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Review Article

Hereditary Breast and Ovarian Cancer Syndrome (BRCA) Gene: Concept, Pathways, Therapeutics, and Future

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Abstract

Hereditary breast and ovarian cancers are most commonly caused by mutations in BRCA1 and 2 genes. These are autosomal dominant mutations with high penetrance into subsequent generations. Affected individuals have deficiency in DNA repair mechanisms such as double strand DNA breaks (DSB) and non-homologous end joining (NHEJ). These tumors are peculiar due to early age of onset, typical histology such as triple negative breast cancers and high grade serous ovarian cancers and exquisite sensitivity to platinum analogues. These patients usually have better survival as compared to their wild type counterparts. Incidence of these mutations is rising due to better awareness about them amongst oncologists and patient population. Various genomic assays are available to detect germline and somatic BRCA mutations. Newer therapeutic frontiers like PARP inhibition have opened up due to better understanding of various mutations and their impact on subsequent pathways. Further studies are required to explore possibility of direct BRCA inhibition which may be useful in treatment of other solid organ cancers as well. This review focuses on understanding the pathophysiology of BRCA mutations, various pathways associated with the same, chemosensitivity patterns amongst affected cancer cells, targeted therapeutic opportunities and potential future developments in this field. We collected data from various published electronic records on google and have no conflicts of interest to be declared.

Keywords: *BRCA syndrome, BRCA protein inhibition, chemosensitivity, DNA repair deficiency, PARP inhibitors*

Epidemiology of Hereditary Breast and Ovarian cancer

Breast and ovarian cancers are major cancers affecting females. Majority of them are sporadic. However, 5%–10% of breast cancers[1] and 20% of ovarian cancers[2] may exhibit hereditary lineage. The most common genetic mutations among familial breast and ovarian cancers happen in BRCA1 and 2 genes. Germline mutations within either of them are found in approximately 5% of all breast cancer cases. These mutations are autosomal dominant with high penetrance and variance. The lifetime probability of developing breast cancer in individuals with BRCA1 and 2 mutations is 57%–65% and 45%–49%, respectively. The probability of developing ovarian cancer in these individuals is 39%–40% and 11%–18%, respectively.[3,4] These individuals are also prone to develop cancers of other organs such as prostate, male breast, and pancreas.[5]

A large epidemiological study in germline BRCA-mutated patients (gBRCA1m or gBRCA2m) showed that hormone receptor positivity (ER/PR) was more common in gBRCA2m than gBRCA1m patients (77% and 22%, respectively).[6] Interestingly, ER-positive tumors in gBRCAm patients exhibit different histological features than sporadic tumors. They are more likely to be Luminal B type; have higher grade and higher Oncotype Dx scores. Furthermore, the proportion of ER-positive tumors increases with increasing patient age in BRCA1m carriers but decreases with increasing age in BRCA2m carriers.[6] About 70% of breast cancers among gBRCA1m patients are triple-negative breast cancer (TNBC)[7] and BRCA1 or 2 mutation is thought to be present in nearly 20% of all TNBCs.[8]

The prevalence of somatic BRCA mutations has not been exactly assessed. Few studies have shown 3%–5% of all breast cancer cases[9,10] and nearly 7%–8% of all ovarian cancer cases

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to have somatic BRCA mutations only.[11] Although the prevalence of pure somatic mutations appears to be low, the growing role of PARP inhibitors in breast and ovarian cancers suggests that these patients might be the best possible beneficiaries of assessment for BRCA mutations in both the tissues and blood.[12] Some preliminary work has also suggested that few prostate cancers may have somatic BRCA mutations, and they may benefit by PARP inhibitors.[13]

DNA Damage and Role of BRCA in Check Point Activation and DNA Repair in Mammalian Cells

The cell triggers checkpoints and starts DNA repair process upon exposure to moieties causing DNA damage. If either of these mechanisms fails, it will lead to uncorrected mutations within the genome. This may lead to development of a cancer cell or in extreme scenario, 'self-destructive or suicidal' phenotype. Such cells are also exquisitely sensitive to DNA damaging agents such as ionizing radiation and platin analogs.[14-17]

Protein kinases (PKs) ATM, ATR, Chk1, and Chk2 are involved in the regulation of G2M transition checkpoint. After ionizing radiation, ATM phosphorylates serine residues in C terminal of BRCA1.[18,19] This activates BRCA1 into further cascade. ATM activation also leads to Chk2 activation which phosphorylates, Ser988, in BRCA1.[20] This causes appropriate localization of BRCA1 upon DNA damage. Deficiency of ATM leads to failure of BRCA1 activation which leads to defective DSB repair. Cancers in patients of Ataxia Telangiectasia exhibit quite clinical similarity to BRCA1-deficient patients.

