

Fig. 2.2 Schematic view of the essential DDR steps. Schematic representation of the main steps of DDR activity in multicellular organism, in response to endogenous or exogenous nuclear DNA damage. The signalling cascade is essentially constituted by sensors, a limited number of apical and distal kinases and hundreds of effectors that activate in a fine-tuned way the correct biological response in relation to damage characteristics.

protein in a heterodimeric association with MSH3 or MSH6, thus forming the MutS complex.

Single-strand breaks (SSBs) directly produced by radiation and radicals or, in some cases, indirectly left during defective BER or NER, are recognized by the poly(ADP-ribose) polymerase (PARP) family of proteins (Caldecott, 2008) and repaired by SSB repair (SSBR) pathway. PARP1 and PARP2 activation and the subsequent synthesis of poly(ADP-ribose) (PAR) chains by these proteins occur within seconds at sites of damage (Fig. 2.4). The major substrates of DNA damage-induced poly(ADP-ribosylation) are PARP1 itself and histones surrounding DNA lesions. PAR structures constitute a platform to start the recruitment of DNA repair

factors. Then PAR chains are rapidly degraded by PARG, an hydrolysing enzyme, thus providing a transient response that lasts for minutes only. This transient nature of the response is an essential feature of the DDR.

Interstrand DNA cross links (ICLs) covalently connect the two strands of DNA and constitute a dangerous bidirectional barrier to replication or transcription. Understanding the mechanism of ICLs repair is extremely important since agents causing this kind of lesions are widely used in cancer therapy. Indeed, nitrogen mustards and derivatives (melphalan, chlorambucil), psoralens, mitomycin C, platinum-based compounds like cisplatin, and nitrosoureas such as bis-chloroethylnitrosourea are clinically useful interstrand

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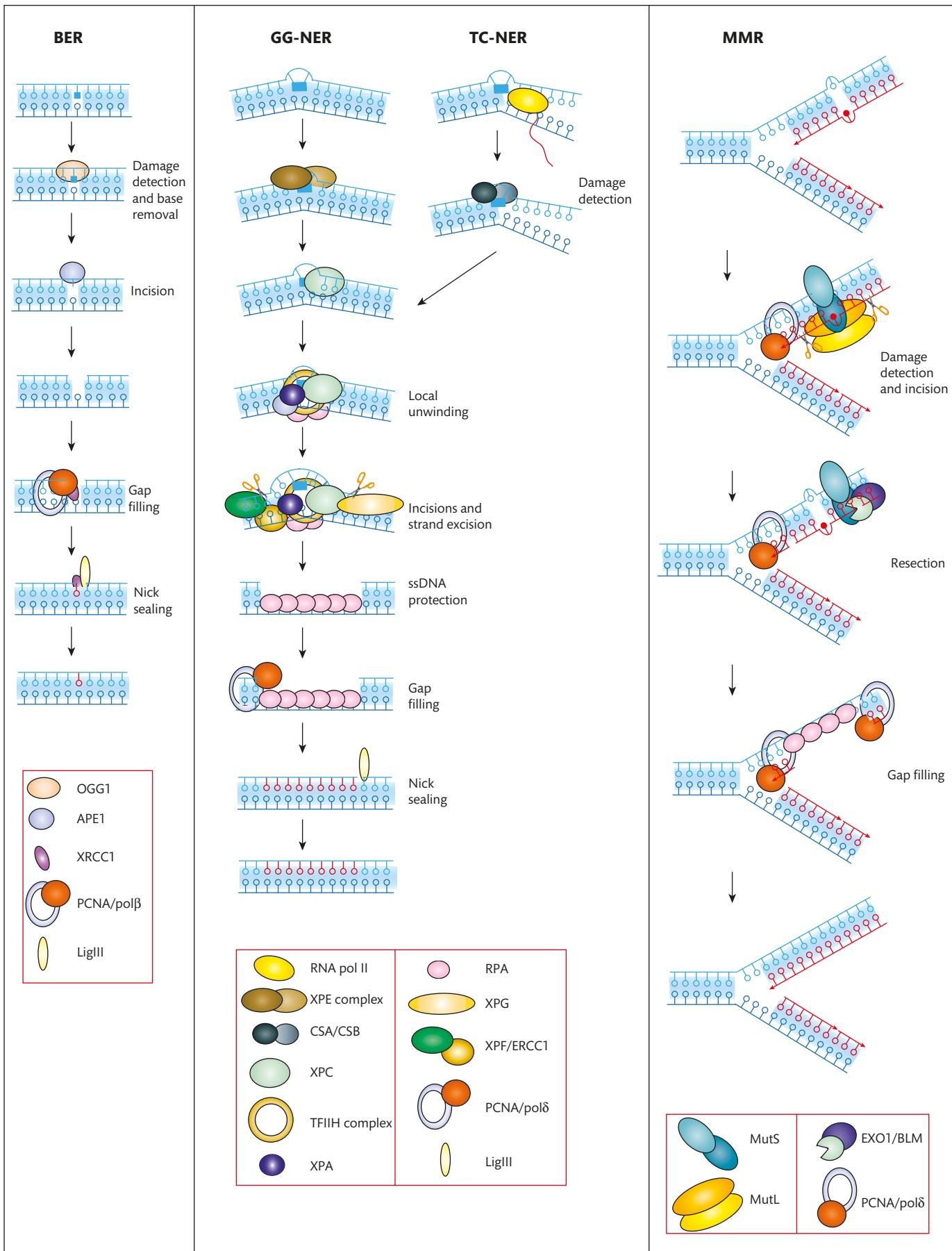


