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BRCA1: A Locus-Specific "Liaison" in Gene Expression and Genetic Integrity

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Abstract Mutations in *BRCA1* predominantly lead to elevated risks of breast and ovarian cancers. In contrast to the tissue-specific nature of *BRCA1*tumors, the normal *BRCA1* gene product functions in diverse nuclear events including transcription, DNA repair, and DNA damage checkpoint. Recent findings of physical and functional associations between BRCA1 and the RNA polymerase II (RNAPII)-dependent transcription machinery may shed some light on this longstanding paradox of BRCA1 biology. Eukaryotic gene expression is now known to be a continuous process, whereby each step is physically and functionally connected to the next. In particular, RNAPII plays a pivotal role in coordinating transcription with various pre-mRNA processing events and stress response. Interestingly, BRCA1 preferentially interacts with the processive form of RNAPII and proteins that regulate RNAPII activity and movement during transcription elongation. In response to DNA damage, BRCA1 dissociates from RNAPII and localizes to DNA damage sites. We propose that BRCA1 may coordinate multiple steps in gene expression, including transcription initiation, elongation, and pre-mRNA processing via its interactions with the transcription machinery at selected gene loci. The same BRCA1-associated transcription apparatus may serve as a sensor for stress signals and facilitate the transition from a transcription state to checkpoint/DNA repair state. Such a coordinating role of BRCA1 in gene expression may ensure the appropriate quantity and quality of the mature transcripts for certain breast and ovarian cancer-related genes, as well as the genetic integrity of the breast and ovary tissues. J. Cell. Biochem. 94: 1103–1111, 2005.

Key words: BRCA1; breast cancer; transcription; pre-mRNA processing; checkpoint; RNA polymerase II

Mutations in *BRCA1* account for close to half of hereditary breast cancers and approximately 80% of the cases where both hereditary breast-and ovarian cancers occur (breast–ovarian families) [Rahman and Stratton, 1998; Narod and Foulkes, 2004]. Although *BRCA1* mutations are rarely found in sporadic cancer, a significant percentage of sporadic breast cancer cases, especially tumors with high nuclear grade, show reduced expression of BRCA1 mRNA and protein [Wilson et al., 1999]. Moreover, the promoter of the *BRCA1* gene is hypermethylated in 10%–15% of sporadic breast and ovarian cancer cases [Catteau et al., 1999; Esteller et al., 2000; Magdinier et al., 2000], further supporting the notion that *BRCA1* may also play a role in suppression of sporadic breast cancer.

The human *BRCA1* gene encodes a 1863-amino acid protein that contains a highly conserved RING finger domain at the amino terminus and two repeats of the BRCT domain at the carboxyl terminus. Since the identification of the *BRCA1* gene 10 years ago, the exact biochemical function of the BRCA1 protein has been the focus of intense research. The ubiquitously expressed protein is implicated in multiple nuclear events, including transcription, chromatin remodeling, ubiquitination, DNA repair, DNA damage checkpoint, and control of centrosome duplication. These diverse roles of BRCA1 have been extensively reviewed in several recent articles [Monteiro, 2000; Scully and Livingston, 2000; Zheng et al., 2000a; Baer and Ludwig, 2002; Deng, 2002; Jasin, 2002; Venkitaraman, 2002; Rosen et al., 2003; Starita

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and Parvin, 2003; Lane, 2004]. To avoid redundancy, we refer readers to these excellent review articles for more detailed overview of BRCA1 functions. Here, we will discuss the functional complexity of BRCA1 in the context of the emerging theme of coordinated gene expression in eukaryotic cells. We suggest that the diverse nuclear functions of BRCA1 may be explained by its role in coordinating various steps in gene expression at certain breast cancer-related genes. Such a gene-specific effect of BRCA1 could also shed light on the long-standing conundrum of why BRCA1 tumors are tissue specific. We apologize to those authors whose work is not cited here due to limited space.