DNA repair in mammalian cells takes place mainly through two processes; homologous recombination (HR) and nonhomologous end joining (NHEJ). NHEJ depends on DNA-dependent PKs which add residues to the broken ends without any direct regard to homology with the sister strand. HR happens through the exchange of information between damaged strand and its normal sister counterpart. While NHEJ is more error prone, HR is more full-proof mechanism of DNA repair and appears to be better conserved among all mammalian and eukaryotic species. BRCA2 appears to be essential for HR only as BRCA2 deficient cells still retain their ability to carry out NHEJ.[14,21,22] Function of BRCA1 in DNA repair is poorly understood. It appears to regulate the activity of the RAD50-MRE11-NBS1complex which may be involved in formation of new single-strand DNA at the site of double-strand breaks (DSBs).[23,24]

Structure and Function of BRCA Protein

BRCA1 and 2 encode two distinct proteins, respectively. These function in cellular pathways involved in DNA repair, especially DSBs.

BRCA1 protein

BRCA1 is a 220 kDa protein composed of 1863 amino acids. It has an N-terminal RING domain useful in various protein–protein interactions.[25] It interacts with BRCA1-associated RING domain protein 1 (BARD1), leading to increased ubiquitin ligase activity. The C-terminus of BRCA1 contains two BRCT (BRCA1 C Terminal) domains, each composed of 95 amino acid sequences.[26] It has four beta-sheets and three alpha-helices.[27,28] The BRCT domain is the site for phosphorylation of various DNA repair proteins. Region of the protein between exon 11 and 13 binds various proteins involved in different cellular pathways, such as retinoblastoma, c-Myc, RAD50, RAD51, and PALB2.[29] The mutations in this region of the protein result in altered three dimensional structure resulting in misfolding or destabilization. This may prevent appropriate localization of the protein as well as faulty dimerization resulting in loss of its function.[28]

BRCA2 protein

BRCA2 is a 385kDA protein is composed of 3418 amino acids. It has N-terminus transactivation domain, a long exon 11 binding specifically to RAD51 and a C-terminus binding DNA.[30] It consists of eight BRC repeats (30–40 amino acid motifs each) encoded by exon 11. It is unique to various mammalian species and appears to perform the essential function of HR for double-stranded DNA breaks.[31,32] BRCA1 and 2 interact with each other through PALB2. The complex associates with RAD51 for HR.[33]

Subcellular dynamics of BRCA proteins

BRCA1 and 2 proteins have similarities in subcellular localization and patterns of expression. Usually, their levels are highest in S phase. They have clusters at subnuclear levels which get redistributed in response to DNA damage. In meiotic cells, both proteins are found to colocalize to the synaptonemal complexes.[34-38]

BRCA2 appears to have high stoichiometry with RAD51 and is demonstrable in yeast two-hybrid system and *in vitro* studies with recombinant protein fragments.[39] It also appears to carry out intracellular transport and control function of RAD51 which is an important enzyme in DNA repair pathway.[40] A similar interaction between BRCA1 protein and RAD 51 is less understood and at best can be of low stoichiometry and indirect involving multiple other proteins yet unknown.[41]

Various BRCA mutations

BRCA mutations are very diverse. Majority have no known functional significance. Certain mutations exhibit strong pathogenicity. We will review a few commonly found pathogenic BRCA mutations.

The classical mutation found in BRCA1 gene in the Ashkenazi Jewish and European population is the 5382insC. Such

individuals are at higher risk of getting ovarian cancer than breast cancer.[42] The most common mutation found in Indian and few Ashkenazi Jewish populations in BRCA1 gene is 185delAG. A peculiar mutation found in Polish community is a missense mutation at the Cys61 (C61G) of BRCA1. This has now been included as a standard test among investigational workup of breast and ovarian cancer patients in Poland.[43,44]

6174delT mutation is classical in BRCA2 gene among the Jewish community.[45] There are many more diverse mutations reported from various parts of the globe.[42] There are also few cases reported having both BRCA1 and 2 mutations in the same individual. These patients develop cancers at a much earlier age and have more severe disease.[46,47]

By and large, mutations causing ovarian cancer tend to be located in the central part of both genes, while mutations related to breast cancer appear to be located at 5' and 3' ends of these genes.[48]

Genetic Changes in Sporadic Tumors with BRCA Dysfunction

Sporadic breast and ovarian cancers may have BRCA1 inactivation due to nongenomic mechanisms like promoter methylation that result in lowering of gene expression. On the contrary, loss of BRCA2 function in sporadic tumors does not occur by promoter hypermethylation. Many of such tumors show amplification of EMSY. This protein is a stabilizer of BRCA2 protein reducing the activity of the later. Hence, it acts like a downregulator of the BRCA2 function in the HR pathway. Amplification of the same causes functional inactivation of BRCA2 protein.[49]