Fig. 2.3 Excision repair systems. Simplified schematic view of base excision repair (BER), global genome (GG-) and transcription coupled (TC-) nucleotide excision repair (-NER), and mismatch repair (MMR). (In red = neosynthesis.)

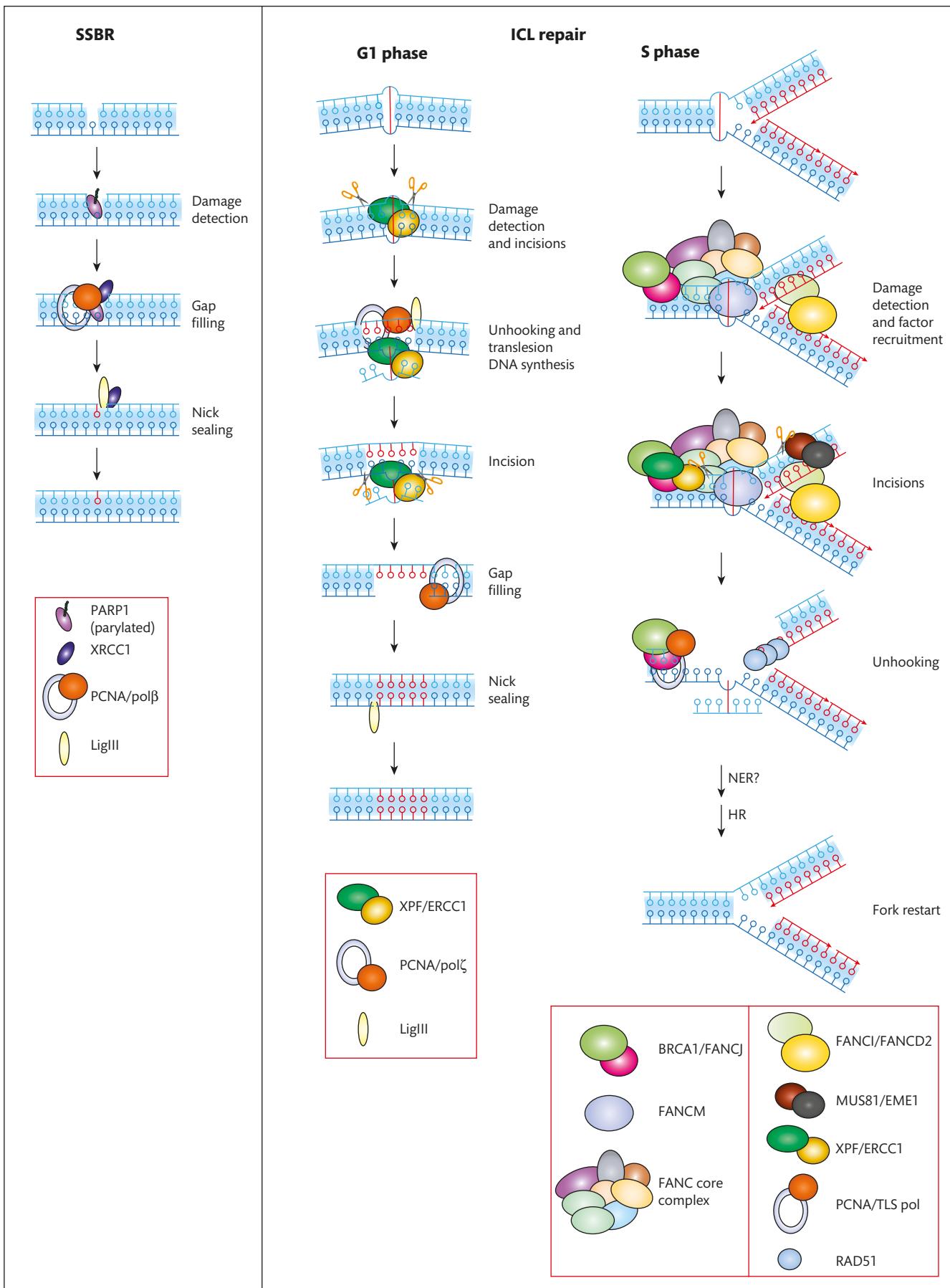


Fig. 2.4 Single-strand break and interstrand cross-link repair systems. Simplified schematic view of single-strand break repair (SSBR) and interstrand cross-link repair (ICL repair) during G1 or in the case that a replicative fork reaches an ICL during S-phase. (In red = neosynthesis.) The last step of ICL repair during S-phase creates a DSB and a hook, repaired, respectively, by homologous recombination and nucleotide excision repair.

