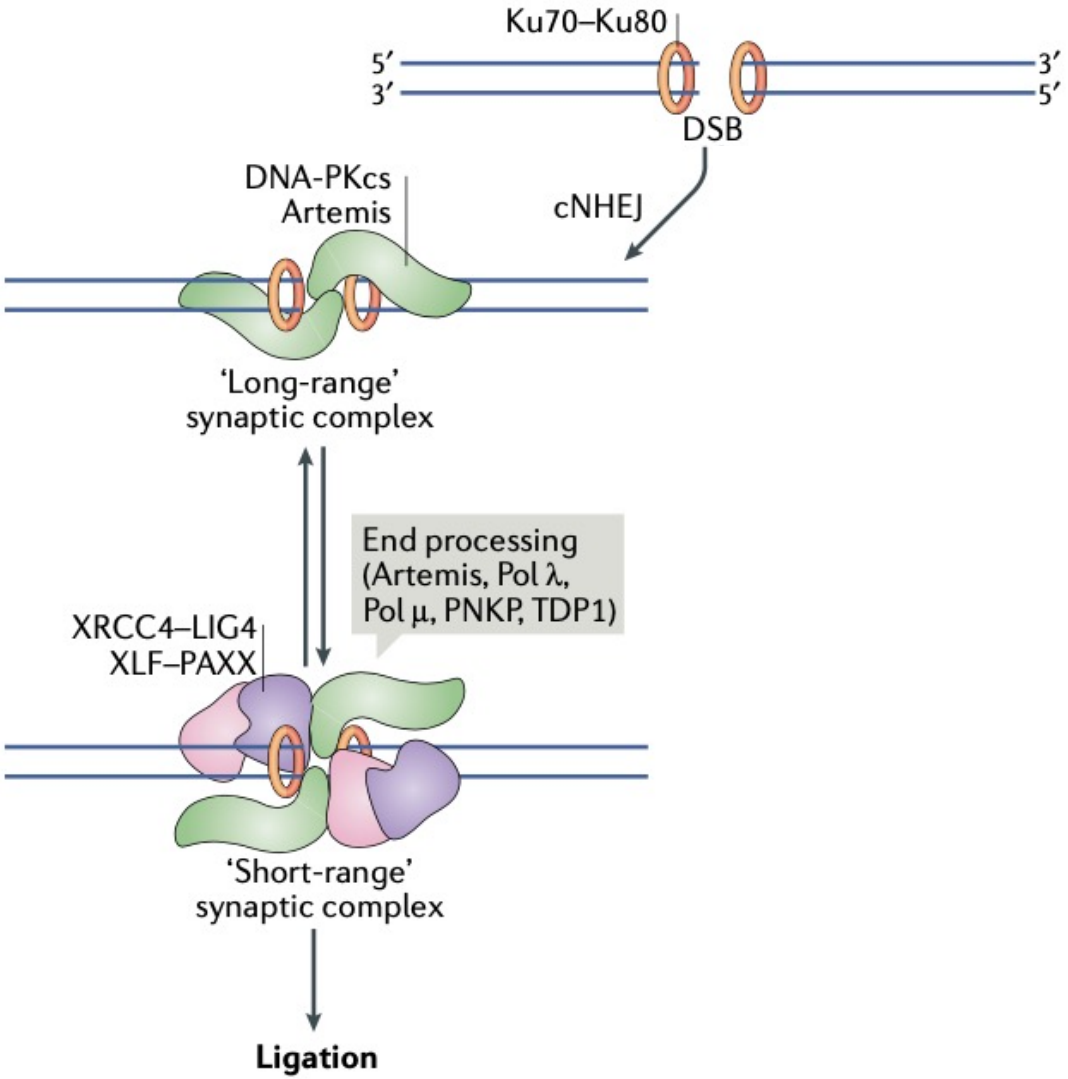
DSB detection