UNIFIED PICTURE OF EUKARYOTIC GENE EXPRESSION

Our understanding of eukaryotic gene expression has been advanced significantly over the past several years. Contrary to the historical view of eukaryotic gene expression as being separate and unconnected individual nuclear events, we now know through a growing number of biochemical and genetic studies that gene expression is a continuous process whereby distinct steps are functionally and physically connected [Orphanides and Reinberg, 2002; Sims et al., 2004]. For example, recent experiments demonstrate that the machinery for capping and processing of nascent RNA transcripts is recruited by the transcription elongation complex, which allows for pre-mRNA processing to occur concomitantly with transcription [Shatkin and Manley, 2000; Proudfoot et al., 2002; Zorio and Bentley, 2004]. Reciprocally, the RNA splicing machinery can play a positive role in transcription elongation [Fong and Zhou, 2001] and export of mature RNA out of the nucleus [Reed and Hurt, 2002]. Such a high degree of functional coordination may be advantageous to eukaryotic gene expression in multiple senses. First of all, it may be parsimonious to employ the same transcription complex as a landing pad for recruiting multiple processing machines. Perhaps more importantly, the physical and functional connections among distinct machineries during transcription may ensure high efficiency in gene expression. From the regulatory perspective, this coordination of events may also enforce a quality control mechanism so that one step has to be appropriately completed before the machinery moves to the next. Last, but not least, this organization may allow a prompt and adequate inhibition of the entire gene expression process in the event of stress signals that are incompatible with gene activation.

Emerging evidence suggests that RNA polymerase II (RNAPII) is the key player in the coordination of transcription and RNA processing [Orphanides and Reinberg, 2002; Zorio and Bentley, 2004]. More specifically, the carboxy-terminal domain (CTD) of the largest subunit of RNAPII appears to serve as a landing platform for the ordered recruitment of the different machineries in gene expression. The CTD of RNAPII in mammals contains 52 repeats of a highly conserved heptapeptide (Tyr-Ser-Pro-Thr-Ser-Pro-Ser). Phosphorylation of the CTD at different serine residues (Ser2 and Ser5) during transcription may constitute a "CTD code" that determines the transition from one step of transcription to the next, as well as the timely recruitment of different machineries [Howe, 2002; Maniatis and Reed, 2002; Neugebauer, 2002]. The coupling role of RNAPII CTD in transcription and RNA processing may also provide the quality control mechanisms as speculated above to ensure a smooth and efficient transition between the steps.

CONNECTIONS BETWEEN BRCA1 AND THE TRANSCRIPTION COMPLEX

Given the central role of RNAPII in the coupling of transcription and pre-mRNA processing, it is plausible that proteins that directly or indirectly bind to RNAPII may regulate or confine the coupling function of RNAPII in a tissue-, cell-, or gene-specific manner. Based upon several recent findings, BRCA1 could serve as such a candidate in several endocrine tissues including breast and ovary. The initial evidence for a link between BRCA1 and the basal transcription machinery comes from studies where BRCA1 was shown to interact with the RNAPII holoenzyme, likely via BRCA1 binding to several components of the core enzyme including RNA helicase A [Scully et al., 1997a; Anderson et al., 1998]. More recent work by Lane and co-workers indicates that BRCA1 preferentially binds to hyperphosphorylated RNAPII (IIO), which is the processive form of the polymerase engaged in transcription elongation [Krum et al., 2003]. It was shown in the same study that BRCA1 binding to RNAPII is a highly conserved feature of BRCA1 homo-

logs from several species. Lastly, it was reported that the BRCA1 C-terminal region can modulate the phosphorylation status of the CTD of RNAPII [Moisan et al., 2004]. Taken together, these results are consistent with the notion that BRCA1 associates with, and may subsequently regulate, the transcriptional apparatus during the elongation stage (Fig. 1).

