



REVIEW ARTICLE

Dysregulation of the centrosome induced by BRCA1 deficiency contributes to tissue-specific carcinogenesis

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Abstract

Alterations in *breast cancer gene 1* (*BRCA1*), a tumor suppressor gene, increase the risk of breast and ovarian cancers. BRCA1 forms a heterodimer with BRCA1-associated RING domain protein 1 (BARD1) and functions in multiple cellular processes, including DNA repair and centrosome regulation. BRCA1 acts as a tumor suppressor by promoting homologous recombination (HR) repair, and alterations in BRCA1 cause HR deficiency, not only in breast and ovarian tissues but also in other tissues. The molecular mechanisms underlying BRCA1 alteration-induced carcinogenesis remain unclear. Centrosomes are the major microtubule-organizing centers and function in bipolar spindle formation. The regulation of centrosome number is critical for chromosome segregation in mitosis, which maintains genomic stability. BRCA1/BARD1 function in centrosome regulation together with Obg-like ATPase (OLA1) and receptor for activating protein C kinase 1 (RACK1). Cancer-derived variants of BRCA1, BARD1, OLA1, and RACK1 do not interact, and aberrant expression of these proteins results in abnormal centrosome duplication in mammary-derived cells, and rarely in other cell types. RACK1 is involved in centriole duplication in the S phase by promoting polo-like kinase 1 activation by Aurora A, which is critical for centrosome duplication. Centriole number is higher in cells derived from mammary tissues compared with in those derived from other tissues, suggesting that tissue-specific centrosome characterization may shed light on the tissue specificity of BRCA1-associated carcinogenesis. Here, we explored the role of the BRCA1-containing complex in centrosome regulation and the effect of its deficiency on tissue-specific carcinogenesis.

KEYWORDS

BRCA1, breast cancer, centrosome, centrosome amplification, HBOC

1 | INTRODUCTION

Breast cancer gene 1 (*BRCA1*) on chromosome 17q is the gene responsible for hereditary breast and ovarian cancer syndrome.¹ Women carrying pathogenic germline variants of *BRCA1* are at high risk of

breast (57%) and ovarian cancers (40%).² Biallelic alterations of *BRCA1* are observed in Fanconi anemia, a syndrome characterized by progressive bone marrow failure and increased risk of cancer.³ Mice with homozygous null alleles of *Brca1* show embryonically lethal between E6 and E13.5 because of growth retardation, apoptosis, and

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aneuploidy.⁴ Mammary-specific knockout of *Brca1* in combination with p53 deficiency leads to basal-like breast cancer with a propensity for the triple-negative subtype, which is the most frequent subtype in *BRCA1*-associated hereditary breast cancer in humans.⁴

The *BRCA1* gene product is a 1863 amino acid (aa) protein with a RING domain in the amino (N)-terminus and 2 tandem BRCT domains in the carboxy (C)-terminus (Figure 1A).⁵ *BRCA1*-associated RING domain 1 (*BARD1*), which was identified as a binding protein to the N-terminal fragment (aa 1-304) of *BRCA1*, also has a RING domain in its N-terminus and BRCT domains in the C-terminus (Figure 1B).⁶ *BRCA1* and *BARD1* form a stable complex through their RING domains⁷ and interact with various proteins involved in DNA damage repair, centrosome regulation, chromatin remodeling, and transcriptional regulation.^{7,8}

DNA double-stranded breaks (DSBs) are repaired by homologous recombination (HR) or non-homologous end joining. HR is an error-free system that repairs DSBs using undamaged DNA homologous to the damaged DNA as a template. *BRCA1* is an essential factor for HR.⁸ Some *BRCA1* variants that are deficient in HR have been identified in hereditary breast cancer and by high-throughput analyses⁹⁻¹³ In addition, alterations in several HR-related factors other than *BRCA1* have been reported in hereditary and sporadic breast cancers.^{14,15} Therefore, HR activities are important for tumor suppression in breast tissues. However, *BRCA1* alterations induce HR deficiency not only in mammary epithelial cells but also in other tissue-derived cells.^{8,9,11,13} These data suggest that *BRCA1* alterations cause additional defects in cellular functions, which may contribute to its mammary tissue-specific carcinogenesis.

Recently, we and other groups reported that deficiencies of *BRCA1* and its interacting proteins induce centrosome aberrations only in mammary epithelium-derived cells.¹⁶⁻¹⁹ In this review, we focus on the function of *BRCA1* in centrosome regulation and discuss how the function of *BRCA1* contributes to tumor suppression.