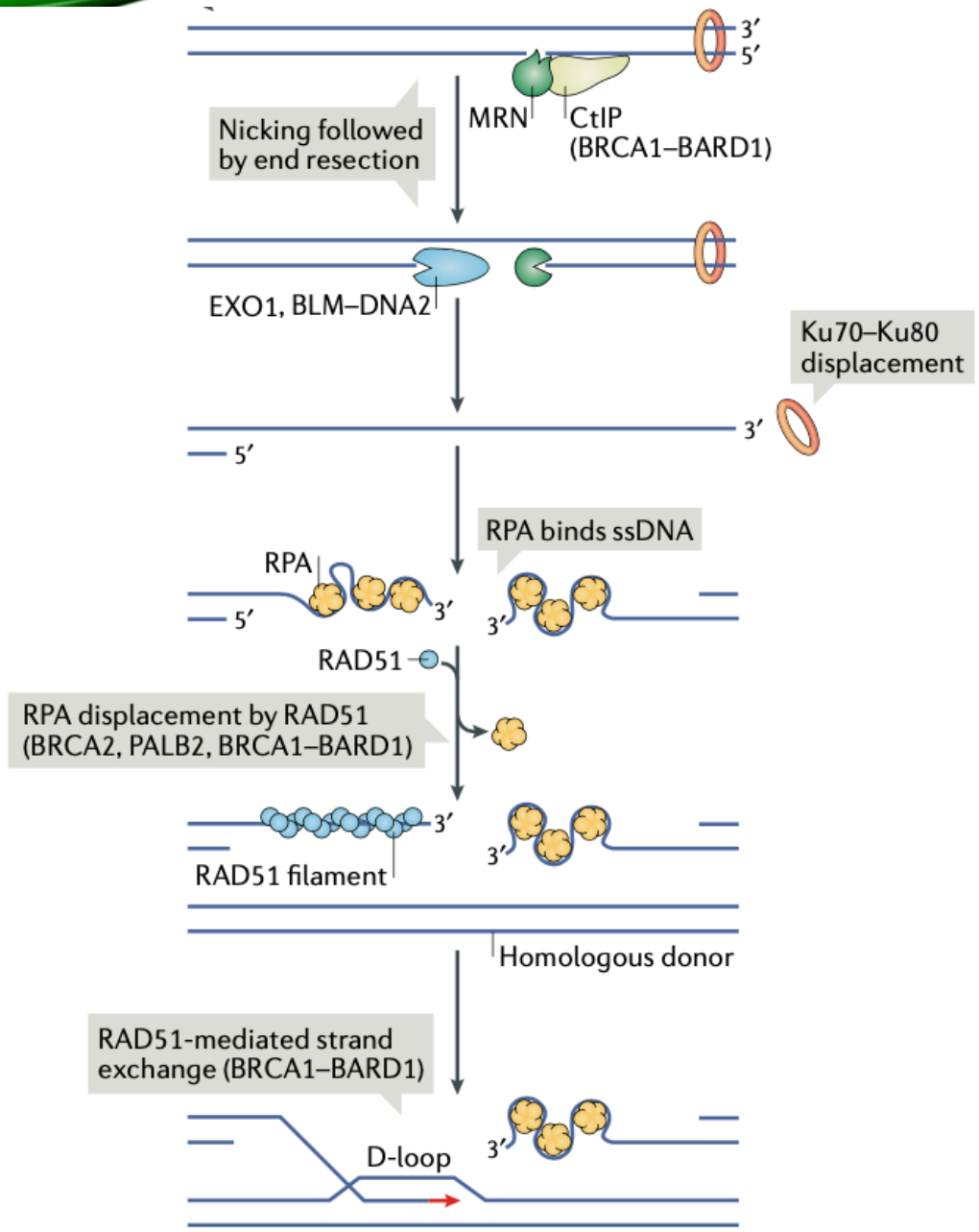
Vitor et al., 2020; Mosammaparast et al., 2013

