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A possible role of repair proteins BRCA1 and DNA-PK in the processing of oxidative DNA damage

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Abstract

BRCA1 and DNA-PK are two significant multifunctional proteins involved primarily in the processing of double strand breaks (DSBs). BRCA1 participates actively in homologous recombination (HR) while DNA-PK in non-homologous end joining (NHEJ). In this mini review, we discuss all recent evidence for a possible involvement of these repair proteins also in the processing of oxidatively-induced DNA damage.

BRCA1 and DNA-PK involvement in the processing of DSBs

DSBs are considered highly genotoxic DNA lesions because they can potentially lead to chromosomal breakage (Burma et al. 2006). DSBs can arise as the result of exposure to exogenous sources like natural and medical radiation or other environmental exposures to chemicals, when chromosomes exchange genetic material in preparation for cell division and finally endogenously either by free radicals that emerge as byproducts of normal cellular metabolism or as repair intermediates during the processing of clustered DNA lesions (Georgakilas 2008). Two major pathways have been implicated in the processing of DSBs: non-homologous end joining (NHEJ) and homologous recombination repair (HR) (Kanaar et al 1998). One of the key protein complexes in the NHEJ pathway is the DNA-PK holoenzyme consisting of the Ku70/80 heterodimer and the catalytic subunit of *DNA-PK* (DNA-PKcs) (Meek et al. 2004). The central role of *DNA-PK* in the processing of DSBs is underlined by several studies showing a severe radiosensitivity and decreased DSB repair in cells with compromised DNA-PK activity or reduced expression of the protein (DiBiase et al. 2000; Peng et al. 2002; Salles et al. 2006). The BRCA1 gene is located on the long (q) arm of chromosome 17 at position 21 and provides instructions for making the corresponding protein that is directly involved in repairing DSBs through HR repair (Holt et al. 1996; Zhong et al. 1999). Interestingly, deficiencies of both proteins (DNA-PK and BRCA1) have been associated with elevated breast (Yu et al. 2001; Fu at al. 2003) or ovarian cancer risk (Futreal et al. 1994; Turner et al. 2006).

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An alternative role of BRCA1 and DNA-PKcs in the processing of oxidative DNA lesions

Recent evidence from our laboratory suggests an additional and alternative role of these two traditional DSB repair proteins in the processing of non-DSB lesions induced by oxidative stress (base damage and single strand breaks-SSBs) (Francisco et al. 2008; [a]Peddi et al. 2008; [b]Peddi et al 2008). In support of this idea, several other laboratories have shown a compromised repair of non-DSB oxidative DNA damage in cells or tissues with *DNA-PK* or *BRCA1* deficiencies. Rodriguez et al. have recently shown a deficient processing of oxidative DNA lesions in lymphoblasts from women with BRCA1 mutations. Additional support for the role of *BRCA1* in DNA DSB repair and potentially oxidative lesions, comes from the finding that *BRCA1* plays a coordinator role of multiple activities required for maintenance of genomic integrity interacting with various DNA damage repair proteins like MSH2, RAD51, ATM, BLM and RAD50-MRE11-NBS1 (Zhong et al 1999; Wang et al. 2000) and actively participates in transcription coupled repair (Le Page et al. 2000). Reduced levels of DNA-PKcs maybe compromising the processing of base damages through base excision repair (BER) since DNA-PKcs has been shown recently to interact with many BER proteins suggested actually forming a repairsome (Levy et al. 2006; Parlanti et al. 2007) i.e., *direct effect.* Another possible explanation can be the strong inhibitory action of existing SSBs (forming a DSB) towards the processing of neighboring base damages i.e., *indirect effect*. Many *in vitro* studies suggest that the existence of a single SSB can significantly inhibit or delay the processing of opposing base damages (Dianov et al. 2001).

Conclusion

Accumulating evidence from different laboratories suggests an alternative (direct or indirect) effect of *BRCA1* and *DNA-PK* in the processing of oxidatively-induced DNA damage like abasic sites, altered bases and/or single strand breaks. This potential function of these proteins in the repair of non-DSB DNA lesions in addition to their verified involvement in the repair of DSBs, raises significant issues in the predisposition of individuals to several diseases like breast and ovarian cancer since both of these genes have been involved in increased breast or ovarian cancer susceptibility.

