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Review

Choosing the right path: Does DNA-PK help make the decision?

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ABSTRACT

DNA double-strand breaks are extremely harmful lesions that can lead to genomic instability and cell death if not properly repaired. There are at least three pathways that are responsible for repairing DNA double-strand breaks in mammalian cells: non-homologous end joining, homologous recombination and alternative non-homologous end joining. Here we review each of these three pathways with an emphasis on the role of the DNA-dependent protein kinase, a critical component of the non-homologous end joining pathway, in influencing which pathway is ultimately utilized for repair.

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1. Introduction

The DNA contained within our cells is constantly exposed, and surprisingly vulnerable, to a variety of agents that can cause DNA damage. Given the critical nature of maintaining DNA, both for cell survival and for genetic fidelity, it is not surprising that organisms have evolved a variety of complex and highly regulated mechanisms that function to repair DNA damage. Among the many types of DNA lesions that can occur, the DNA double-strand break (DSB) is arguably the most deleterious. It has been reported that even a single DSB can be fatal to a cell if left unrepaired [1], and misrepair of DSBs can result in large-

Abbreviations: a-NHEJ, alternative non-homologous end joining; B-NHEJ, backup non-homologous end joining; c-NHEJ, classical non-homologous end joining; DNA-PK, DNA-dependent protein kinase; DNA-PKcs, DNA-dependent kinase catalytic subunit; DSB, double strand break; HR, homologous recombination; IR, ionizing radiation; LigIV, DNA ligase IV; NHEJ, non-homologous end joining; RAG, recombination activating gene; RSS, recombination signal sequence; VDJ, variable diversity joining; XLF, XRCC4-like factor; XRCC4, X-ray cross complementing protein 4.

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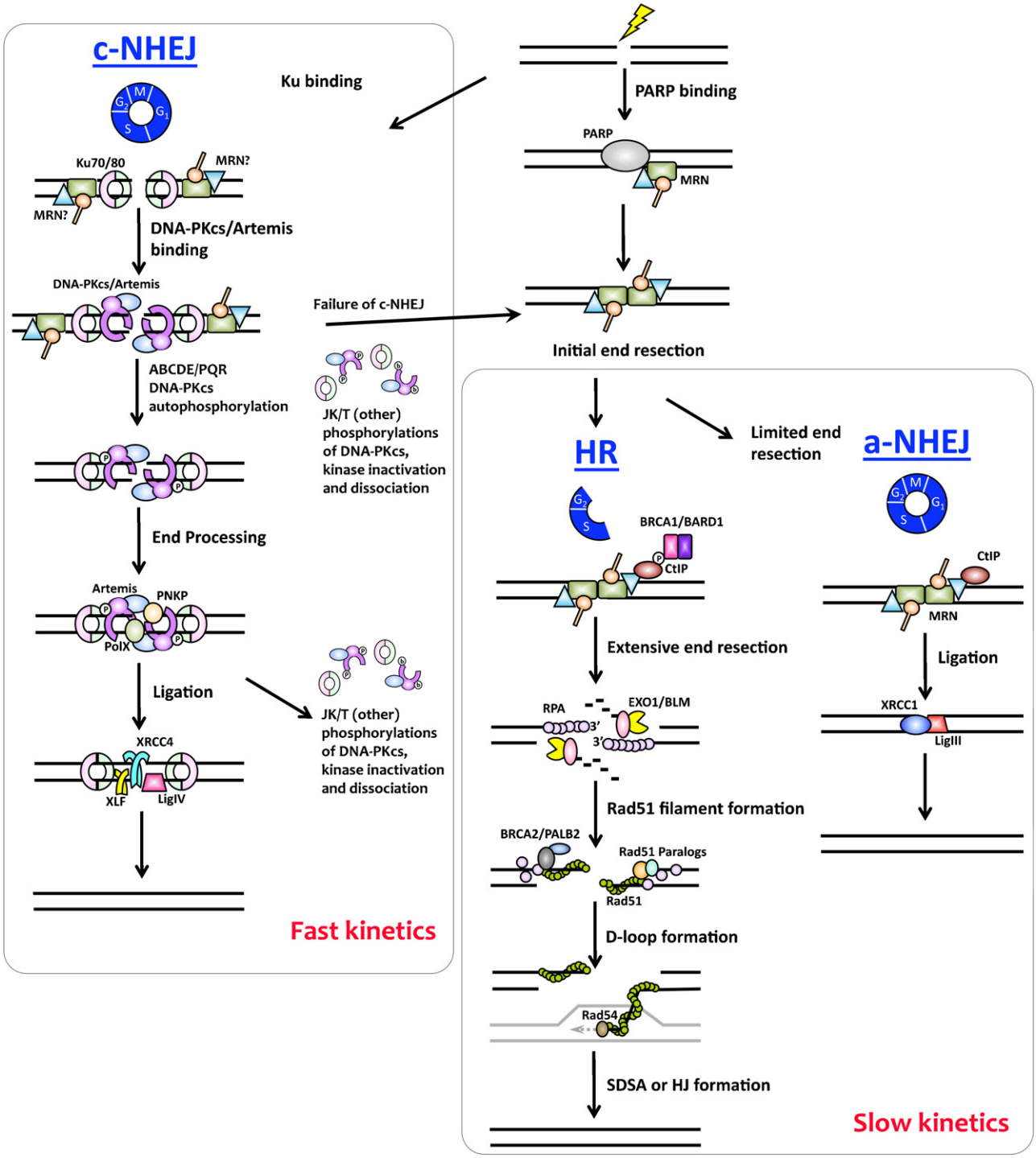