2 | THE CENTROSOME

2.1 | Structure and function of the centrosome

The centrosome is a non-membranous organelle that contains a pair of centrioles surrounded by proteinaceous pericentriolar material

(PCM) (Figure 2A).^{20,21} The centriole is a barrel-shaped structure composed of 9 microtubule triplets (Figure 2A). A daughter centriole is attached to the side wall of the mother centriole. The PCM is composed of several layers of proteins.²¹ The outer layer of the PCM contains abundant γ -tubulin ring complexes, which are required for microtubule nucleation. Therefore, the centrosome acts as a major microtubule-organizing center that is involved in the regulation of the cytoskeleton, cell polarity, intracellular trafficking, and cell division.²² During mitosis, microtubules sprouting from centrosomes are attached to the centromere of chromosomes and form mitotic spindles.²⁰

2.2 | Regulation of centrosome number

The centrosome is duplicated only once during each cell cycle²³ (Figure 3). After mitosis, a daughter cell inherits 1 centrosome from the mother cell. In G1 phase, the centrosome has 2 mother centrioles interconnected by a linker. At the end of G1 phase, polo-like kinase 4 (PLK4) is activated and phosphorylates several centrosomal proteins, including STIL, triggering the formation of a procentriole containing cartwheel on the side wall of the mother centriole.²⁴ During S phase, a daughter centriole is generated from the procentriole. In late G2 phase, the linker is degraded by the activation of NIMA-related kinase 2 (NEK2), which allows the movement of each centrosome to opposite poles of the cell.²⁵ Before mitosis, the daughter centriole is tightly connected to the mother centriole (called engagement). Engagement is disrupted by the cleavage of several proteins, including pericentrin and cohesion, by separase during mitosis (called disengagement), and a new linker is formed between the disengaged centrioles.^{26,27} The engagement of centrioles inhibits further procentriole formation.²⁸ Therefore, disengagement is the licensing step for centriole duplication.²⁷ If the disengagement occurs before mitosis, which is known as premature disengagement, centrioles can undergo additional duplication (called reduplication), resulting in extra-centrioles.^{29,30} Disengagement is promoted by polo-like kinase 1 (PLK1) through the phosphorylation of pericentrin, sSgo1, or other centrosomal proteins.^{31,32} The activity of PLK1 is regulated by phosphorylation catalyzed by several kinases, among which Aurora A phosphorylates PLK1 at Thr-210 with scaffold proteins, thereby regulating PLK1 activity spatio-temporally.³³⁻³⁸

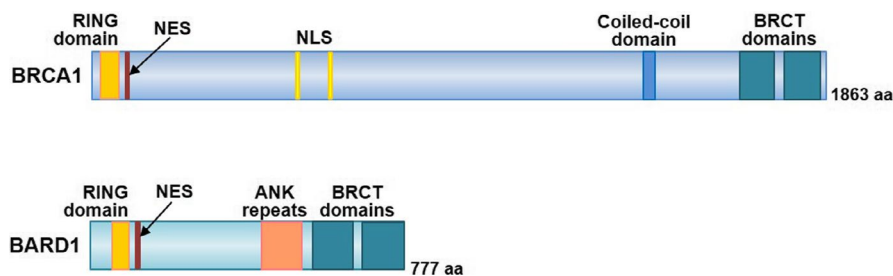
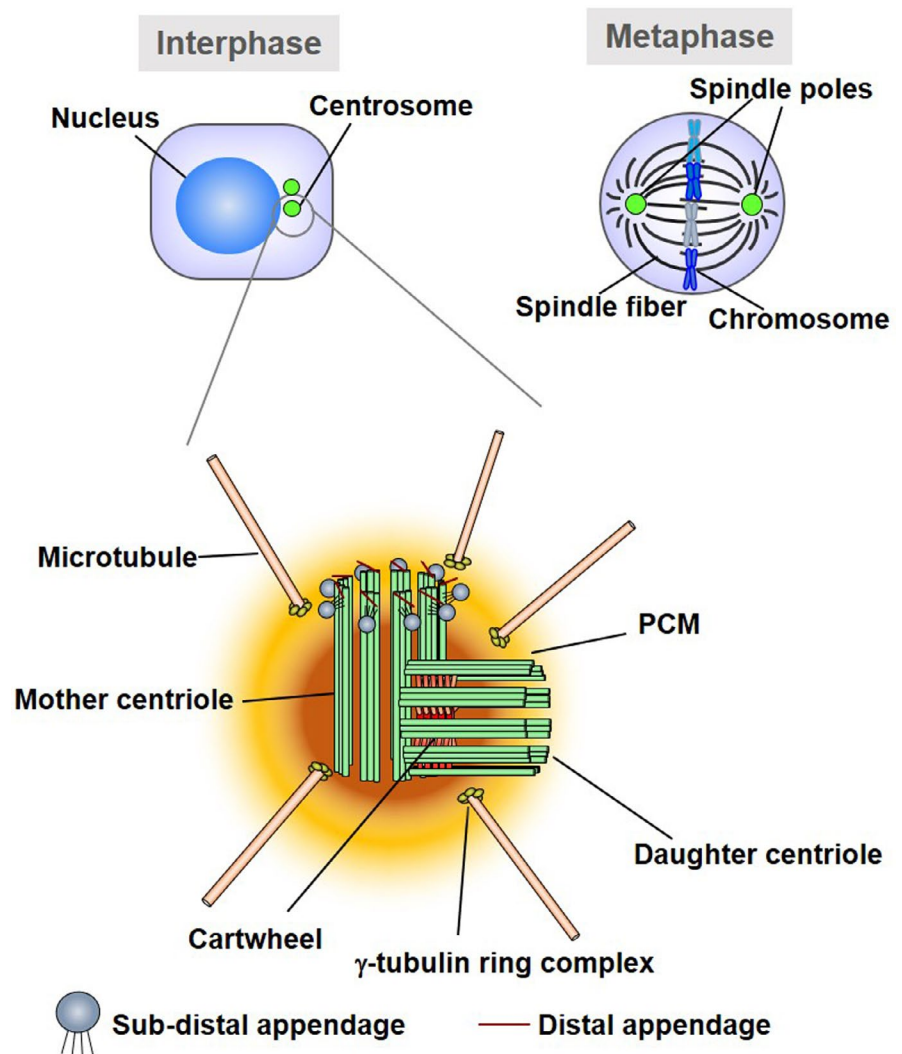


