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Editorial Open Access

# Versatility of DNA Double Strand Break Repair

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## Editorial

The generation of DNA double strand breaks (DSBs) is considered a lethal insult to the integrity of chromosomes. If not repaired, DSBs can lead to daunting consequences such as chromosome fragmentation, deletion, or rearrangement. While a plethora of DSB repair activities are available to cells, inappropriate execution of DSB repair pathways can also be a source for chromosome aberrations. It is proposed that inaccurate joining of DSBs is involved in the generation of the extraordinarily clustered chromosome rearrangements, i.e. chromothripsis, in primary tumors and cancer cell lines [1,2]. Cells are commonly equipped with at least two major DSB repair pathways – homologous recombination (HR) and non-homologous end joining (NHEJ). These two repair pathways are necessitated for the maintenance of genome stability. Although physiologic DSBs are essential for meiosis and immunoglobulin gene rearrangements, the majority of them are pathologic. It is estimated that 10 DSBs can occur in an average human cell per day [3]. Generally, two-ended DSBs are preferred substrates for NHEJ, and the repair of one-ended DSBs can only be carried out by HR [4].

NHEJ represents a major end-joining activity that is available for cells in every phase of the cell cycle, which operates through coordinated actions of Ku70/Ku80, DNA-PKcs, and the ligase complex XRCC4-Ligase IV-XLF [5]. The Ku70/Ku80 heterocomplex protects the break ends from nucleolytic degradation by physically binding to the ends of DSBs and recruiting downstream NHEJ factors [6,7]. DSBs with compatible ends can be ligated directly without end processing; however, incompatible ends have to be processed before rejoining can occur – this process is often associated with deletions or rearrangements at the repair junctions [8-10]. In addition to this well-defined NHEJ pathway, recent evidence suggests the existence of alternative end-joining activities that are normally masked by the canonical pathway [11].

DSBs can also undergo HR-mediated repair; however, HR is commonly confined to the S and G2 phases of the cell cycle in which donor templates are generally available on sister chromatids [12]. HR-based DSB repair is frequently considered to be an "error-free" pathway, but inappropriate execution of HR can also lead to genome alterations. This is largely reflected by the aberrant (ectopic) recombination between repetitive sequences in diseased human genomes [13]. HR initiates from a two-tier 5'-3' end resection event [14]. The first step is a short end resection carried out by the activities of the MRE11-CtIP complex. This creates a DNA structure that can be processed by a nuclease complex, containing either DNA2 or EXO, to generate long resected ends that are required for HR [15,16]. Repair commences when a homologous donor sequence is identified by the long single-stranded DNA-Rad51 filament. It appears that the short end resection alone is not sufficient to shuttle DSBs towards the HR pathway. In fact, recent evidence indicates that DSBs with short end resections can be rejoined by activities not supported by HR or canonical NHEJ [17-21]. It is conceivable that such end-joining activities can be problematic while maintaining nucleotide sequence fidelity at the repair junctions. It has been increasingly recognized that harnessing long end resection is a key factor in the repair pathway choice for cells at S or G2/M phase [22]. The end resection event is controlled by the interplay between 53BP1 and BRCA, of which 53BP, together with Rif, obstruct end resection and promote NHEJ [23,24]. In contrast, by antagonizing 53BP1's interaction with DSBs, BRCA1 promotes end resection and ultimately HR-based DSB repair [15]. The outcomes of DSB-inducing anticancer treatments are at least partially dictated by how cancer cells process therapeutic DSBs; therefore, understanding the precise regulation of DSB repair will enable a better prognostic prediction.