In addition to its interaction with the RNAPII holoenzyme, BRCA1 is also associated with certain transcription elongation factors and RNA processing proteins. Co-factor of BRCA1 (COBRA1) was identified as a BRCA1-interacting protein [Ye et al., 2001] and subsequently found to be NELF-B, one of the four subunits of the negative elongation factor complex NELF. The NELF complex was biochemically purified based on its ability to inhibit transcription elongation by stalling RNAPII within the promoter-proximal region [Wada et al., 1998; Yamaguchi et al., 1999]. One possible purpose for the transcriptional arrest is to allow ample time for coordinating transcription elongation with pre-mRNA processing [Sims et al., 2004]. Consistent with this notion, a recent biochemical study showed that the NELF-mediated transcriptional repression was relieved following the recruitment of the 5′ capping enzyme (CE) by the RNAPII CTD to the stalled elongation complex, which could in turn allow the transcription complex to proceed to the next stage of elongation [Mandal et al., 2004]. The NELF-mediated transcriptional arrest may also serve as a venue for regulating the levels of gene expression, as was demonstrated by our recent work that NELF inhibits estrogen-dependent transcription activation by estrogen receptor α (ER-α) in breast cancer cells [Aiyar et al., 2004]. In addition to its interaction with COBRA1, BRCA1 was also shown to associate with positive transcription elongation factors [Cabart et al., 2004] as well as polyadenylation factors [Kleiman and Manley, 1999; Kleiman and Manley, 2001]. Thus, the interactions between BRCA1 and various components of the elongating transcription complex may facilitate "transcriptional checkpoint" and/or control the overall transcription rate at specific genes (Fig. 1).

DNA DAMAGE RESPONSE: ANOTHER PIECE OF THE PUZZLE

It is well accepted that BRCA1 plays an important role in DNA damage response and

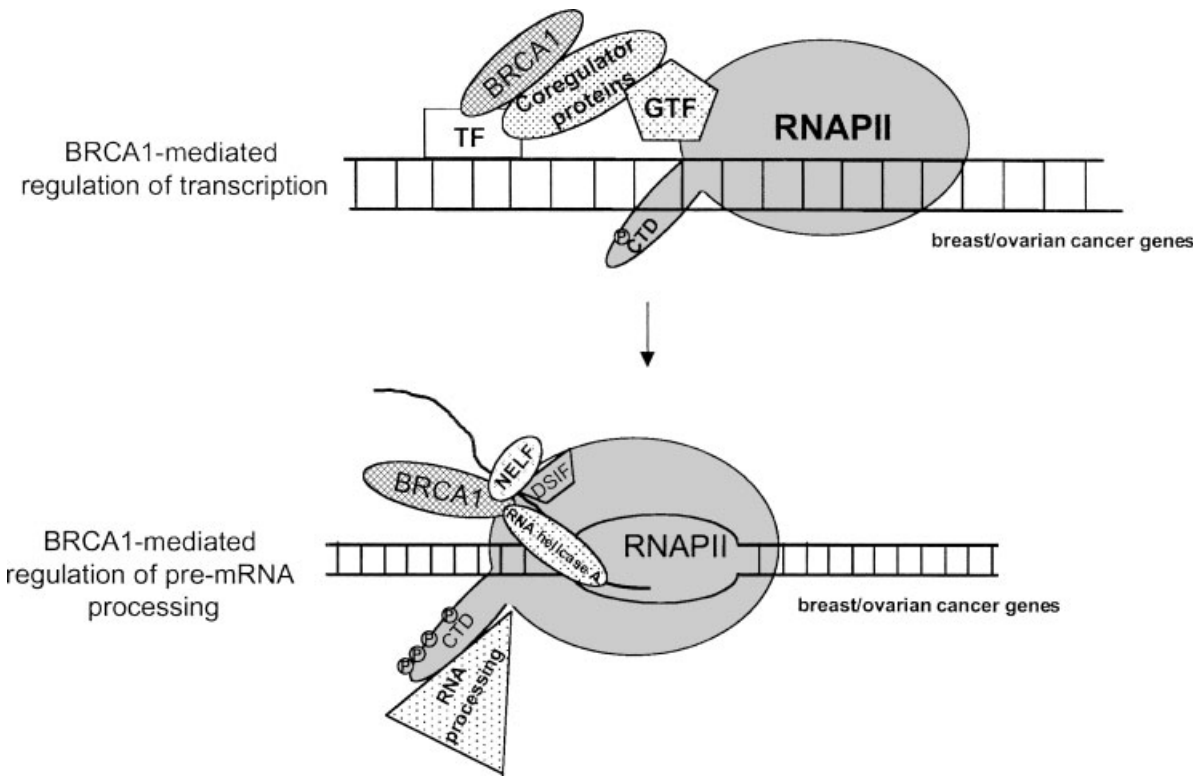

Fig. 1. A coordinating role of BRCA1 in gene expression.