FIGURE 1 Structure of *BRCA1* and *BARD1*. *BRCA1* and *BARD1* have a RING domain and nuclear export signal (NES) in the N-terminus and 2 BRCT domains in the C-terminus. *BRCA1* includes a nuclear localization signal (NLS) and a coiled-coil domain. *BARD1* contains ankyrin (ANK) repeats

FIGURE 2 Schematic diagram of the centrosomes. The centrosome consists of mother centriole and daughter centriole, embedded in the pericentriolar matrix (PCM). The PCM contains γ -tubulin ring complexes required for microtubule nucleation



2.3 | Centrosome aberrations in cancer

Structural and numerical aberrations of centrosomes were reported in various malignancies.³⁹ Regulators of centrosome duplication, including Aurora A and PLK1, are frequently dysregulated or mutated in cancers including breast cancer.⁴⁰ In breast tissues, centrosome aberrations are present in pre-malignant lesions.⁴¹⁻⁴³ The frequency of centrosome aberrations increases in correlation with progressive tumor stage⁴² and is associated with the degree of chromosomal instability.⁴² Estrogen stimulation is associated with the induction of centrosome aberrations in breast tissues, suggesting that estrogen promotes tumor development via centrosome aberrations in estrogen-dependent tissues.⁴⁴ In mouse models, overexpression of Plk4 induces centrosome amplification resulting in carcinogenesis.⁴⁵ These data suggest that centrosome aberrations contribute to carcinogenesis at an early stage by inducing chromosomal instability.

Excess centrosomes promote remodeling of the cytoskeleton by increasing Rac1 activity⁴⁶ and affecting cell-cell adhesion,⁴⁷ which increase the invasiveness of cancer cells. In addition, centrosome aberrations or upregulation of centrosome regulators, including NEK2 and PLK4 in cancer cells, are related to the resistance

to chemotherapeutics.^{48,49} These processes may be involved in the poor prognosis of cancer patients with centrosome aberrations.⁵⁰

3 | ROLES OF BRCA1 IN CENTROSOME REGULATION

3.1 | BRCA1 dysfunction induces centrosome aberration

In invasive breast cancers, centrosome aberrations are more common in the triple-negative subtype than in other histological subtypes.⁵⁰ Centrosome aberrations are frequently observed in *BRCA1*-associated hereditary breast cancers and sporadic breast cancers lacking *BRCA1* expression,^{51,52} and are found even in non-cancerous mammary epithelia in carriers of pathogenic *BRCA1* variants.⁵³ These findings suggest that *BRCA1* dysfunction induces centrosome aberrations during carcinogenesis in breast tissues.

