Review

The role of the breast cancer susceptibility gene 1 (BRCA1) in sporadic epithelial ovarian cancer

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Abstract

Mutations within the BRCA1 tumor suppressor gene occur frequently in familial epithelial ovarian carcinomas but they are a rare event in the much more prevalent sporadic form of the disease. However, decreased BRCA1 expression occurs frequently in sporadic tumors, and the magnitude of this decrease has been correlated with increased disease progression. The near absence of somatic mutations consequently suggests that there are alternative mechanisms that may contribute to the observed loss of BRCA1 in sporadic tumors. Indeed, both allelic loss at the BRCA1 locus and epigenetic hypermethylation of the BRCA1 promoter play an important role in BRCA1 down-regulation; yet these mechanisms alone or in combination do not always account for the reduced BRCA1 expression. Alternatively, misregulation of specific upstream factors that control BRCA1 transcription may be a crucial means by which BRCA1 is lost. Therefore, determining how regulators of BRCA1 expression may be co-opted during sporadic ovarian tumorigenesis will lead to a better understanding of ovarian cancer etiology and it may help foster the future development of novel therapeutic strategies aimed at halting ovarian tumor progression.

Introduction

Epithelial ovarian cancer is the most lethal of all gynecological malignancies [1]. The poor survival associated with ovarian carcinoma is due, at least in part, to the fact that the disease is usually asymptomatic in its early stages. As a result, detection often occurs at a late, metastatic stage when the prognosis is poor. While the etiology of ovarian carcinogenesis is poorly understood, evidence from histopathological studies and recently developed mouse models of ovarian cancer progression suggest that the majority of the tumors originate from the ovarian surface epithelium (OSE), a simple cuboidal layer that covers the surface of the ovary [2–5]. It remains unclear at this time, however, if a predictable progression of molecular events within the OSE gives rise to a well-defined neoplastic precursor that can be used to improve early detection and diagnosis. Changes in a number of genes, including p53, k-Ras, HER2/neu and c-Myc, have been implicated in ovarian carcinoma progression. However, none of these changes appear to occur in a stage-specific manner [6,7]. While global gene profiling approaches have recently identified a number of genes that are differentially expressed in epithelial ovarian cancer these alterations have not yet been be fully characterized with respect to stage, grade or functional importance [8–10]. Thus, to date, the most compelling target gene linked to the development of ovarian cancer continues to be the breast and ovarian cancer susceptibility gene 1 (BRCA1).

The protein products of the BRCA1 gene regulate, at least in part, transcriptional activation, DNA repair, cell-cycle checkpoint control, and chromosomal re-modeling [11]. Such multi-faceted contributions to essential cellular functions imply a truly fundamental role for BRCA1 in normal development but they also confound our understanding of its role in tumorigenesis [12]. This confusion was initially compounded by the finding that complete BRCA1 ablation in transgenic mice blocks embryonic proliferation [13,14]. However, the subsequent generation of a targeted knockout in the mouse mammary epithelium did result in tumor formation, which is direct experimental evidence that BRCA1 can act as a tumor suppressor in a susceptible tissue [15]. While a BRCA1 knockout has not yet been targeted to the OSE there is compelling clinical evidence that the gene is also a tumor suppressor in the ovary. Drawing on parallels with the situation in the breast, this review will focus on the possible means by which a non-mutational suppression of BRCA1 can be achieved in highly prevalent, non-familial, sporadic epithelial ovarian carcinoma.

BRCA1 in familial and sporadic tumors

BRCA1 was originally isolated using positional cloning techniques and inactivating mutations were found in families with a high incidence of breast and ovarian cancer [16]. Specifically, germline alterations in the BRCA1 gene result in a predisposed likelihood of developing early-onset breast and ovarian cancer with a dominant penetrance as high as 85% and 65% respectively [17]. Tumorigenicity only occurs in these familial BRCA1 heterozygotes if there is also a loss of the second wild type BRCA1 allele. The latter observation supports the notion that the original germline BRCA1 mutation acts recessively at the cellular level [18–20]. Although the presence of an inherited mutation in one BRCA1 allele continues to be one of the best-defined overall risk factors for the development of breast or ovarian cancer, these familial mutations, together with familial BRCA2 mutations, occur in less than 10% of all diagnosed cases [21,22]. The great majority of breast and ovarian carcinomas arise sporadically where inherited BRCA1 mutations do not occur. In addition, somatic BRCA1 mutations are virtually undetectable in sporadic breast cancers and they are extremely rare in sporadic ovarian cancers [19,23–26]. Thus, at first glance, it would not be unreasonable to conclude that BRCA1 does not play a significant role in sporadic tumor development. However, mounting evidence suggests that alternative, non-mutational, mechanisms may suppress BRCA1 expression in these tumors [27].