NHEJ



Scully et al., 2019

HR



Scully et al., 2019

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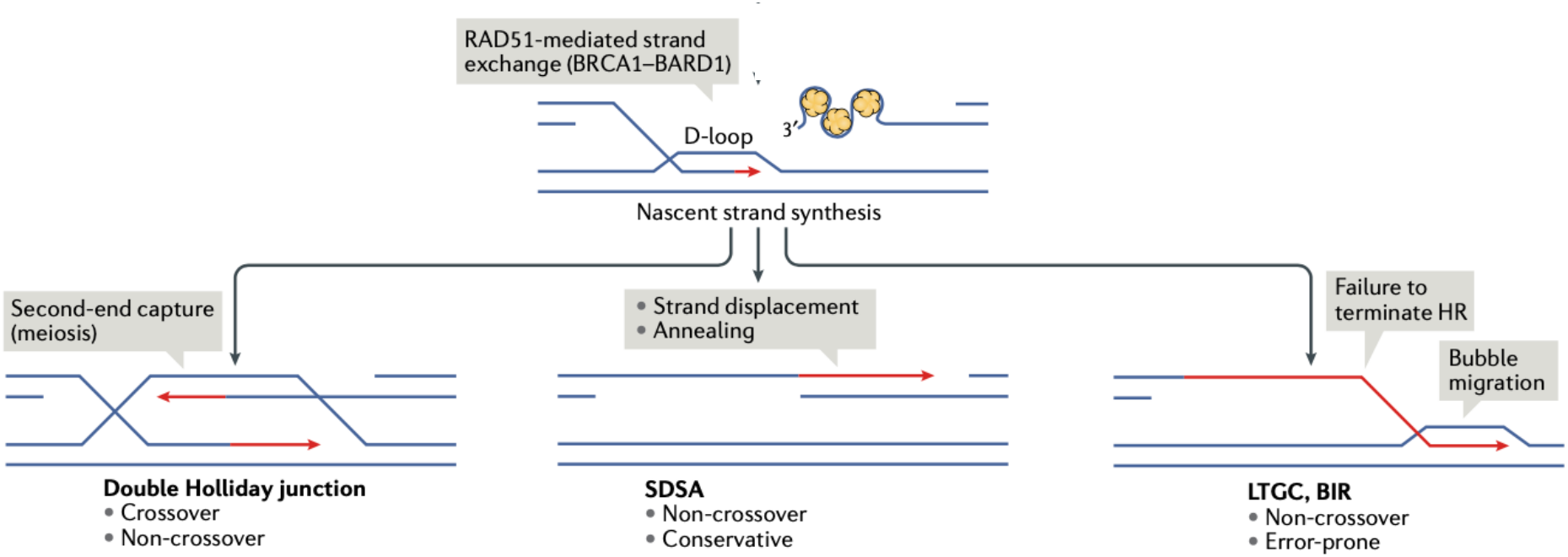
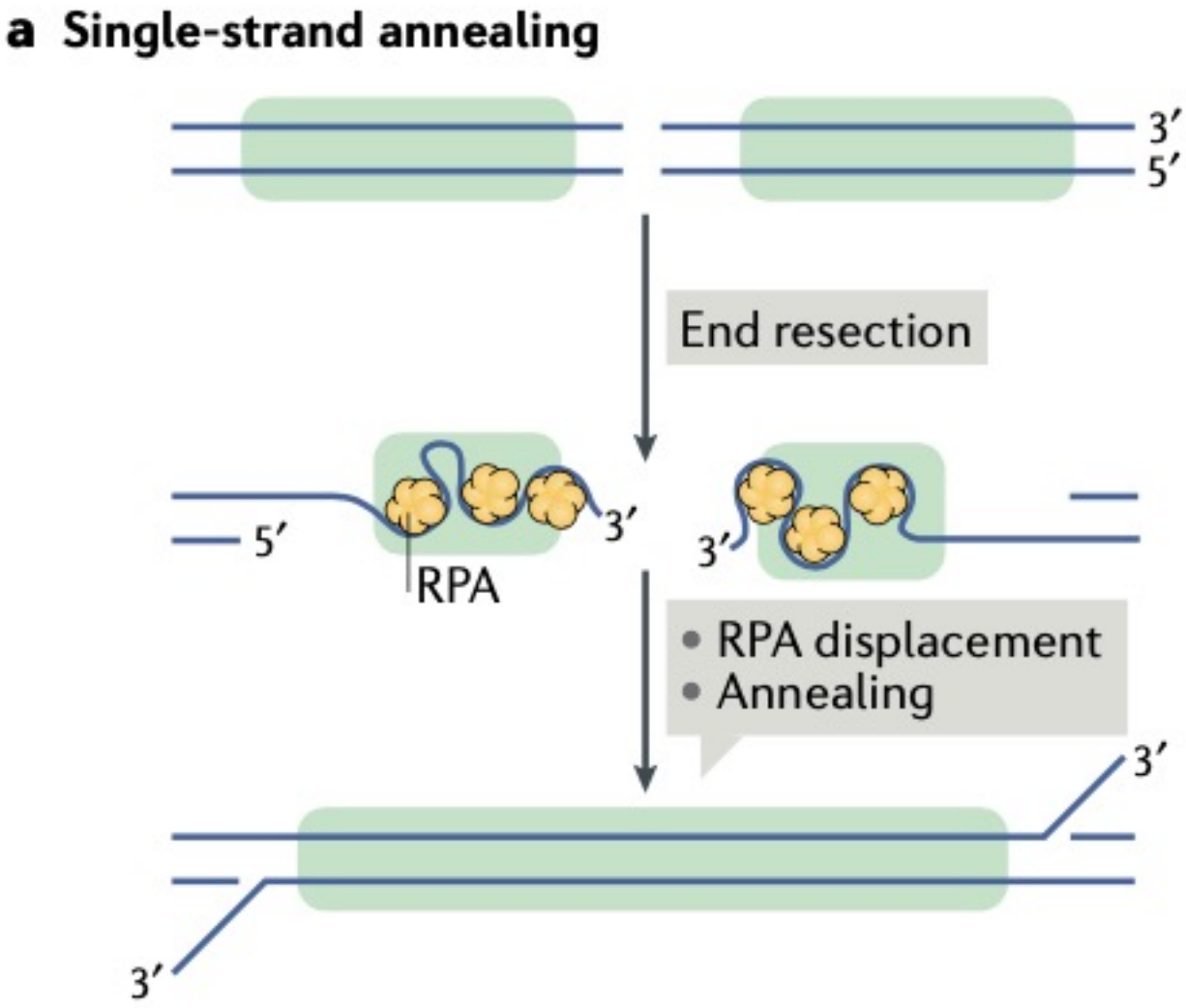