BRCA1 localizes to centrosomes during interphase and to spindle poles during mitosis.⁵⁴⁻⁵⁷ Inhibition or knockdown of *BRCA1* induces centrosome amplification in cell lines derived from mammary

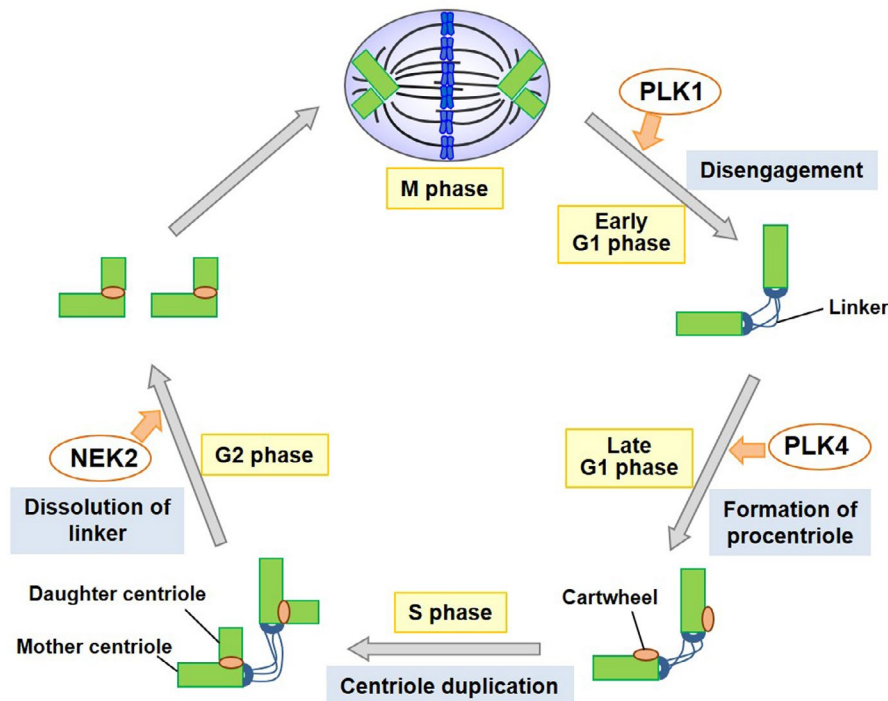


FIGURE 3 Schematic diagram of the centrosome duplication cycle. The mother and daughter centrioles are disengaged in late mitosis-early G1 phase. After centriole disengagement, linkers are established between the 2 centrioles. In late G1 phase, a procentriole containing cartwheel is formed at each centriole. The building of the new centriole starts in the early S phase and 1 new daughter centriole forms perpendicularly to each mother centriole during the S phase. The new daughter centriole gradually elongates during the S and G2 phases. In the G2 phase, the 2 centrosomes separate through the dissolution of the linker and move to opposite sides of the cell to form the spindle poles

epithelia.¹⁶ Centrosome amplification induced by BRCA1 knock-down is rescued by wild-type BRCA1, but not by several BRCA1 variants reported in hereditary breast cancer cases.⁵⁸ Missense variants of BRCA1, including I42V and L52F, are proficient in HR, but deficient in centrosome regulation.⁵⁸ Therefore, BRCA1 contributes to centrosome regulation independently of its DNA repair activity.

3.2 | Regulation of BRCA1 localization to centrosomes

BRCA1 localizes to the mother centriole and is recruited to the new mother centriole in late G1 phase before procentriole formation.⁵⁵ The centrosomal localization of BRCA1 is decreased by disruption of the nuclear export signal (NES) of BRCA1 or inhibition of nucleus-to-cytosol transport by leptomycin B,⁵⁶ suggesting that centrosomal BRCA1 is derived from the nucleus.

Both the N-terminus and C-terminus of BRCA1 are required for its centrosomal localization, whereas the RING domain is dispensable.⁵⁶ There are 2 pools of centrosomal BRCA1, the slow turnover pool and the fast turnover pool, which is enhanced by association with BARD1.⁵⁶ However, the differences in the function and regulatory mechanisms between the 2 pools are not clear.⁵⁶

Receptor for activated protein C kinase 1 (RACK1) consists of 7 WD40 motifs exhibiting β -propeller structures.⁵⁹ RACK1 directly binds to the N-terminal region of BRCA1 (aa 70-304), although the RING domain of BRCA1 is dispensable for the interaction.¹⁹ Knockdown of RACK1 changes the centrosomal localization of BRCA1 from a discrete dot-like pattern colocalizing with centrioles to a dispersed pattern with spike-like protrusions.¹⁹ Conversely, RACK1 overexpression intensifies centrosomal BRCA1 signals.¹⁹ The

BRCA1 variants R133H and E143K and the RACK1 variant K280E, which decrease the affinity of BRCA1 for RACK1 (Figure 4A), decrease its centrosomal localization.¹⁹ These findings suggest that the N-terminus of BRCA1 contributes to the regulation of BRCA1 localization by mediating the interaction with RACK1. Given that RACK1 functions as a scaffold protein,⁵⁹ other unknown proteins might also associate with BRCA1 via RACK1 to regulate BRCA1 localization.