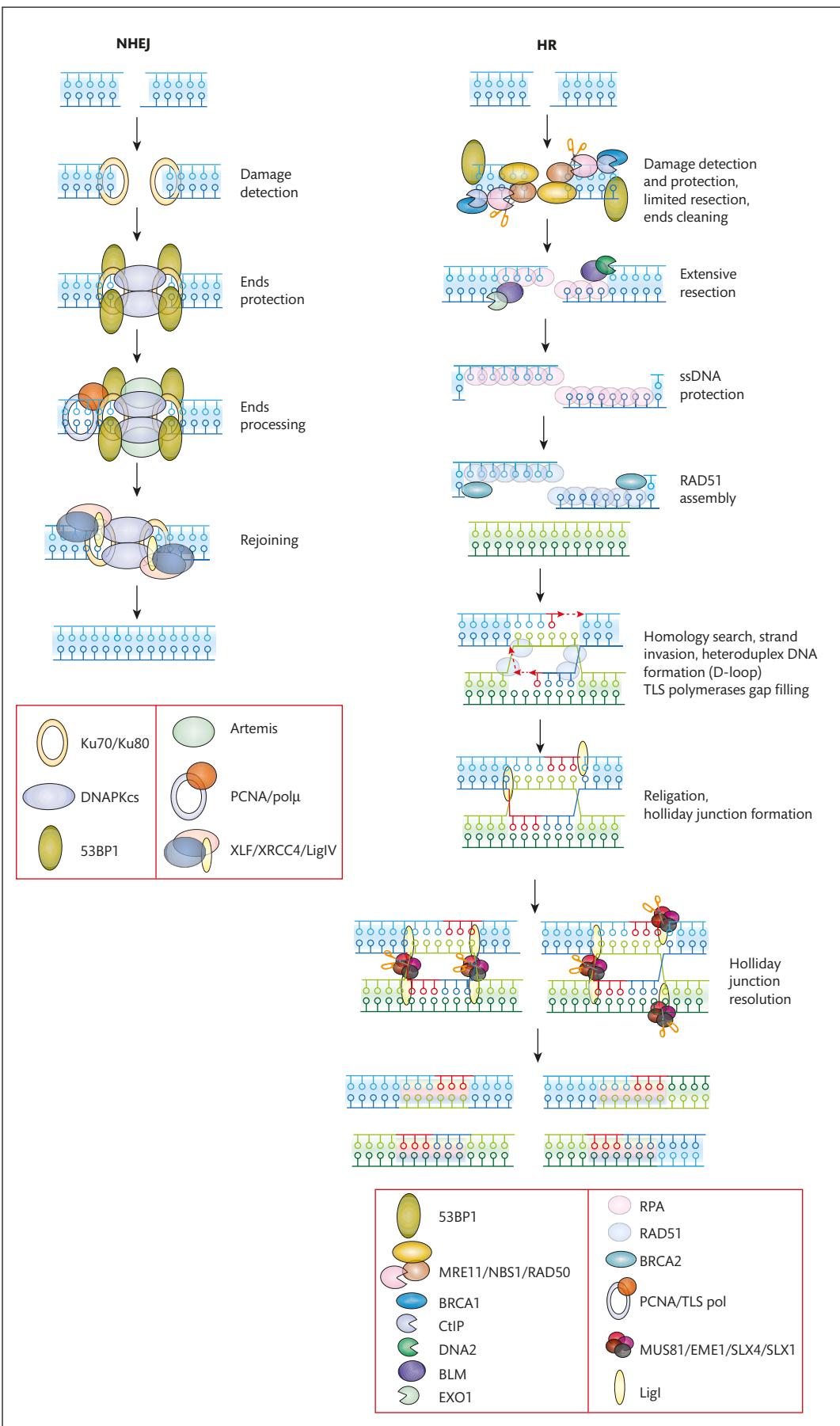


Fig. 2.5 Double-strand break repair pathways. Simplified schematic view of double-strand break repair by non-homologous end joining (NHEJ) or homologous recombination (HR). (Pale blue/blue and pale green/green DNA strands represent sister chromatids, neosynthesis is in red.) The final outcome of HR repair can significantly differ depending on D-loop and Holliday junction (HJ) formation, migration, and resolution. The activation of different HR subpathways could influence the presence and extension of crossover between chromatids. The MUS81/EME1/SLX4/SLX1 complex is depicted but HJ resolution can be performed by GEN1 and HJ dissolution by BLM/TopIII/RMI1/RMI2 complex.