Scully et al., 2019

Meccanismi alternativi di riparazione del DSB



Scully et al., 2019

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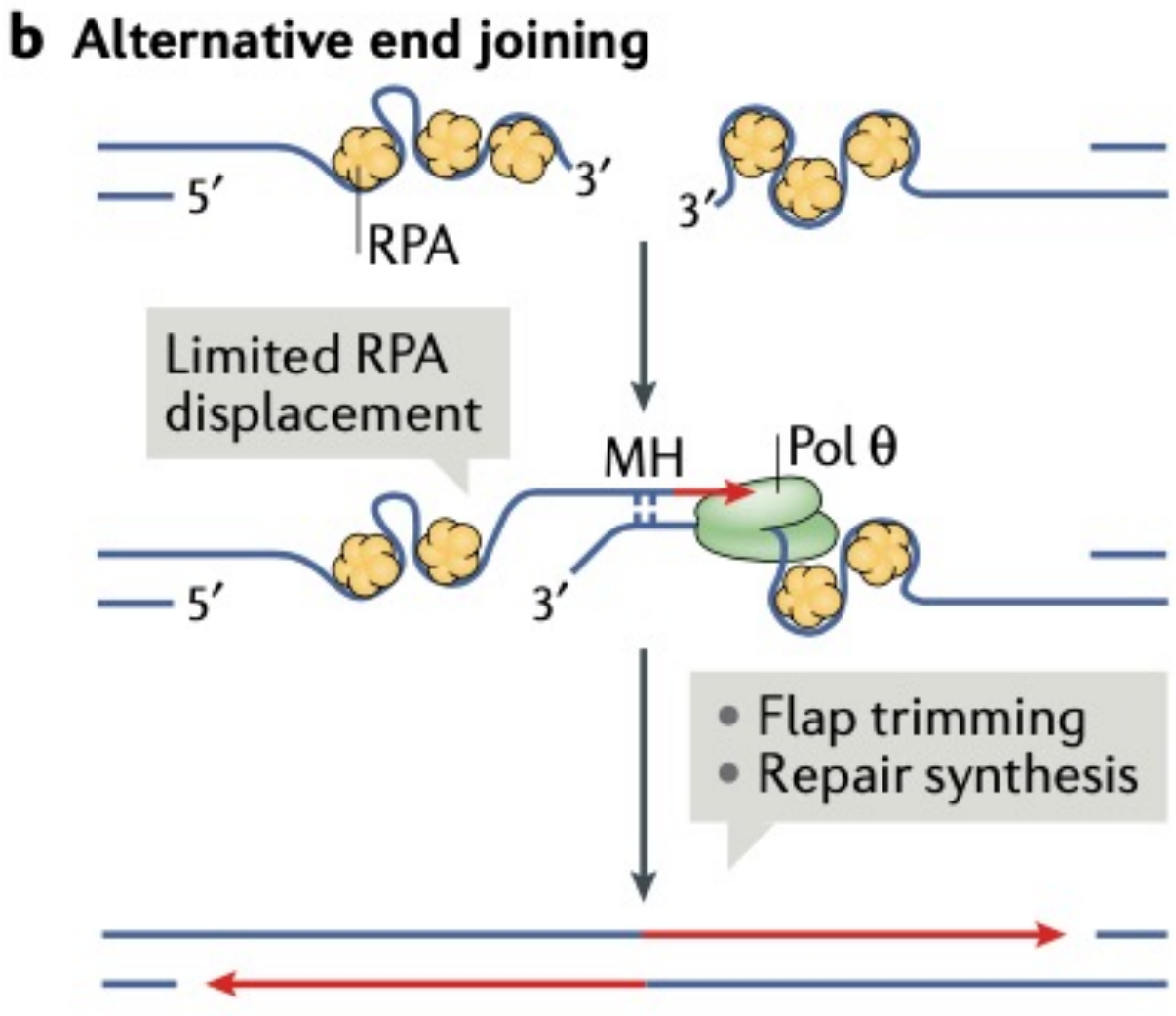

