perspective

Members of the BRCA1 complexes as new susceptibility genes for breast cancer

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Breast cancer was considered a multifactorial disease resulting from the interplay of molecular, genetic and environmental factors. Germline mutations, including mutations in the tumor suppressor genes *BRCA1* and *BRCA2*, have been identified as a cause of familiar breast cancer.

BRCA1 plays an important role in both DNA damage repair mechanisms, as well as in the cell cycle checkpoint controls that maintain genome stability. BRCA1 acts as a substrate of the ATM/ATR DNA damage response kinases and is required for the homology-directed repair that facilitates the error-free repair of double-strand breaks (DSBs). Moreover, it maintains heterochromatin integrity via H2A ubiquitination (1). BRCA1 interacts with several proteins organizing into complexes. The interaction takes place through a phosphopeptide binding domain (BCRT domain) recognizing a phospho-SPxF motif (S, serine; P, proline; x, varies; F, phenylalanine). The Abraxas (also known as Abra1, CCDC98), Bach1 (also known as Brip1, FancJ) and CTIP (also known asRBBP8) proteins bind directly to the BCRT domain in a phosphorylation dependent manner, forming at least three mutually exclusive complexes.

Abraxas was the last of these three proteins identified. Wang and collaborators in 2007, using phosphopeptide affinity proteomic analysis described Abraxas as a novel protein that binds directly to the BRCT repeats of BRCA1 through a phospho-SPxF motif. Additionally, Abraxas contains a MPN domain that interacts with ubiquitin (Ub), a coiled-coil domain that binds BRCC36 and an ATM/ATR phosphorylation site (T368). Abraxas recruits Rap80 protein to form the third BRCA1 complex. Both Abraxas and Rap80 are essential factors in DNA damage resistance, repair and cell cycle checkpoint. Moreover, at least three additional components form this complex: NBA1 (also known as MERIT40), BRE (also known as BRCC45) and BRCC36 (2-9). Abraxas is the central organizer that mediates the interaction with BRCA1 and bridges the interaction of each member of the complex. Rap80 binds specifically to k63-linked polyUb chains that are mainly implicated in protein-protein interaction, protein function and subcellular localization. Furthermore, the deubiquitinating enzyme BRCC36 has activity specifically toward these chains (7,10). Even though the exact role of this complex is still not clear, it is believed that it may play an important role in the recruitment of BRCA1 to DNA damage sites through the recognition of ubiquitinated proteins (9).

Cells lacking Abraxas or Rap80 show defects in the G2/M control checkpoint, reduction homologous recombination induced by DSBs and sensitivity to the killing effect of ionizing radiation (IR), although less sensitive than BRCA1-depleted cells. These fates suggest that Abraxas and Rap80 mediate only a subset of BRCA1 functions and that additional BRCA1 complexes playing part of the roles of BRCA1 in maintaining genome stability and tumor suppression exist.

BRCA1 appears as the central mediation mechanism that maintains genome stability in response to DNA damage. Mutations in this gene have been described as clinically relevant. These mutations, however, account for no more than 20% of familiar breast cancer cases (11). This suggests that additional germline mutations are still unknown. Among these, the different members of the BRCA1 complexes are promising candidates because of their essential role in the maintenance of the BRCA1 functions.

Many of the BRCA1 mutations take place in the BRCT repeats, the domain of phosphopeptide recognition with

the capability to bind phosphorylated proteins which are essential to the functions of BRCA1. Frequently, these mutations have clinical relevance. The M1775R BRCA1 mutation disrupts the integrity of the BRCT repeat motif and avoids the interaction with Abraxas (9).

In addition to the described BRCA1 mutations, others have been found for members of the complexes. An alteration in the Rap80 UIM domain impairs the DNA damage response function (12). Common genetic variants in MERIT40 have been related to a predisposition for ovarian and hormone negative breast cancer (13,14). Germline mutations that disrupt Bach1 activity or impair the association with BRCA1 have been identified in breast cancer, indicating its role as a tumor suppressor (15). Other mutations relate this gene to ovarian and breast cancer risk (16). Furthermore, mutations of CtIP that generate a truncated form of the protein cause genome instability disorders and are associated with cancer predisposition (17).

The work of Solyom and collaborators (18) presents a novel germline mutation in Abraxas exclusively associated with familial breast cancer which disrupts the DNA damage repair functions of BRCA1. The authors screened 125 northern Finnish breast cancer families for mutations in Abraxas. Only one of the changes found has been identified by computer simulation to result in functional changes in the protein. The c.1082G>A alteration results in Arg361Gln (R361Q) changes on a putative nuclear localization signal (4). This mutation was detected in three of the families studied, but was absent in healthy controls and in the cohort of breast cancer without familiar cancer background. These data suggest that this Abraxas variant specifically correlates with familiar cancer and segregates with disease within families. The R361Q Abraxas mutant reduces the biological function in the DNA damage response in part by decreasing the efficacy of homology-directed DSB repair as a result of the defective G2 checkpoint in response to IR. R361Q maintains the interaction with BRCA1 and other components of the complex as probed by coimnunoprecipitation. Unlike wild-type, however, its location is primarily cytoplasmic and not nuclear. It suggests a deficiency in DNA repair because of an impaired nuclear location. Abraxas emerges as a new cancer susceptibility gene in breast cancer and other malignancy types in a manner similar to that of BRCA1 and BRCA2.

The identification of mutations in the components of the BCRA1 complexes is a promising strategy in the clinical setting. It has been described that PARP inhibitors (19) induce increased cellular apoptosis in patients with BCRA1 or BCRA2 mutations (20). Presumably, these drugs would act optimally on carriers of other mutations in components of the complexes. Complementary studies are necessary to assess the significance of mutations in Abraxas and other members of BRCA1 complexes in breast cancer diagnosis and in their possible use in treatment.

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Footnote

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.3978/j.issn.2218-676X.2013.04.06). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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