Enhanced Susceptibility of BRCA-Mutated Cells to Platins

Platinum analogues such as cisplatin and carboplatin etc., have shown higher efficacy against breast and ovarian cancer cells lacking BRCA function. This is due to DNA cross-links formed by platins which remain unrepaired in BRCA-mutated cells causing "Synthetic Lethality."[50-52] TNBC cell lines show up to 83% pathologic complete response rates upon treatment with neoadjuvant cisplatin-based chemotherapy. Such high responses have been also associated with BRCA mutations or lack of BRCA expression.[53] TNT trial showed significant OS and PFS benefit due to carboplatin in BRCA-mutated TNBC patients.[54,55] Similar results have been seen in ovarian cancer patients with BRCA mutations. They have shown higher responses to platinum drugs with a better survival (91 vs. 54 months) and longer disease-free interval (49 vs. 19 months) as compared to BRCA wild type cancers.[56,57]

Therapeutic Impact of BRCA Mutations

BRCA mutational status has been shown to have a significant influence on the decision-making in management of these patients and their affected relatives. Breast conservative surgery and radiotherapy data have shown that local recurrence rates in BRCA-mutated and wild-type patients are similar.[58-61] Risk-reducing salpingo-oophorectomy (RRSO) after diagnosis of breast cancer in BRCA-mutated patients has been shown to reduce subsequent breast cancer recurrence and related mortality by 50%–70%. This effect is more pronounced for ER-negative breast cancer than ER-positive patients. RRSO also has shown to reduce risk of ovarian cancer by 90%.[62]

Cells with defective DNA repair pathways rely on mechanisms for single-stranded DNA repair prominently through poly (ADP-ribose) polymerase-1 (PARP-1). So if PARP-1 is also inhibited, cell cannot repair any DNA lesions, and this produces a condition called 'Synthetic Lethality' in which cell undergoes apoptosis due to accumulating DNA lesions.[63] This phenomenon has been therapeutically exploited and such PARP inhibitors have shown significant and sustained reduction in proliferation and survival of BRCA mutated cancer cells and xenografts.[64,65] PARP inhibitors have shown good response rates among BRCA-mutated breast and ovarian cancer patients.[66]

BRCAness and Scoring Systems

With better understanding of BRCA gene functions, its mutations and their impact on DNA repair mechanisms resulting in malignancies with peculiar phenotype; researchers are trying to assess a broader entity of deficiency of HR. Various histopathology based assays are being developed and tested to understand the level of HR deficiency regardless of specific genes responsible for it. This, so-called BRCAness, can be imparted due to epigenetic silencing or germline mutations in various genes involved in HR.[52] Such a deficit can potentially be exploited therapeutically with advent of specific inhibitors of various enzymes involved in DNA repair, such as PARP inhibitors, which would induce 'Synthetic Lethality' in such tumors.[13,67,68]

Most widely studied scoring systems for assessing HR deficiency are; HR defect (HRD) large-scale transition, HRD-loss-of-heterozygosity, and HRD-telomeric allelic imbalance.[69-71] Various studies have shown them to be able to predict response to platinum therapy in metastatic TNBC patients.[72] Studies are underway to predict their utility in the neoadjuvant setting also.[71,73]

A more direct approach to understand the possibility of BRCA1/2 mutations in the tumor (somatic or germ line) depending on six different molecular signatures, called HRDetect, is being evaluated to predict BRCA dysfunction (direct/indirect). Preliminary analysis has shown it to be highly sensitive (up to 99%) to identify functionally BRCA-deficient tumors.[74]

Future Perspectives

With increasing knowledge of BRCA function, its associated pathways and potential therapeutic implications

in these patients; there are many questions which need to be answered about these pathways. There needs to be accurate population-wise assessment of the prevalence of these dysfunctions in various communities. Furthermore, role of germ line or somatic BRCA dysfunction in other malignancies such as prostate cancers and gastrointestinal cancers needs to be probed. Therapeutic exploitation of the concept of synthetic lethality needs to be taken to a next level beyond PARP inhibition. We need to explore the feasibility of BRCA protein inhibition; which if comes true can pave the way to greater utilization of this phenomenon into all solid organ malignancies as an adjunct for platinum-based chemotherapy even in BRCA wild-type cases. More defined interdisciplinary approach toward exploring these mutations involving clinicians, basic scientists, experts from proteomics, etc., needs to be developed in future.

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