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Review Article

The role of BRCA1 in DNA double-strand repair: Past and present

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ABSTRACT

The breast cancer type 1 susceptibility protein (BRCA1) is involved in several important cellular pathways, including DNA damage repair, chromatin remodeling and checkpoint activation. The BRCA1 tumor suppression function has been attributed to its role in homologous recombination damage repair. In this review, historical facts concerning BRCA1, together with recent research advances regarding our understanding of the BRCA1 interacting proteins that are involved in, homologous recombination (HR) double strand break (DBS) repair and how these interacting proteins maintain chromosomal integrity, are discussed. In addition, this review poses the questions as to what extent HR repair cannot be properly fulfilled when breast cancer related mutations in the *BRCA1* gene occur and how the recent and excessive studied poly-ADP ribose polymerase (PARP) inhibiting therapy approach links with the proposed tumor suppression function of the different BRCA1 domains.

Contents

Abbreviations: 53BP1, p53 binding protein 1; ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia mutated rad3-related; ATRIP, ATR-interacting protein; BACH1, BRCA1-associated C-terminal helicase; BARD1, BRCA1-associated RING domain; BASC, BRCA1-associated genome surveillance complex; BRCA1, breast cancer susceptibility gene 1; BRCT, BRCA1 C-terminal domain; Chk1/2, checkpoint kinase 1/2; CstF, cleavage stimulation factor; DSB, double strand break; CtIP, CtBP interacting protein; FANC, Fanconi anemia; HAT, histone acetyltransferase; HDAC, histone deacetylase; HR, homologous repair; IRIF, ionizing radiation-induced foci; MDC1, Mediator of DNA Damage protein 1; Mre11, Meiotic recombination 11; MRN, Mre11-RAD50-Nbs1 complex; Nbs1, Nibrin; NES, nuclear export signal; NHEJ, non-homologous end-joining repair; NLS, nuclear localization signal; PALB2, partner and localizer of BRCA2; PARP, poly-ADP ribose polymerase; PARPi, poly-ADP ribose polymerase inhibiting therapy; RAP80, receptor-associated protein 80; PI3K, phosphoinositide 3-kinase; PIKK, PI3K-related protein kinase; RING, really interesting new gene; RNF, RING finger containing nuclear; RPA, replication protein A; SWI/SNF, SWItch/sucrose non-fermentable; SQCD, serine (S) threonine (Q) cluster domain; TopBP1, topoisomerase IIB binding protein 1; UBC, ubiquitin conjugating enzyme; UIM, ubiquitin-interacting motif; UIMC1, ubiquitin interaction motif-containing 1 protein

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Introduction

The *Breast cancer susceptibility gene 1 (BRCA1)* is a gene which was originally mapped in 1990 and subsequently cloned in 1994 [1,2]. This gene has 24 exons and encodes the BRCA1 protein of 1863 amino acids (aa), which collaborates with DNA damage repair proteins, signal transducers and tumor suppressors. Because of the abundant and overwhelming information that is available in literature, BRCA1 is not the easiest protein to get familiar with.

For a long time, researchers thought BRCA1 and its interactors formed a large multi-subunit complex known as the BRCA1-associated genome surveillance complex (BASC), however, nowadays it is believed that BRCA1 is associated with a series of complexes with distinct functions, indicating the versatility of BRCA1 [1,3–5]. Numerous proteins bind on the several domains of BRCA1 (Fig. 1), resulting in a broad spectrum of functions that can be attributed to this protein such as cell cycle checkpoint activation, transcription regulation and DNA repair [4,6]. At the N-terminus, the BRCA1 protein contains a really interesting new gene (RING) finger domain and a nuclear export signal (NES), and at the C-terminus, the protein comprises two BRCA1-C-terminal (BRCT) domains [7–9] (Fig. 1). More central, BRCA1 has two nuclear localization signals (NLS), of which only the first one is important for the nuclear localization of BRCA1, and an SQ cluster domain (SQCD) that contains several threonine and serine residues which can become phosphorylated [10,11] (Fig. 1). Of all functions, the role of BRCA in DNA repair is pushed forward to explain its tumor suppression role [12]. Indeed, BRCA1 is involved in several DNA repair pathways, including both double strand break (DSB) and single strand break repair.

Therefore, the present review aims to give an update on the essential role of BRCA1 in DNA repair, with an emphasis on homologous recombination (HR) DSB repair. Hereby, the intention is to provide the most essential historical as well as the recent data on the role of BRCA1 in DBS repair for readers with little or no experience on this topic.

Double strand break DNA repair mechanisms

When DNA lesions occur, the genome can rely on different DNA repair mechanisms. In general, these mechanisms can be classified into two different groups: one group of mechanisms, which repairs double strand breaks (DSB), and another group of mechanisms, which operate on single strand solitary nucleotide lesions (SSB repair). DSB are considered to be the most menacing form of DNA damage because the integrity of both DNA strands is compromised at the same time. The mechanisms that repair DSB include the BRCA1 homologous recombination repair and the non-homologous end-joining repair. Because BRCA1 has been shown to be involved in both these repair mechanisms, they will be shortly discussed.

The *homologous recombination* (*HR*) *repair* is the most accurate DSB repair mechanism, of which the absence can lead to gross genome rearrangements and hence genomic instability. In HR, a homologous stretch of DNA on a sister chromatid serves as a template to guide repair of the broken strand [13]. Since sister chromatids are present during the S- and G2-phase of the cell cycle, HR repair can only occur during these phases of the cell cycle. During this repair, the 5′ and 3′ ends of the DSB become resected by exonucleases, after which the DSB ssDNA nucleoprotein filament invades the intact sister chromatid and serves as if it was a primer (Fig. 2A). Because of this invasion, the second strand of the sister chromatid gets displaced and a D-loop structure will be formed. There are two models of HR repair: (i) the classical HR model and (ii) the alternative synthesis-dependent strand annealing model. In the classical HR model, the displaced strand of the sister chromatid anneals to the 3′-overhang from the

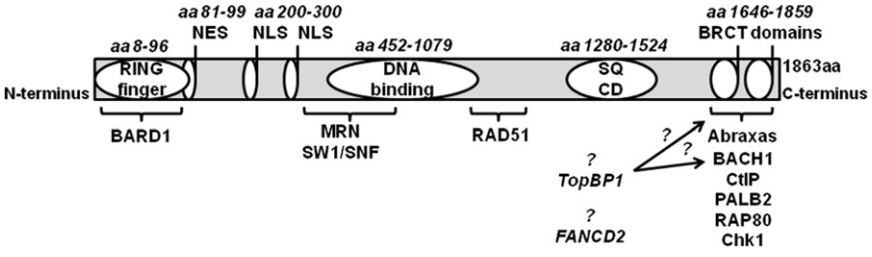

Fig. 1 – BRCA1, its functional domains and its most important binding proteins involved in double strand break (DBS) repair (based on Narod and Foulkes, 2004). NES: nuclear export signal; NLS: nuclear localization signal; SQCD: SQ cluster domain and BRCT domains: BRCA1 C-terminal domains.