Scully et al., 2019

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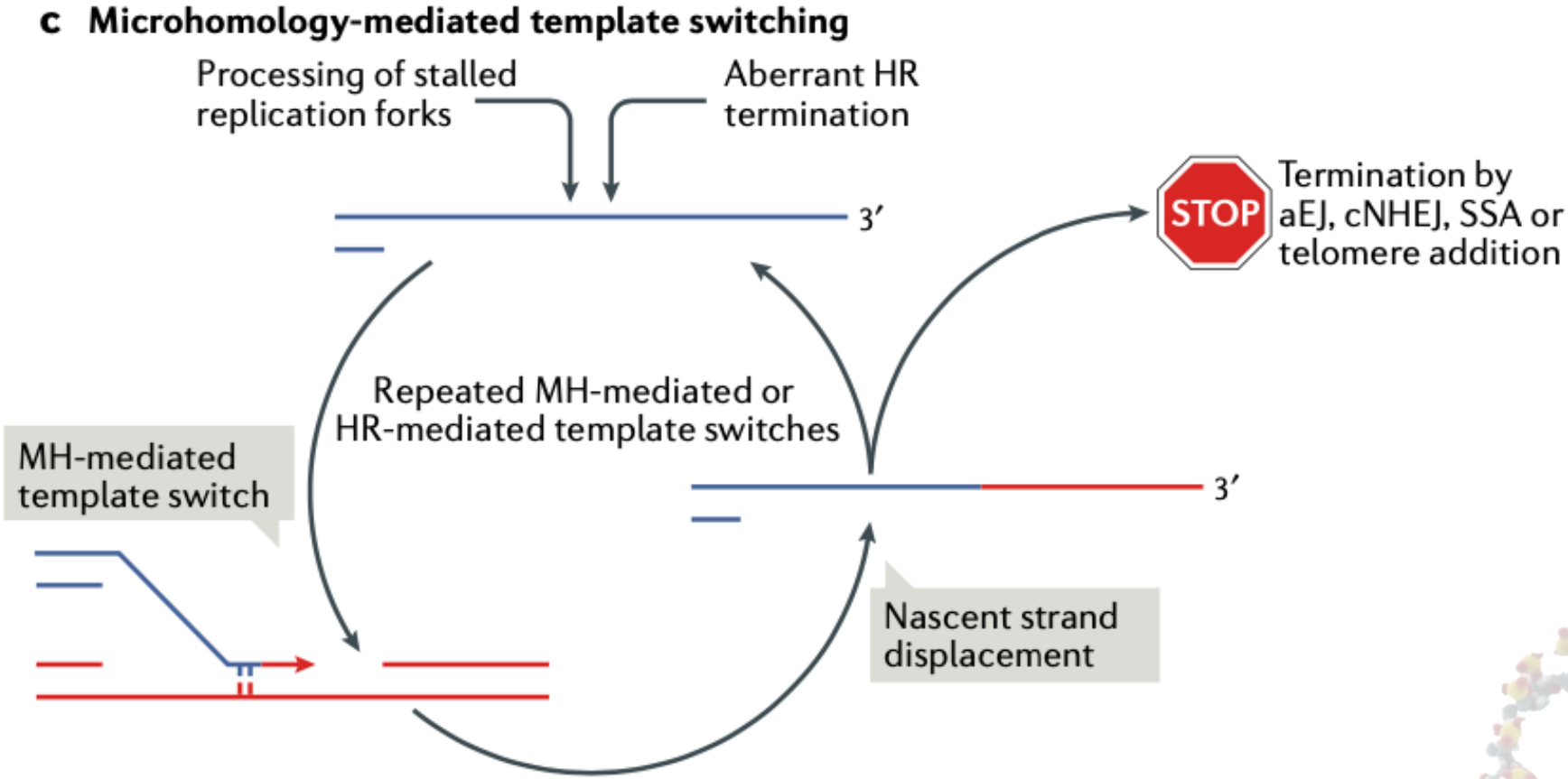
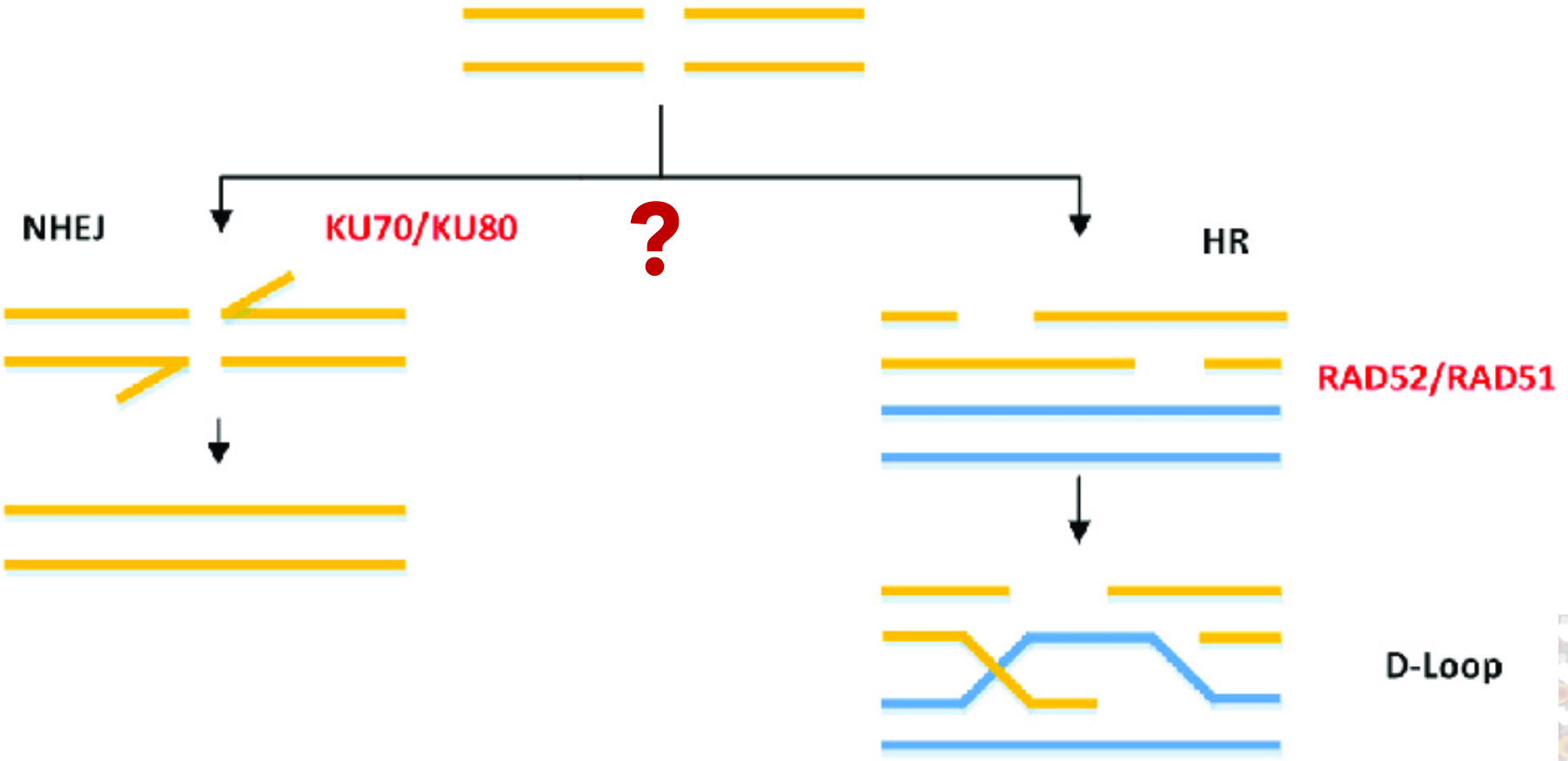