References

Burma S, Chen BPC, Chen DJ (2006) Role of non-homologous end joining (NHEJ) in maintaining genomic integrity. DNA Repair 5:1042-1048

Georgakilas AG (2008) Processing of DNA damage clusters in human cells: Current status of knowledge. Mol Biosyst 4:30-35

Kanaar R, Hoeijmakers JH, Van Gent DC (1998) Molecular mechanisms of DNA double strand break repair. Trends Cell Biol 8:483-489

Meek K, Gupta S, Ramsden DA, Lees-Miller SP (2004) The DNA-dependent protein kinase: the director at the end. Immunological Reviews 200:132-141

DiBiase SJ, Zeng ZC, Chen R et al (2000) DNA-dependent protein kinase stimulates an independently active nonhomologous, end-joining apparatus. Cancer Res 60:1245-1253

Peng Y, Zhang Q, Nagasawa H et al (2002) Silencing expression of the catalytic subunit of DNA-dependent protein kinase by small interfering RNA sensitizes human cells for radiation-induced chromosome damage, cell killing, and mutation. Cancer Res. 62:6400-6404

Salles B, Calsou P, Frit P, Muller C (2006) The DNA repair complex DNA-PK a pharmacological target in cancer chemotherapy and radiotherapy. Pathologie Biologie 54:185-193.

Holt JT, Thompson ME, Szabo C et al (1996) Growth retardation and tumour inhibition by BRCA1. Nat Genet 12:298-302

Zhong Q, Chen CF, Li S et al (1999) Association of BRCA1 with the hRad50-hMre11-p95 complex and the DNA damage response. Science 285:747-750

Yu Y, Okayasu R, Weil MM et al (2001) Elevated breast cancer risk in irradiated BALB/c mice associates with unique functional polymorphism of the Prkdc (DNA-dependent protein kinase catalytic subunit) gene. Cancer Res. 61:1820-1824

Fu YP, Yu JC, Cheng TC et al (2003) Breast cancer risk associated with genotypic polymorphism of the nonhomologous end-joining genes: a multigenic study on cancer susceptibility. Cancer Res 63:2440-2446

Futreal PA, Liu Q, Shattuck-Eidens D et al (1994) BRCA1 Mutations in Primary Breast and ovarian carcinomas. Science 266:120-122

Turner NC, Reis-Filho JS, Russell AM (2006) BRCA1 dysfunction in sporadic basal-like breast cancer. Oncogene 26:2126-2132

Francisco DC, Peddi P, Hair JM et al (2008) Induction and processing of complex DNA damage in human breast cancer cells MCF-7 and non-malignant MCF-10A cells. Free Radic Biol Med 44:558-569.

[a]Peddi P, Francisco DC, Cecil A et al (2008) Deficient processing of clustered DNA damage in human breast cancer cells MCF-7 with silenced DNA-PKcs expression. Cancer Lett.:In press

[b]Peddi P, Francisco DC, Hair JM et al. (2008) Accumulation of complex DNA damage in human breast cancer cells MCF-7 deficient in DNA-PKcs. In: Meeting, A. A., ed. AACR Annual Meeting, volume 49. San Diego, California, USA.

Rodriguez H, Jaruga P, Leber R et al (2007) Lymphoblasts of women with BRCA1 mutations are deficient in cellular repair of 8,5'-cyclopurine-2'-deoxynucleosides and 8-hydroxy-2'-deoxyguanosine. Biochemistry 46:2488-2496

Wang Y, Cortez D, Yazdi P et al (2000) BASC, a super complex of BRCA1-associated proteins involved in the recognition and repair of aberrant DNA structures. Genes Dev 14:927-939

Le Page F, Randrianarison V, Marot D et al (2000) BRCA1 and BRCA2 are necessary for the transcription-coupled repair of the oxidative 8-oxogunanine lesion in human cells. Cancer Res. 60:5548-5552

Levy N, Martz A, Bresson A et al (2006) XRCC1 is phosphorylated by DNA-dependent protein kinase in response to DNA damage. Nucleic Acids Res 34:32-41

Parlanti E, Locatelli G, Maga G, Dogliotti E (2007) Human base excision repair complex is physically associated to DNA replication and cell cycle regulatory proteins Nucleic Acids Res. 35:1569-1577

Dianov GL, O'Neill P, Goodhead DT (2001) Securing genome stability by orchestrating DNA repair: removal of radiation-induced clustered lesions in DNA. BioEssays 23:745-749