The repair gene *BACH1* - a potential oncogene

Katheeja Muhseena N, Sooraj Mathukkada, Shankar Prasad Das, Suparna Laha

Yenepoya Research Centre, Yenepoya (Deemed to be University), Mangalore, Karnataka, India

Abstract

BACH1 encodes for a protein that belongs to RecQ DEAH helicase family and interacts with the BRCT repeats of *BRCA1*. The N-terminus of *BACH1* functions in DNA metabolism as DNA-dependent ATPase and helicase. The C-terminus consists of BRCT domain, which interacts with *BRCA1* and this interaction is one of the major regulator of *BACH1* function. BACH1 plays important roles both in phosphorylated as well as dephosphorylated state and functions in coordination with multiple signaling molecules. The active helicase property of BACH1 is maintained by its dephosphorylated state. Imbalance between these two states enhances the development and progression of the diseased condition. Currently *BACH1* is known as a tumor suppressor gene based on the presence of its clinically relevant mutations in different cancers. Through this review we have justified it to be named as an oncogene. In this review, we have explained the mechanism of how *BACH1* in collaboration with *BRCA1* or independently regulates various pathways like cell cycle progression, DNA replication during both normal and stressed situation, recombination and repair of damaged DNA, chromatin remodeling and epigenetic modifications. Mutation and overexpression of *BACH1* are significantly found in different cancer types. This review enlists the molecular players which interact with *BACH1* to regulate DNA metabolic functions, thereby revealing its potential for cancer therapeutics. We have identified the most mutated functional domain of *BACH1*, the hot spot for tumorigenesis, justifying it as a target molecule in different cancer types for therapeutics. *BACH1* has high potentials of transforming a normal cell into a tumor cell if compromised under certain circumstances. Thus, through this review, we justify *BACH1* as an oncogene along with the existing role of being a tumor suppressant.

Correspondence:Suparna Laha, Molecular Biology Division, Yenepoya Research Centre, Yenepoya University, University Road, Derlakatte, Mangalore 575018, Karnataka, India.
Tel.: +91.824.2203943 - Far: +91.824.2203943.
E-mail: suparnalaha@yenepoya.edu.in

Key words: *BACH1/BRIP1*; genomic stability; tumorigenesis; Chromatin remodeling; Chl1p.

Acknowledgements: the authors would like to acknowledge government of Karnataka for supporting the fellowship for the researcher and Yenepoya (Deemed to be) University to support my laboratory. The authors also acknowledge Yenepoya (Deemed to be) University for providing the laboratory space and infrastructure to carry out my research activities. The authors acknowledge Mr. Sandip Koyla for his helpful guidance on the bioinformatic part to Ms. Katheeja Muhseena in doing the data analysis.

Funding: this work is supported by Minority/fellowship/CR-97/2018-19 from Directorate of Minority, Government of Karnataka to K.M.N. This work has also been supported by the seed grant YU/seed grant/055/2016 from Yenepoya (Deemed to be) University, Mangalore to S.L. and by ICMR grant 5/13/2018/NCD-III.

Contributions: KMN, original draft, investigation and validation of the work; SM, formal analysis and data curation; SPD, resources, visualization, review and editing; SL, original draft, conceptualization, methodology, supervision and project administration.

Conflict of interests: the authors declare no potential conflict of interests.

Received for publication: 19 September 2020.
Revision received: 2 February 2021.
Accepted for publication: 2 March 2021.

Oncology Reviews 2021; 15:519
doi:10.4081/oncol.2021.519

Introduction to BACH1

BACH1/BRIP1 /FANCJ/hCHLR1 (*BRCA1* associated C-terminal helicase 1), which is the homolog of yeast Chl1p helicase, is a phosphoprotein located on chromosome 17q22.[1-3] It consists of 1249 amino acid residues with the protein size of 130 KDa, the gene length of 180kb and contains 20 exons (Figure 1).[1,4,5] BACH1 helicase is present in both active and inactive forms depending on the phosphorylation status at the K52 position of the protein. The dephosphorylated BACH1 leads to the activation of helicase, which is involved in the timely progression of S-phase, repair of DNA cross-links and secondary structures formed during replication and replication induced stress.[6,7] Thus phosphorylated-dephosphorylated state of *BACH1* plays a major role in cell cycle regulation through activation of various pathways in *BRCA1* dependent and independent manner.[4] During replication stress, it acts with DNA topoisomerase-2-binding protein TOPBP1 to load replication protein A (RPA) onto the chromatin. Presence of RPA is required for activation and control of replication checkpoints and to undergo repair by homologous recombination.[8,9] In the case of management of DNA damage responses like interstrand crosslinks (ICLs), the helicase activity of BACH1 and its interaction with the mismatch repair protein MLH1 provides ICL resistance.[10]