Scully et al., 2019

Scelta del meccanismo di riparazione del DSB



Scully et al., 2019

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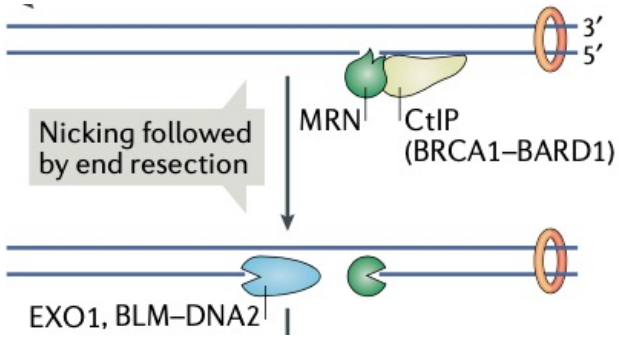
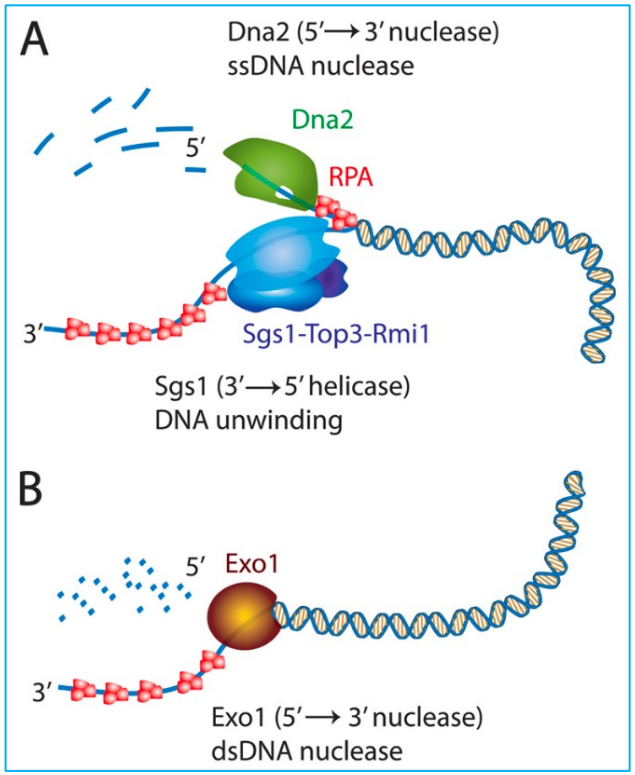
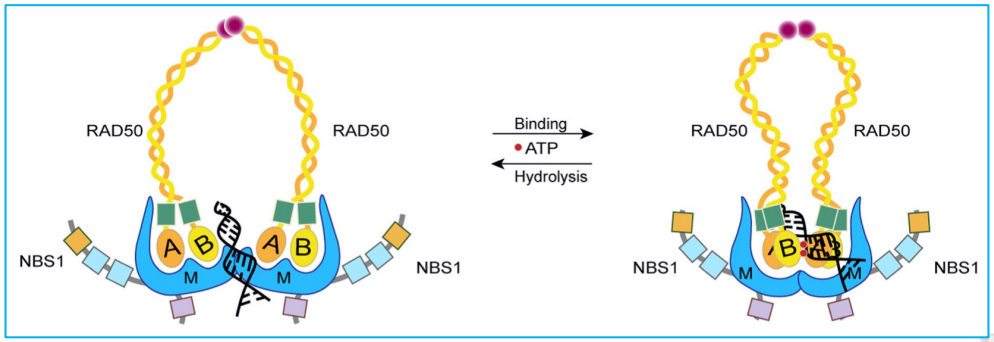
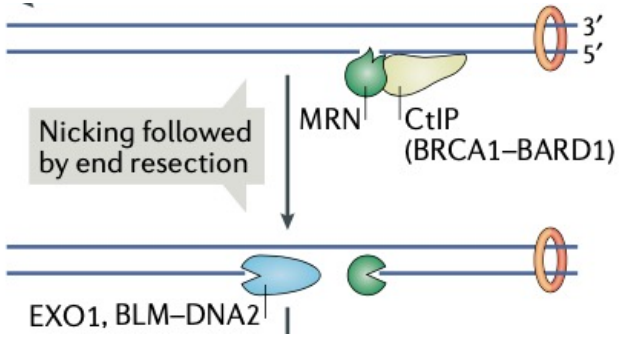