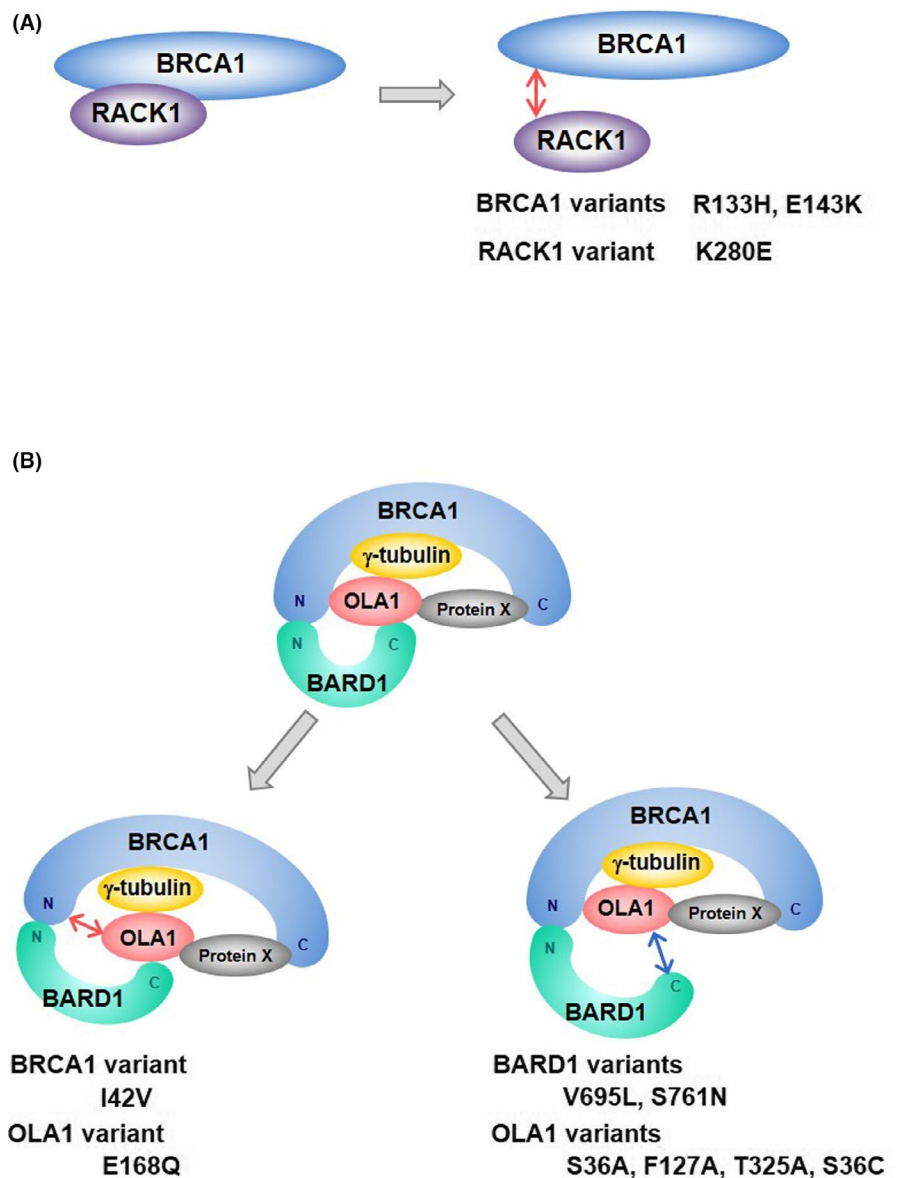
The role of the C-terminus of BRCA1 in its centrosomal localization is poorly understood. The 2 BRCT domains in the C-terminus interact with various phospho-proteins.⁵ Fanconi anemia group J protein (FANCI, also called BACH1 or BRIP1) binds to the BRCT domains of BRCA1 and promotes the centrosomal localization of BRCA1 after DNA damage.⁶⁰ However, the role of FANCI in the physiological BRCA1 localization to the centrosome remains undetermined. Furthermore, although the second BRCT domain of BRCA1 binds to p53, which functions in centrosome regulation,^{61,62} whether p53 contributes to the regulation of BRCA1 localization to centrosomes is not clear.