BACH1 also acts as a tumor suppressor in different cancer types.[7,11] It maintains chromosomal integrity and prevents genomic instability by resolving the G-quadruplexes and processing replication intermediates.[12-14] It has the ability to recognize G-quadruplexes mostly those formed upon replication and mediates their stepwise unfolding and refolding to modulate epigenetic pro-

gramming and chromatin remodeling also.[12-15] *BACH1* maintains as well as preserves the chromatin structure and its epigenetic information hence facilitating the smooth progression of the replication fork when it encounters altered/ damaged/ complex DNA structures (Figure 2).[11,12,14] As it is involved in regulating many vital pathways, any aberration to it can cause multifactorial diseases like cancer. *BACH1/BRIP1* plays a role in hereditary breast and ovarian cancer suppression as well as instrumental in progressive bone marrow failure disorder, Fanconi anemia (FA).[17] Germline mutations in the *BACH1/FANCJ* gene leads to chromosomal instability which results in bone marrow failure defects, developmental abnormalities and sets up favorable conditions to develop cancer.[18] Clinical data analysis of *BRIP1* mutations by Seal *et al.* indicates that majority of the *BRIP1* missense mutants/variants are not linked with a risk of familial breast cancer, whereas the truncated variant of *BACH1* are more susceptible alleles of breast cancer running in the family.[19] The biological explanations for the differences in cancer risk for mutant variant and truncated variant are unclear. Moreover, the group identified that, biallelic *BRIP1* mutations confers less risk of breast cancer compared to the monoallelic truncated version.[19] Mutations in *BACH1* also lead to liver carcinogenesis, among patients with viral cirrhosis, due to impaired DNA mismatch repair pathway.[20] In summary to the above lines, the mutated version of *BACH1* gene leads to the development of oncogenicity (Figure 1).

BACH1 functionally and physically interact with a bunch of proteins, like BRCA1, MUTLα, MLH1, PMS2, MMS19, TOPBP1, TLS polymerase, BLM, RPA1, MRE11 and FANCD2 and plays a significant role in regulating the metabolic pathways in combination with them.[10,21,22] The BACH1 interactors play major and minor roles in maintenance of genomic integrity, cell cycle regulation, DNA damage detection and repair processes.[11] The interactors MUTLα, MLH1, PMS2 and RPA1 play important role in mismatch repair.[21,23,24] The *BACH1* homolog, *BRIP1* interacts with the mismatch repair heterodimer complex, MUTLα, which is composed of mismatch repair proteins MLH1 and PMS2. It also interacts with MLH1 directly independent of BRCA1. The interaction with the single-stranded DNA-binding protein RPA (Replication Protein A) through its helicase domain enhances the DNA unwinding activities at the difficult sites of replication.[25] The other interactors MMS19 and TOPBP1 maintains genomic integrity with *FANCD2* in Fanconi anemia DNA damage repair pathway.[24] The interaction of DNA helicase BACH1 with BLM, another helicase, coordinated with DNA damage signaling protein molecules, structure-specific nucleases, polymerases, RPA, and RAD51 imparts a delicate balance between homologous recombination (HR) and non-homologous end-joining (NHEJ) to repair double strand breaks (DSBs) and maintain genomic stability.[26]

The most important event is the physical interaction of BACH1 with BRCA1 which justifies the possible role of *BACH1* in cancer development.[7,11] This interaction is dependent on the phosphorylation-dephosphorylation function of BACH1, as the interaction increases in presence of phosphatase inhibitors, whereas in the presence of λ phosphatase the interaction is lost,[27] which proves that the phosphorylated form of BACH1 interacts with BRCA1. BRCA1 is localized to the site of DNA double strand break by forming a complex with different interacting molecules like RAP80, CTIP and FANCJ. The BRCA1-RAP80 complex comes through Abraxas ubiquitinase and follows the non-homologous end-joining at the DSBs. The parallel pathway of homologous recombination repair is followed by the BRCA1–FANCJ-CTIP complex. This complex is also regulated by heterochromatin binding protein 1 (HP1) pathway in response to DNA damage for its accumulation at the site of DNA double strand break which mediates DNA repair. FANCJ interacts with HP1 in a BARD1 dependent manner and mediates homologous recombination.[28] The association of BRCA1 with BACH1 adds on to the functioning of the G2/M checkpoint.[29] The BRCA/BACH1 complex prevents DNA breakage resulting in lowering of genomic instability.[30] BACH1 status affect the recruitment of BRCA1 to double strand breaks depending on the type of damage.[31] Presence of change in amino acid sequence in the BRCA1 binding domain of the protein