DNA repair [Scully and Livingston, 2000; Zheng et al., 2000a; Jasin, 2002; Venkitaraman, 2002]. Two lines of evidence support this role of BRCA1. The first comes from the physical or cytological associations between BRCA1 and various DNA repair/checkpoint proteins. For example, BRCA1 forms distinct nuclear foci in response to various DNA damage signals; and these damage-induced foci co-localize with several well-known checkpoint/DNA repair proteins such as γ-H2AX, RAD50, and RAD51 [Scully et al., 1997b; Paull et al., 2000]. Furthermore, BRCA1 was co-immunoprecipitated with various DNA replication, repair, or recombination proteins such as RAD51 [Scully et al., 1997c], RAD50/MRE11/NBS1 [Zhong et al., 1999; Wang et al., 2000], and MSH2/MSH6 [Wang et al., 2000]. BRCA1 also interacts with, and is phosphorylated by, ATM, ATR, and CHK2 [Cortez et al., 1999; Lee et al., 2000; Tibbetts et al., 2000], which are protein kinases that are key players in the damage checkpoint control. The second line of evidence for a role of BRCA1 in DNA damage response comes from functional studies using BRCA1-knockout mouse embryonic fibroblasts or BRCA1-deficient human breast cancer cells. Various defects in DNA damage response have been reported in these cells, including deficiencies in double strand break-induced homologous recombination [Moynahan et al., 1999], crosslink repair [Moynahan et al., 2001], non-homologous end-joining [Wang et al., 2001; Zhong et al., 2002], transcription-coupled repair [Abbott et al., 1999; Le Page et al., 2000], nucleotide excision repair [MacLachlan et al., 2000; Hartman and Ford, 2002], and cell-cycle checkpoint [Xu et al., 1999; Xu et al., 2001]. Mechanistically, the effect of BRCA1 in DNA damage response could be due to its ability to activate expression of those genes that are involved in checkpoint and DNA repair. Alternatively, BRCA1 may directly participate in DNA repair through its physical and functional interactions with DNA repair proteins at damage sites.

Despite the compelling evidence for its function in DNA damage response, it remains unclear whether BRCA1 indeed acts as part of the "core" DNA repair machinery to maintain genetic integrity in a global manner. Unlike the essential components of damage checkpoint and DNA repair apparatuses, *BRCA1* orthologs are not found in lower eukaryotes such as *Saccharomyces cerevisiae*. The fact that the *BRCA1* gene emerges relatively late during evolution is consistent with a more specialized role of the protein product. Moreover, the highly tissue-specific nature of *BRCA1*-associated tumors is also more in line with a context-dependent function of BRCA1 in maintenance of genome stability. It has been proposed that the RNAPII-associated BRCA1 may function in the surveillance for DNA damage along actively transcribed genes [Starita and Parvin, 2003; Lane, 2004]. Consistent with this model, it was found that, following DNA damage, BRCA1 dissociates from RNAPII holoenzyme and instead interacts with damage-induced proteins or protein complexes [Chiba and Parvin, 2001; Krum et al., 2003]. In addition, BRCA1 and its partner BARD1 interact with polyadenylation factors and are involved in inhibition of polyadenylation in response to ultraviolet irradiation [Kleiman and Manley, 1999; Kleiman and Manley, 2001]. Interestingly, RNAPII itself was also shown to be ubiquitinated and subsequently degraded following DNA damage [Bregman et al., 1996; Beaudenon et al., 1999]. Thus, the ubiquitin E3 ligase activity of BRCA1 and BARD1 may trigger degradation of RNAPII, and thus disintegration of the entire transcription complex in response to DNA damage [Dong et al., 2003] (Fig. 2). Another possibility is that the interactions between BRCA1 and various elongation factors may allow prompt disassembly of the elongating transcription and pre-mRNA processing apparatuses in the advent of genotoxic stress, which in turn may lead to degradation of RNAPII. BRCA1 and some of its associated proteins may remain on the DNA template to facilitate the removal of DNA lesions in a timely fashion by recruiting checkpoint and DNA repair proteins to the same gene loci (Fig. 1). In this regard, it is worth mentioning that, although the initial report implicating BRCA1 in transcription-coupled repair (TCR) has been retracted [Gowen et al., 1998], more recent work by Le Page and co-workers demonstrates that BRCA1 is involved in TCR of oxidative DNA damage [Le Page et al., 2000].