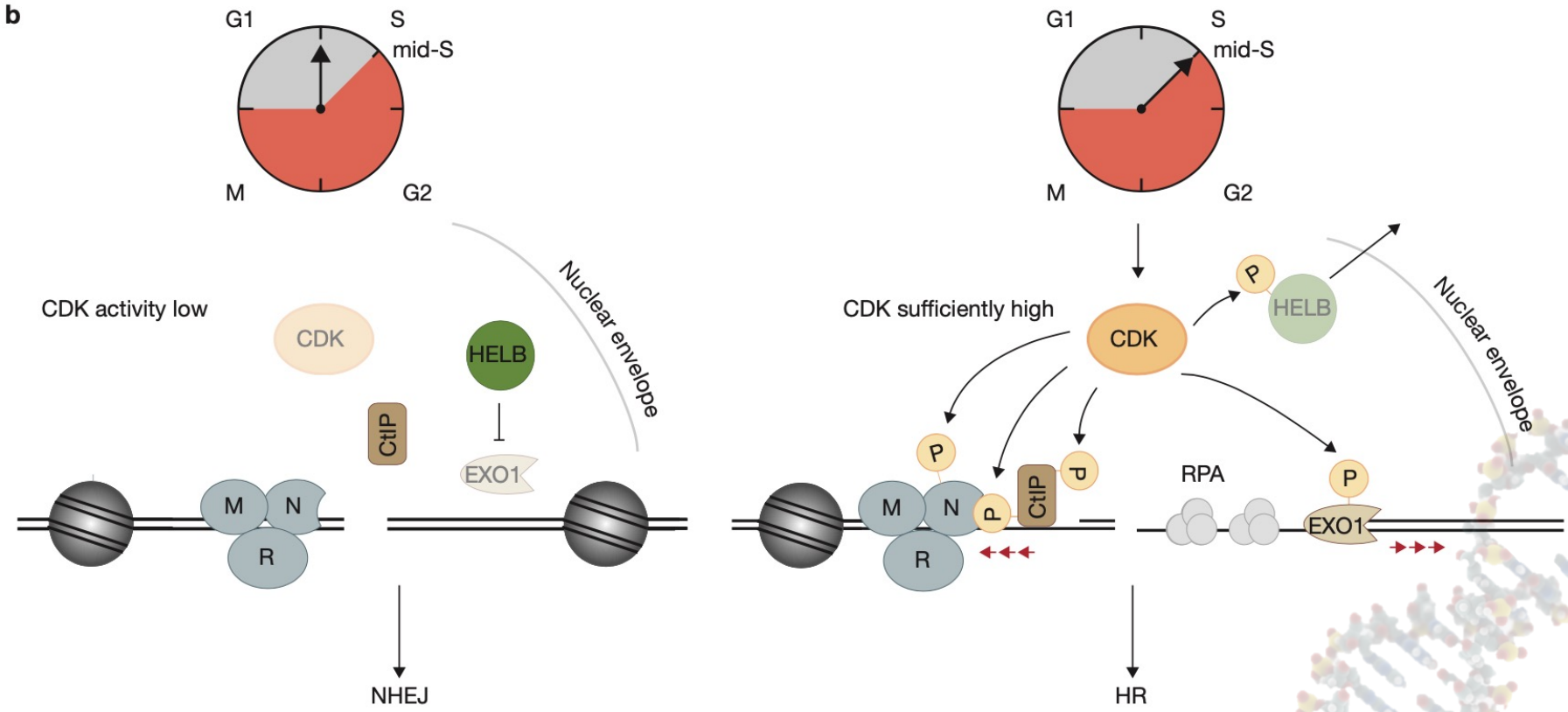




Cejka, 2015;

Scelta del meccanismo di riparazione del DSB





Hustedt and Durocher, 2017