## References

1. Stephens PJ, Greenman CD, Fu B, Yang F, Bignell GR, et al. (2011) Massive genomic rearrangement acquired in a single catastrophic event during cancer development. Cell 144: 27-40.
2. Forment JV, Kaidi A, Jackson SP (2012) Chromothripsis and cancer: causes and consequences of chromosome shattering. Nat Rev Cancer 12: 663-670.
3. Martin GM, Smith AC, Ketterer DJ, Ogburn CE, Disteche CM (1985) Increased chromosomal aberrations in first metaphases of cells isolated from the kidneys of aged mice. Isr J Med Sci 21: 296-301.
4. Helleday T, Lo J, van Gent DC, Engelward BP (2007) DNA double-strand break repair: from mechanistic understanding to cancer treatment. DNA Repair (Amst) 6: 923-935.
5. Lieber MR (2010) The mechanism of double-strand DNA break repair by the nonhomologous DNA end-joining pathway. Annu Rev Biochem 79: 181-211.
6. Mimori T, Hardin JA (1986) Mechanism of interaction between Ku protein and DNA. J Biol Chem 261: 10375-10379.
7. Blier PR, Griffith AJ, Craft J, Hardin JA (1993) Binding of Ku protein to DNA. Measurement of affinity for ends and demonstration of binding to nicks. J Biol Chem 268: 7594-7601.
8. Gu J, Lu H, Tippin B, Shimazaki N, Goodman MF, et al. (2007) XRCC4:DNA ligase IV can ligate incompatible DNA ends and can ligate across gaps. EMBO J 26: 1010-1023.
9. Chappell C, Hanakahi LA, Karimi-Busheri F, Weinfeld M, West SC (2002) Involvement of human polynucleotide kinase in double-strand break repair by non-homologous end joining. EMBO J 21: 2827-2832.
10. Ma Y, Pannicke U, Schwarz K, Lieber MR (2002) Hairpin opening and overhang processing by an Artemis/DNA-dependent protein kinase complex in nonhomologous end joining and V(D)J recombination. Cell 108: 781-794.
11. Fattah F, Lee EH, Weisensel N, Wang Y, Lichter N, et al. (2010) Ku regulates the non-homologous end joining pathway choice of DNA double-strand break repair in human somatic cells. PLoS Genet 6: e1000855.

12. Saleh-Gohari N, Helleday T (2004) Conservative homologous recombination preferentially repairs DNA double-strand breaks in the S phase of the cell cycle in human cells. Nucleic Acids Res 32: 3683-3688.
13. Hagstrom SA, Dryja TP (1999) Mitotic recombination map of 13cen-13q14 derived from an investigation of loss of heterozygosity in retinoblastomas. Proc Natl Acad Sci U S A 96: 2952-2957.
14. Chapman JR, Taylor MR, Boulton SJ (2012) Playing the end game: DNA double-strand break repair pathway choice. Mol Cell 47: 497-510.
15. Bunting SF, Callén E, Wong N, Chen HT, Polato F, et al. (2010) 53BP1 inhibits homologous recombination in Brca1-deficient cells by blocking resection of DNA breaks. Cell 141: 243-254.
16. Nimonkar AV, Genschel J, Kinoshita E, Polaczek P, Campbell JL, et al. (2011) BLM-DNA2-RPA-MRN and EXO1-BLM-RPA-MRN constitute two DNA end resection machineries for human DNA break repair. Genes Dev 25: 350-362.
17. Helmink BA, Tubbs AT, Dorsett Y, Bednarski JJ, Walker LM, et al. (2011) H2AX prevents CtIP-mediated DNA end resection and aberrant repair in G1-phase lymphocytes. Nature 469: 245-249.
18. Lee-Theilen M, Matthews AJ, Kelly D, Zheng S, Chaudhuri J (2011) CtIP promotes microhomology-mediated alternative end joining during class-switch recombination. Nat Struct Mol Biol 18: 75-79.
19. Rass E, Grabarz A, Plo I, Gautier J, Bertrand P, et al. (2009) Role of Mre11 in chromosomal nonhomologous end joining in mammalian cells. Nat Struct Mol Biol 16: 819-824.
20. Xie A, Kwok A, Scully R (2009) Role of mammalian Mre11 in classical and alternative nonhomologous end joining. Nat Struct Mol Biol 16: 814-818.
21. Truong LN, Li Y, Shi LZ, Hwang PY, He J, et al. (2013) Microhomology-mediated End Joining and Homologous Recombination share the initial end resection step to repair DNA double-strand breaks in mammalian cells. Proc Natl Acad Sci U S A 110: 7720-7725.
22. Symington LS, Gautier J (2011) Double-strand break end resection and repair pathway choice. Annu Rev Genet 45: 247-271.
23. Escribano-Díaz C, Orthwein A, Fradet-Turcotte A, Xing M, Young JT, et al. (2013) A cell cycle-dependent regulatory circuit composed of 53BP1-RIF1 and BRCA1-CtIP controls DNA repair pathway choice. Mol Cell 49: 872-883.
24. Zimmermann M, Lottersberger F, Buonomo SB, Sfeir A, de Lange T (2013) 53BP1 regulates DSB repair using Rif1 to control 5' end resection. Science 339: 700-704.