The first group to conclude that BRCA1 may be important in sporadic tumor development observed a significant decrease in BRCA1 mRNA in high grade, invasive breast tumors [28]. The same investigators also demonstrated that a suppression of BRCA1 activity has functional consequences in cultured breast carcinoma cells [28]. Since then, a number of studies have confirmed the association between decreased BRCA1 mRNA and sporadic tumorigenesis in both the breast and the ovary [29–31]. Furthermore, immunohistochemical analyses of BRCA1 expression in sporadic breast and ovarian cancers revealed a significant reduction in BRCA1 protein [32,33]. This suppression of BRCA1 expression appears to be achieved through multiple means. For example, loss of heterozygosity (LOH) at the BRCA1 locus occurs in a significant proportion of sporadic of ovarian tumors [19,34]. Additionally, a comprehensive study by Russell et al. [35] found that 44% of the tumors had BRCA1 allelic loss, yet, strikingly, this event did not account for the loss of BRCA1 protein expression. Finally, 18% of the tumors exhibited a complete loss of BRCA1 protein in the absence of both LOH and allelic loss [35]. Taken together, these data indicate that epigenetic misregulation also contributes to the reduction of BRCA1 expression in sporadic tumors.

Epigenetic regulation of BRCA1
Hypermethylation of the BRCA1 promoter
Promoter hypermethylation is used during normal development to epigenetically downregulate gene expression in a tissue-specific manner. Methylation of the DNA occurs most frequently on the 5' cytosine residues within 5'-CpG-3' di-nucleotides, which often cluster together in CpG islands that can stretch for several kilobases [36]. In actively transcribed genes, CpG islands within regulatory regions are often unmethylated. In contrast, methylation at these sites represses transcription by altering chromatin structure such that the transcriptional machinery does not have proper access to functionally important regions of the promoter [37]. The proximal BRCA1 promoter lies within such a methylation-sensitive island and a developmentally inappropriate hypermethylation of the promoter does occur in some sporadic breast and ovarian tumors [38,39]. This hypermethylation may be functionally significant as it correlates with decreased BRCA1 mRNA [40]. An important question, yet to be answered, is whether such an abnormal promoter hypermethylation is the cause or consequence of an initial transcriptional repression [41]. Regardless, promoter hypermethylation has only been found in tumors where BRCA1 LOH has also occurred [40]. Thus, hypermethylation may serve as an epigenetic 'second hit' that inactivates the remaining wild type BRCA1 allele after LOH has occurred. While inappropriate promoter hypermethylation is very likely a powerful repressor of BRCA1 expression it is important to point out that it only occurs in a small subset of sporadic tumors [42,43].

Transcriptional regulation of BRCA1

The primary proximal BRCA1 promoter, which consists of less than 300 base pairs (bp), lies immediately upstream of the major breast-specific transcription start site located within the gene's first exon [44,45]. The regulation of this promoter is complex and a number of candidate regulatory sites have been identified and partially characterized (Fig 1). One of these elements, the positive regulatory region (PRR) at the 5' end of the promoter is both necessary and sufficient to maximally activate BRCA1 transcription [46]. Of particular interest, one putative regulatory site located within the PRR is a cyclic-AMP response element, which is capable of specifically binding to CREB, the cyclic-AMP response element binding protein [47]. Importantly, this element is a site of frequent hypermethylation in breast and ovarian tumors [48] and experimental methylation of this site decreases BRCA1 promoter activity *in vitro* [49]. Mutation of the CREB-binding con-sensus sequence within the context of an intact BRCA1 promoter [49] also causes a significant reduction in promoter activation in non-tumorigenic human OSE cells in culture [50]. Taken together, these findings indicate that the cAMP-response element is very likely an important positive regulator of BRCA1 expression in both the normal OSE and in tumor tissue. As an initial transcriptional repression is capable of contributing to the later hypermethylation of sensitive sites [41] misregulation of the transcriptional complex that binds to the cAMP-response element in the BRCA1 promoter could contribute to sporadic ovarian carcinoma development. Therefore, a careful examination of the signal transduction pathways that influence the activity and/or binding of transcriptional complexes to the cAMP-response element in the BRCA1 promoter may identify potentially important oncogenic events in sporadic ovarian carcinoma development.
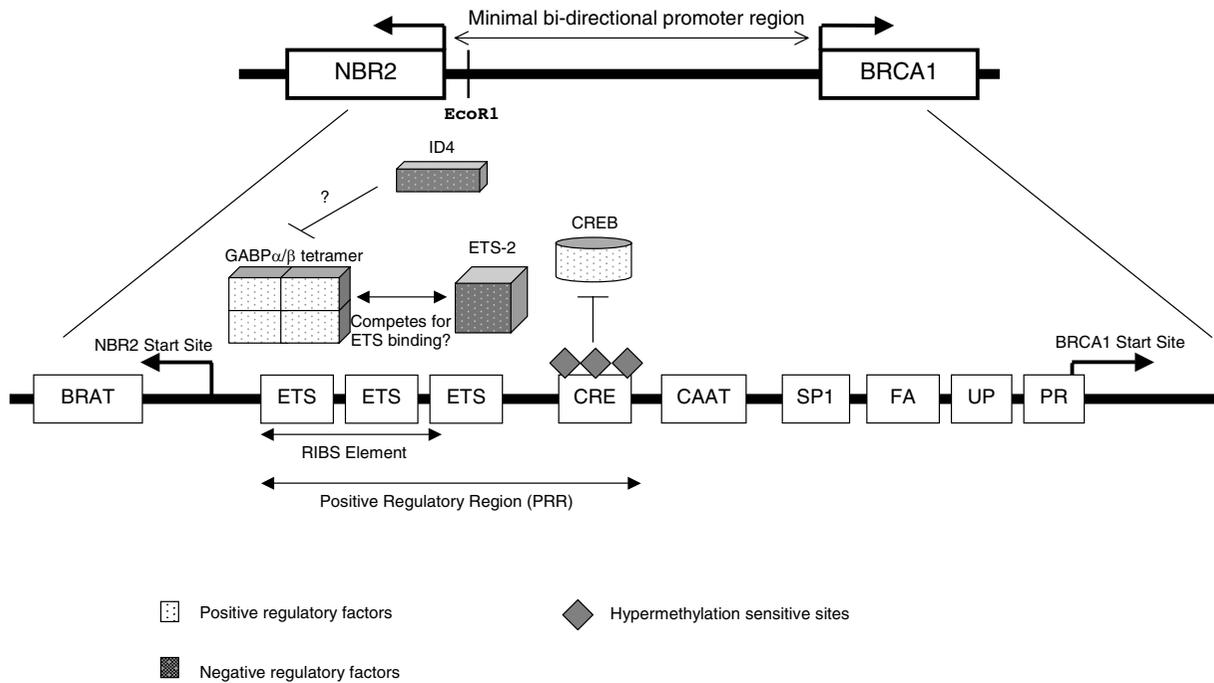

