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Targeting DNA Double-Strand Break Repair in Cancer Therapy

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Description

DNA double-strand breaks (DSBs) are common DNA lesions that often arise from exposure to DNA damaging agents and as a consequence of replication fork collapse. Due to their predilection for generating chromosomal discontinuities, DSBs are the most deleterious DNA damage in cells [1]. Therefore, it is not surprising that DSB repair has been actively explored as a target in cancer treatment [2]. Recent studies have clearly demonstrated the existence of redundant DSB repair activities, which together play an essential role in the maintenance of genome stability and cell survival. It is noteworthy that these activities are orchestrated and dynamically regulated at multiple levels. The most robust and omnipresent DSB repair is performed by the non-homologous end-joining (NHEJ) pathway, which is highly efficient, active at all times, and characteristically independent of homologous templates [3]. However, NHEJ mediated DSB repair is frequently associated with nucleotide deletions and/or insertions at the repair joints when DSB end processing precedes the ligation step. Contrariwise, the completion of homologous recombination (HR)-based DSB repair relies on the availability of the homologous donor template; thus, HR is mainly restricted to cells at the S/G2 phases of the cell cycle [4,5]. Although it is generally error-free, commitment to the relatively lengthy HR process requires a two-tier process—comprised of a short initial end resection and an extensive end resection—to generate recombinogenic single-stranded DNA. It has been increasingly recognized that the initial end resected intermediates could also be shunted to less accurate and highly mutagenic DSB repair processes, i.e., alternative NHEJ (Alt-EJ) and single-strand annealing (SSA). Unlike HR, Alt-EJ and SSA do not require homologous templates, and it is conceivable that the DSB repair pathway choice could be harnessed by the extent of end resection. However, it is contentious whether the decision to carry out extensive end resection is made before or after the initial end resection.

Prompt DSB repair is important to cells since failure of repair is frequently associated with genomic instability and cell death. Inappropriate regulation of DSB repair activities and misuse of repair pathways could empower genomic instability and promote cancer development. Evidently, mutations in genes involved in DSB repair are prominent risk factors for cancer development in humans. This is well exemplified by the causal relationship between inactivating mutations in the tumor suppressor genes BRCA1 and BRCA2, encoding proteins that play essential roles in the process of HR, and the development of breast and ovarian cancers. Likewise, mutations in NHEJ genes, such as ligase IV, XLF and DNA-PKcs, lead to lymphoid as well as non-lymphoid cancers. These mutations are also associated with microcephaly and growth delay. Intriguingly, microcephaly in ligase IV defective patients was not progressive after birth; however, it was progressive in patients with defective DNA-PK [6,7]. The exact molecular nature underlying this discrepancy is unknown.

Given that the induction of DSBs is the major underlying molecular mechanism of many anticancer regimens, intuitively, the selective blocking of DSB repair in cancer cells should boost the effectiveness of these regimens. Ironically, cancer cells can also fuel genomic instability through aberrant DSB repair provoked by interference with either the HR or NHEJ pathway – similar to the effects exerted by cancer-causing mutations in DSB repair genes. Clearly, an in-depth understanding of the precise regulation of DSB repair in normal and tumor cells is needed to identify unique therapeutic targets for devising more selective anti-cancer strategies. To this end, the successful exploitation of PARP1 inhibitors in the treatment of BRCA1/2 deficient tumors has warranted future investigations for novel synthetic lethal relationships within the network of DNA damage repair and signaling [8]. The revelation of new synthetic lethality will undoubtedly aid the development of more selective, individualized, anticancer strategies.

References

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