3.3 | The centrosomal BRCA1 complex contributes to the regulation of centrosome number

The BRCA1/BARD1 heterodimer interacts with various proteins, forming distinct complexes with corresponding molecular functions. Olg-like ATPase (OLA1) was isolated by immunoprecipitation using the C-terminus of BARD1 as bait.¹⁷ In addition to the C-terminus of BARD1, OLA1 directly binds to the N-terminus of BRCA1 and γ -tubulin to form BRCA1 complex (Figure 4B).¹⁷

Upregulation of OLA1 is observed in various cancers,⁶³ and is associated with poor prognosis in breast and hepatocellular

FIGURE 4 BRCA1 complex. A, The BRCA1-RACK1 interaction and the effects of the BRCA1 and RACK1 variants. B, BRCA1 complex and abnormal complexes containing variants of BRCA1, BARD1, or OLA1. "N" indicates the N-terminus. "C" indicates the C-terminus



carcinomas.^{64,65} Although OLA1 has ATPase or GTPase activity and contributes to stress responses in cells,^{64,66} the precise role of OLA1 in carcinogenesis remains to be elucidated.

OLA1 localizes to centrosomes during interphase and to mitotic spindles and spindle poles during mitosis.¹⁷ Deficiency and excess of OLA1 increase centrosome number in mammary epithelium-derived cells but not in non-breast cancer cells.^{17,18} Conversely, OLA1 knockdown suppresses cell proliferation even in non-breast cancer cell lines (unpublished data), suggesting that other activities of OLA1 affect cell proliferation irrespective of tissue type.

The proper formation of the complex composed of BRCA1, BARD1, and OLA1 is critical for the regulation of centrosome number (Figure 4B).⁶⁷ BRCA1 I42V decreases the interaction with OLA1.¹⁷ Conversely, OLA1 E168Q, a substitution found in a breast cancer cell line, abrogates the interaction with BRCA1.¹⁷ These

variants do not rescue centrosome amplification in BRCA1 or OLA1 knockdown cells.¹⁷ Substitutions of amino acids located at the interaction surface between BARD1 and OLA1, such as S761N of BARD1 and T325A of OLA1, abolish the interaction between the 2 proteins.¹⁸ In addition to those variants, the BARD1 V695L variant and OLA1 S36A and F127A variants are deficient in binding of BARD1-OLA1 and centrosome regulation.¹⁸ We recently found that the OLA1 S36A variant decrease the centrosomal localization of OLA1 (unpublished data). Ser-36 of OLA1 faces the ATP binding pocket of OLA1.⁶⁶ Binding of ATP to OLA1 may contribute to the loading of OLA1 into the centrosomal BRCA1 complex. The OLA1 S36C variant, which was found in cervical cancer, is also deficient in binding to BARD1 and in the regulation of centrosome number.¹⁸ Collectively, these findings indicate that formation of the centrosomal BRCA1 complex composed of BRCA1, BARD1, and OLA1 is necessary for centrosome regulation (Figure 4).

3.4 | Molecular mechanism of centrosome regulation by the BRCA1 complex

Centrosome amplification induced by BRCA1 deficiency is associated with centriole overduplication and premature disengagement.⁶⁸ Centriole overduplication is also induced by abnormal expression of OLA1^{17,18} and can occur through several pathways, including concomitant overduplication, reduplication, elongation, and fragmentation of centrioles. The pathways contributing to centriole overduplication induced by the deficiency of BRCA1, BARD1, or OLA1 remain to be elucidated.

Overexpression of RACK1 induces centriole reduplication following premature centriole disengagement.^{19,38} RACK1 acts as a scaffold protein to facilitate the interaction of Aurora A with PLK1, resulting in the Thr-210 phosphorylation and activation of PLK1 in S phase (Figure 5, upper panel).³⁸ The Aurora A/PLK1 interaction can also be mediated by Bora, CEP192, and Furry in G2 and M phases.³³⁻³⁸ RACK1 overexpression results in the accumulation of phosphorylated PLK1 at the centrosome before G2 and M phases, when PLK1 activity physiologically is maximal. Overactivation of PLK1 in S phase induces premature disengagement resulting in centriole overduplication (Figure 5, lower panel). Functional BRCA1 is required for centriole overduplication in RACK1-overexpressing cells,¹⁹ suggesting that the BRCA1 complex contributes to the regulation of PLK1 activity.

BRCA1 binds to and ubiquitinates γ -tubulin to regulate centrosome activity.^{16,54} BRCA1 monoubiquitinates γ -tubulin at Lys-48 and Lys-344.¹⁶ Forced expression of γ -tubulin with the K48R, K344R, and K48R/K344R mutations, which abolish ubiquitination, induces centrosome amplification.¹⁶ In addition, BRCA1 suppresses

the formation of microtubule asters from centrosomes by inhibiting microtubule anchoring.⁵⁵ BRCA1 knockdown and forced expression of non-ubiquitinatable γ -tubulin mutants enhance the formation of large microtubule asters from centrosomes.⁵⁷ These data suggest that BRCA1 deficiency causes centrosome aberrations by altering the mechanical forces that centriole enable disengagement.⁶⁹