Fig. 1. Pathways for repairing DNA double-strand breaks. DSBs are repaired by one of three pathways, c-NHEJ (left panel) HR (middle panel) or a-NHEJ (right panel). c-NHEJ occurs with rapid kinetics throughout the cell cycle, and is initiated when DSBs are recognized and bound by the Ku 70/86 heterodimer. The MRN complex may co-localize to the same break (potentially through interaction with Ku70). Ku recruits DNA-PKcs forming the DNA-PK holoenzyme. Artemis, which is less abundant than DNA-PKcs, is complexed with DNA-PKcs. Upon recruitment to a DSB by Ku, the nuclease activity of Artemis is activated by *trans* autophosphorylation at the ABCDE cluster within DNA-PKcs. ABCDE phosphorylations promote end processing whereas PQR phosphorylations (also in *trans*) limit end processing. This provides tight regulation of end access to various processing factors, including Artemis, PNKP, and X family polymerases. If c-NHEJ fails, the HR and a-NHEJ pathways can gain access to the break; this would be facilitated by the presence of the MRN complex. In this case, DNA-PK might be inactivated by phosphorylation at the J, K or T sites as well as other, not yet identified, sites. J, K and T phosphorylations have been shown to inhibit c-NHEJ and promote HR. It is not known whether J, K or T phosphorylations occur in *cis* or *trans*, but clearly DNA-PKcs autophosphorylates some sites in *cis* (K.M. unpublished data). Ligation is carried out by the XLF/XRCC4/LigIV complex. Filament formation by XRCC4 and XLF may also contribute to synapsis. Further autophosphorylation of DNA-PKcs induces kinase inactivation (N, J, K, and T sites) and finally dissociation (sites responsible for dissociation are not known, although phosphorylation of ABCDE may contribute to complex dissociation). Although assembly and action or the c-NHEJ pathway is presented sequentially, it is also possible that c-NHEJ factors are simultaneously recruited to the site of a DSB through interaction with Ku and/or DNA-PKcs. Such a supercomplex would likely require the presence of Ku to be maintained, and as a result may cause Ku to be "stuck" on the DNA following repair. Proteolysis could provide a mechanism for subsequent removal of Ku. If c-NHEJ fails or if the DSB is first recognized by PARP, MRN is recruited to the DSB. During the S and G_2 phases of the cell cycle, MRN along with CtIP and BRCA1 perform initial, short range DNA end resection which promotes HR (adapted from [178]). HR proceeds with slower kinetics than c-NHEJ. More extensive end resection is carried out by EXO1 in collaboration with the BLM helicase. The exposed 3′ overhangs are then rapidly coated with RPA, which is ultimately replaced by Rad51