GLOBAL VERSUS LOCUS-SPECIFIC EFFECT OF BRCA1

As an extension of the "surveillance" model [Starita and Parvin, 2003; Lane, 2004], we would like to propose that a "liaison" function of BRCA1 in gene expression and damage response may occur primarily on a specific subset

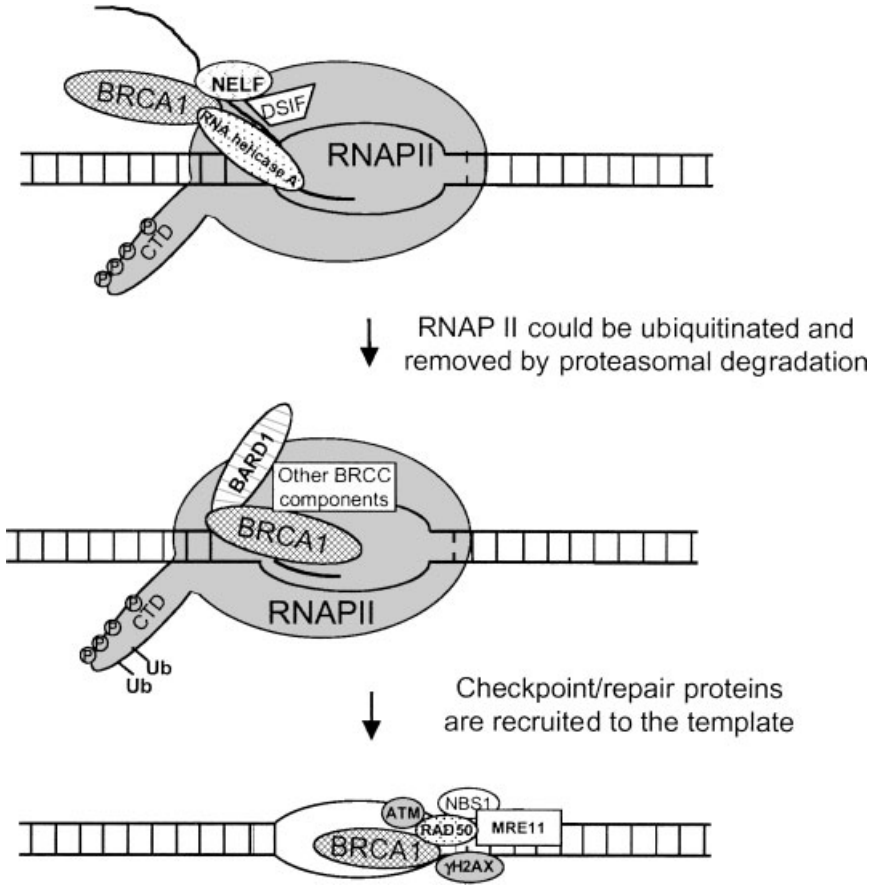

Fig. 2. A ''liaison'' role of BRCA1 during the transition from transcription to checkpoint/DNA repair state.