3.5 | BRCA1 regulates the centrosome in a tissue-specific manner

BRCA1 localizes to centrosomes in various cells derived from breast and non-breast tissues.^{19,54-57} Starita et al reported that inhibition of BRCA1 activity induces centrosome amplification in breast cancer cell lines (Hs578T and T47D) and immortalized mammary epithelial cell lines (MCF10A and MTSV1-7), but not in cells derived from non-breast tissues (DLD1, HeLa, PC3, and U2OS).¹⁶ The effect of BRCA1 knockdown on inducing centrosome amplification was confirmed in Hs578T and MCF10A cells.^{58,68}

Abnormalities of other components of the centrosomal BRCA1 complex also induce centrosome aberrations specifically in mammary epithelium-derived cells.¹⁷⁻¹⁹ Overexpression of OLA1 induces centrosome amplification in Hs578T, MCF7, T47D, and MCF10A cells, but not in HeLa, PC3, Saos-2, and U2OS cells.¹⁸ Overexpression of BARD1 induces centrosome amplification in Hs578T and T47D cells but not in HeLa cells.¹⁸ Overexpression of RACK1 induces centrosome amplification in Hs578T, MCF7, T47D, and MCF10A but not in 6 cell lines derived from non-breast tissues.¹⁹ Although Zou et al reported that BRCA1 knockdown causes centrosome amplification in U2OS cells, dysfunction of the centrosomal BRCA1 complex

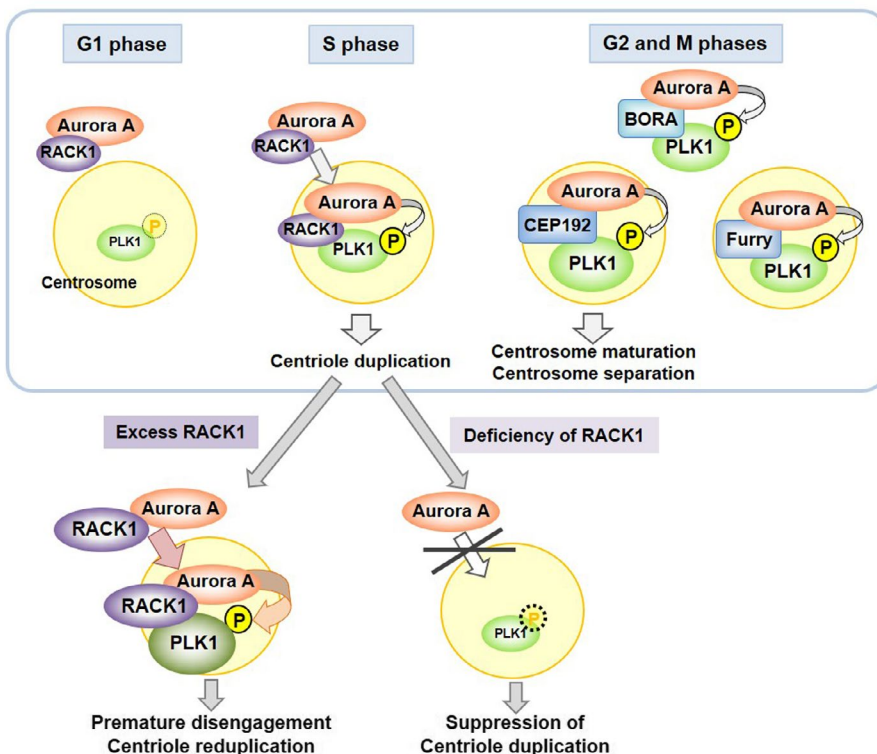


FIGURE 5 Regulation of PLK1 activity by RACK1. Under physiological conditions, RACK1 recruits Aurora A to centrosomes, thereby facilitating Aurora A binding to and phosphorylating PLK1 in the S phase. In G2 and M phases, activation of PLK1 is supported by Bora, CEP192, and Furry. Excess RACK1 induces overactivation of PLK1 in the S phase, resulting in premature centriole disengagement and centriole reduplication. Deficiency of RACK1 suppresses centriole duplication due to inadequate activation of PLK1

tends to cause centrosome aberrations in a tissue-specific manner (Table 1).

However, the mechanism underlying the tissue specificity of centrosome regulation by the BRCA1 complex is not understood. The expression and localization of BRCA1, BARD1, OLA1, and RACK1 to centrosomes is not tissue specific.^{17-19,54-57} To the best of our knowledge, a centrosomal protein that is specifically expressed in breast tissues has not been reported. However, mammary epithelium-derived cells contain a larger fraction of cells with duplicated centrioles than non-breast tissue-derived cells.¹⁹ As reduplication of centrioles occurs after the first duplication, mammary epithelium-derived cells may be more amenable to centriole reduplication. The differences in the mechanisms of centrosome regulation among tissues should be investigated in future studies.