Figure 1
Schematic of the proximal BRCA1 promoter and the 8 functional sites that have been well characterized in breast cells. The RIBS and CREB sites have recently been partially characterized in ovarian surface epithelial and in ovarian carcinoma cells (see text for details).

It is conceivable that a number of the other transcriptional regulators of the BRCA1 promoter may also play a role in sporadic ovarian and breast carcinogenesis [27]. One such example is the GA-binding protein α/β (GABPα/β) which is a member of the ETS family of transcription factors [51]. GABPα/β specifically binds to three consecutive ETS factor-binding domains (described as the RIBS element) located immediately upstream of the CRE element in the positive response region (Fig 1) [52]. Transient overexpression of GABPα/β in breast carcinoma cells is able to stimulate BRCA1 promoter transactivation, thus demonstrating that it is potentially a direct positive regulator of BRCA1 expression [52]. Thus, loss of GABPα/β or lost responsiveness to GABPα/β-containing transcription factor complexes could result in decreased BRCA1 expression in sporadic tumors. Indeed, the promoter binding ability and transcriptional induction by GABPα/β is significantly reduced in mammary carcinoma cells. Comparatively, in the ovary the GABPα/β-binding RIBS element is highly active in normal OSE cells but not in ovarian carcinoma cells [50]. This intriguing observation suggests that the RIBS element, and perhaps aberrant function of the factors responsible for its regulation, may be specifically important in the repression of BRCA1 in sporadic ovarian tumors.

Other DNA-binding proteins that may act on the RIBS element in the BRCA1 promoter are ID4 and ETS-2. ID4 is a recognized repressor of BRCA1 expression in both breast and ovarian carcinoma cell lines [53] that negatively regulates transcription by forming heterodimers with transcription factors through their helix-loop-helix domain [54]. ETS-2 is a member of the ETS family of transcription factors related to GABPα/β that also directly binds to the BRCA1 promoter in the RIBS domain [55]. Unlike GABPα/β, ETS-2 overexpression represses BRCA1 transcription which raises the possibility that multiple ETS factors may compete for binding within the RIBS domain such that upstream signaling pathways which differentially modulate the activation of these transcriptional complexes may be the critical regulators of BRCA1 expression.

Conclusion

Transcriptional suppression of the BRCA1 promoter occurs in sporadic ovarian carcinoma. Clearly, hypermethylation of the promoter plays an important role in this process. In addition, alterations in the transcription factor complexes that bind to the promoter also have a role to play, either upstream of hypermethylation or independent of it. Therefore, the future identification of critical regulators of these complexes will point the way to functionally important signaling pathways that are co-opted during sporadic ovarian tumor formation and progression.

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