of breast/ovarian cancer-related genes (Fig. 2). This putative locus-specific role of BRCA1 could potentially reconcile the diverse activities ascribed to BRCA1 with the tissue-specific nature of *BRCA1* tumors. This predicts that: (1) BRCA1 is physically associated with the promoter and/or intragenic region of its target genes and (2) the target genes play a critical and unique role(s) in the development of breast and ovarian cancer. As reviewed extensively in several recent review articles [Monteiro, 2000; Rosen et al., 2003; Starita and Parvin, 2003; Lane, 2004], BRCA1 interacts with numerous site-specific transcription factors including p53 [Somasundaram et al., 1997; Ouchi et al., 1998], ZBRK [Zheng et al., 2000b], Jun [Hu and Li, 2002], STAT [Ouchi et al., 2000], and estrogen receptor α (ER-α) [Fan et al., 1999]. In addition, both gene-specific and whole-genome microarray approaches lead to the identification of an extensive list of potential BRCA1-regulated genes in breast epithelial cells [Harkin et al., 1999; MacLachlan et al., 2000; Andrews et al., 2002; Hartman and Ford, 2002; MacLachlan et al., 2002; Welcsh et al., 2002]. These include p53-regulated genes such as p21 and GADD45 [Somasundaram et al., 1997; Ouchi et al., 1998; Harkin et al., 1999; MacLachlan et al., 2002], 14-3-3σ [Aprelikova et al., 2001]), and ERα-regulated genes such as pS2 and cathepsinD [Zheng et al., 2001]. Furthermore, BRCA1 has a role in establishing X chromosome inactivation in female cells [Ganesan et al., 2002]. A recent study by Deng et al. indicates that BRCA1 is also required for recruitment of the checkpoint kinase ATR to the X and Y chromosomes during spermatogenesis, which results in chromosomal condensation and transcriptional repression on the two sex chromosomes at the pachytene stage of sperm development [Turner et al., 2004]. Using chromatin immunoprecipitation, it was shown that BRCA1 physically associates with several of these BRCA1 target genes [Zheng et al., 2001; Ganesan et al., 2002; Kim et al., 2003; Murtagh et al., 2004], indicating a direct effect of BRCA1 on transcription of these genes. Notwithstanding these findings, it remains unclear whether dysregulation of any of the

known BRCA1-regulated genes can account for the tissue specificity of *BRCA1* tumors. Further functional analysis of these known target genes of BRCA1 and perhaps identification of additional genes that have a more direct and specific impact on breast and ovarian cancer development will shed light on this "holy grail" of BRCA1 biology.

Several models have been proposed to explain the tissue-specific nature of BRCA1-associated breast and ovarian cancers [Monteiro, 2003]. For example, it is suggested that a limited "window" during puberty may render highly proliferating breast epithelial cells most susceptible to the genome-destabilizing effect of *BRCA1* mutations [Scully and Livingston, 2000]. It is also proposed that, compared to other cell types, breast and ovarian epithelial cells with loss of BRCA1 functions may result in delayed apoptosis, which could allow them to accumulate additional genetic and epigenetic changes necessary for tumorigenesis [Elledge and Amon, 2002]. In addition, the tissue specificity of *BRCA1* tumors could also be explained by a possibly accelerated rate in loss of heterozygosity at the *BRCA1* locus in breast and ovary [Monteiro, 2003]. More recently, Starita and coworkers showed that reduced BRCA1 expression in breast cancer, but not non-breast cell lines, resulted in centrosome deregulation [Starita et al., 2004]. Thus, a cell type-dependent function of BRCA1 in maintenance of centrosome number may also contribute to the tissue specificity of BRCA1-mediated tumor suppression. Lastly, based upon the model proposed in the current article, BRCA1 may coordinate various events of gene expression and stress response via its association with the transcription complex in selected gene loci. A role of BRCA1 in regulating the expression of a set of breast and ovarian cancer-related genes could dictate the tissue-specific effect of BRCA1 functions, whereas the DNA repair function of BRCA1 may contribute to genetic stability in a broader tissue spectrum. This could explain why *BRCA1* mutation carriers have a significant increase of cancer risk in breast and ovary, but only modest elevation of cancer risk in several other tissues [Thompson et al., 2002].

CONCLUSION

Despite the enriched knowledge of BRCA1 that was gained over the past decade, two outstanding questions with regard to its biological functions remain to be answered. Are the diverse nuclear functions of BRCA1 mechanistically linked? Why does lack of BRCA1 functions predominantly lead to tumors in breast and ovary, two major hormone-responsive organs in women? We favor the possibility that, upon being recruited to a specific set of breast cancer-related genes, BRCA1 may coordinate multiple steps in gene expression through its association with the elongating transcription complex. This could ensure control of both the quantity and quality of gene expression at several levels, including the amplitude and duration of gene expression during transcription initiation and elongation, the proper processing of pre-mRNA, and sensing transcriptional arrest and triggering a checkpoint response upon DNA damage and other stress signals.

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