3.6 | BRCA1 contributes to DNA damage-induced centrosome amplification

DNA damage-induced centrosome amplification (DDICA) is induced by various insults including ionizing radiation, mitomycin C, and hydroxyurea.^{60,61,70-72} Although the precise mechanism underlying DDICA is unclear, the involvement of BRCA1 in DDICA has been reported.⁶⁰ Mitomycin C treatment increases BRCA1 localization to centrosomes, thereby increasing centrosomal PLK1. FANCI is involved in the recruitment of BRCA1 to the centrosome in mitomycin C-treated cells. Knockdown of either BRCA1 or FANCI suppresses the increase of centrosomal PLK1 and the induction of DDICA.

The biological significance of DDICA is not well understood. When cells with extra centrosomes enter into mitosis, some cells undergo abnormal cell division, such as multipolar cell division, and finally die by apoptosis or mitotic catastrophe.^{73,74} Some cells complete mitosis by forming pseudo-bipolar spindles through

centrosome clustering to evade cell death during mitosis.^{73,75} However, these cells usually undergo cell death or cell cycle arrest after cell division.⁷³ Therefore, DDICA may be a mechanism to eliminate cells after prolonged, intolerable DNA damage.

By contrast, DDICA may be beneficial for the survival of cancer cells. Extra centrosomes increase chromosome mis-segregation during mitosis, which could confer advantages for cell survival and proliferation.⁷³ Loss of p53 spares cells with extra centrosomes from cell death or cell cycle arrest during and after mitosis⁷⁶⁻⁷⁸, therefore p53-deficient cancer cells may particularly benefit from extra centrosomes for cell proliferation.

In addition, various DNA repair factors localize to centrosomes.⁷⁹ DDICA may contribute to DNA damage repair by amplifying centrosomes, which act as signaling hubs for these DNA repair factors. DDICA has been detected in various cell lines^{71,72,80} and is not tissue specific (unpublished data). However, the regulatory mechanism of DDICA and tissue specificity of BRCA1 deficiency in DDICA should be investigated in the future.

4 | CONCLUSION

The centrosomal BRCA1 complex contributes to the maintenance of chromosomal stability by regulating centrosomes. Dysfunction of the BRCA1 complex causes centrosome aberrations in mammary epithelium-derived cells. Concomitant alterations in the regulation of centrosomes and other functions including HR caused by BRCA1 deficiency may especially increase the risk of cancer in the breast tissue of pathogenic BRCA1 variant carriers. The precise mechanism by which the BRCA1 complex regulates centrosomes, and the specific effect of BRCA1 complex dysfunction on inducing tumors in mammary epithelial cells, are issues that remain to be investigated. Improving our understanding of these mechanisms will facilitate the

TABLE 1 Summary of the effects of BRCA1 complex deficiency in various cell lines

References	Proteins	Treatments	Cell lines from breast tissue	Cell lines from non-breast tissue
Starita et al, 2004 ¹⁶	BRCA1	Inhibition by BIF	Hs578T, T47D, MCF10A, MTSV1-7, ZR75-1	DLD1, HeLa, PC3, U2OS
		Knockdown	Hs578T	U2OS
Ko et al, 2006 ⁶⁸	BRCA1	Knockdown	Hs578T, MCF10A	
Kais et al, 2012 ⁵⁸	BRCA1	Knockdown	Hs578T	
Zou et al, 2014 ⁶⁰	BRCA1	Knockdown		U2OS
Matsuzawa et al, 2014 ¹⁷	OLA1	Knockdown	Hs578T, T47D, HCC1937	HeLa
Yoshino et al, 2018 ¹⁸	OLA1	Overexpression	Hs578T, MCF-7, T47D, MCF10A	HeLa, PC3, Saos-2, U2OS
	BARD1	Overexpression	Hs578T, T47D	HeLa
Yoshino et al, 2019 ¹⁹	RACK1	Knockdown	MCF7	HeLa
	RACK1	Overexpression	Hs578T, MCF7, T47D, MCF10A	HeLa, KMST-6, PC3, OVCAR-3, Saos-2, U2OS

Note: In the cell line columns, cell lines presented in red characters show centrosome amplification; the cell line presented in blue characters show suppression of centriole duplication; and cell lines presented in black characters do not show centrosome abnormalities. BIF; a fragment of RNA helicase A that binds to the C-terminus of BRCA1.

diagnosis of hereditary breast cancer and enable the development of novel therapies targeting centrosome aberrations.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest for this article.

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