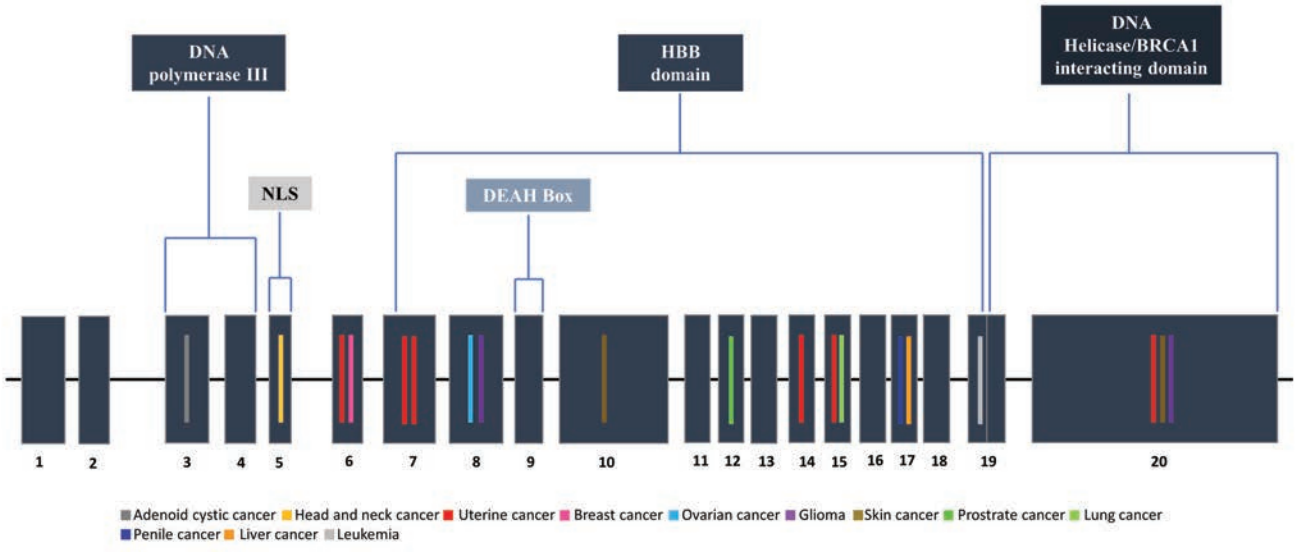

Figure 1. Schematic representation of *BACH1* gene with conserved domains and reported pathogenic mutations in different cancer types. The *BACH1* gene comprises of 20 exons of which exon 3&4 belongs to DNA polymerase domain (18-61aa residue), exon 5 nuclear localization signal (NLS; 158-175aa), exon7-19 HBB domain (245-881aa), exon9 DEAH box (393-396aa) and exon 19 &20 DNA helicase/*BRCA1* interacting domain (888-1063aa) respectively. The large boxes represent exons and small colored thick lines represent verified pathogenic mutations in the respective exons in different cancers (data analyzed from cBioPortal.org).

BACH1, in case of tumorigenesis, proves that recognition of BRCT phosphoprotein by BACH1 is necessary for tumor suppression activity of BRCA1.[32]

BACH1 in cell cycle regulation and replication

The most fascinating characteristic of *BACH1* is observed during its regulation of the cell cycle through its helicase activity.[33] Though the expression of BACH1 protein remains the same throughout the cell cycle, its association with the chromatin increases in S-phase only.[6] The helicase activity of BACH1 is regulated by its phosphorylated-dephosphorylated state. The sequence of steps explaining the functioning of BACH1 in the cell cycle is represented in Figure 3. At G1-phase, BACH1 is phosphorylated leading to the interaction with BRCA complex with low ATPase/helicase activity. As a result, the movement of the replication complex slows down enhancing the proof reading of the polymerase. Adversely, during the slowdown of the fork, the nascent leading and lagging strands tend to anneal to each other due to fork regression or reversal to form secondary structures.[34] The complex of BACH1/BRCA along with the combination of BLM1, a helicase with opposite polarity, resolves these difficult structural motifs encountered by the replication forks during DNA replication. Once the proofreading and resolving activity of the secondary structures are over, the de-phosphorylation of BACH1 takes place. On dephosphorylation, the BACH1/BRCA complex breaks down, leaving behind BACH1 at the fork generating the space for the replication machinery to start replication. Simultaneously dephosphorylated BACH1 regains the helicase activity to unwind the DNA for timely progression through S-phase. The helicase and translocase activities of BACH1 are also modulated by protein-protein interactions.[1] Replication protein A (RPA), comes with BACH1 to facilitate the removal of the DNA bound protein obstacles like the replication complex and increases the ability of BACH1 to unwind the secondary structures.[35,36] So BACH1 plays a major role in regulating the kinetics of replication in S-phase (Figure 3).[6] *BACH1* also have a role during replication stress when there is a damage to DNA or forks are blocked by blocking molecules. It resolves the blocked forks so that they can progress into S-phase and complete

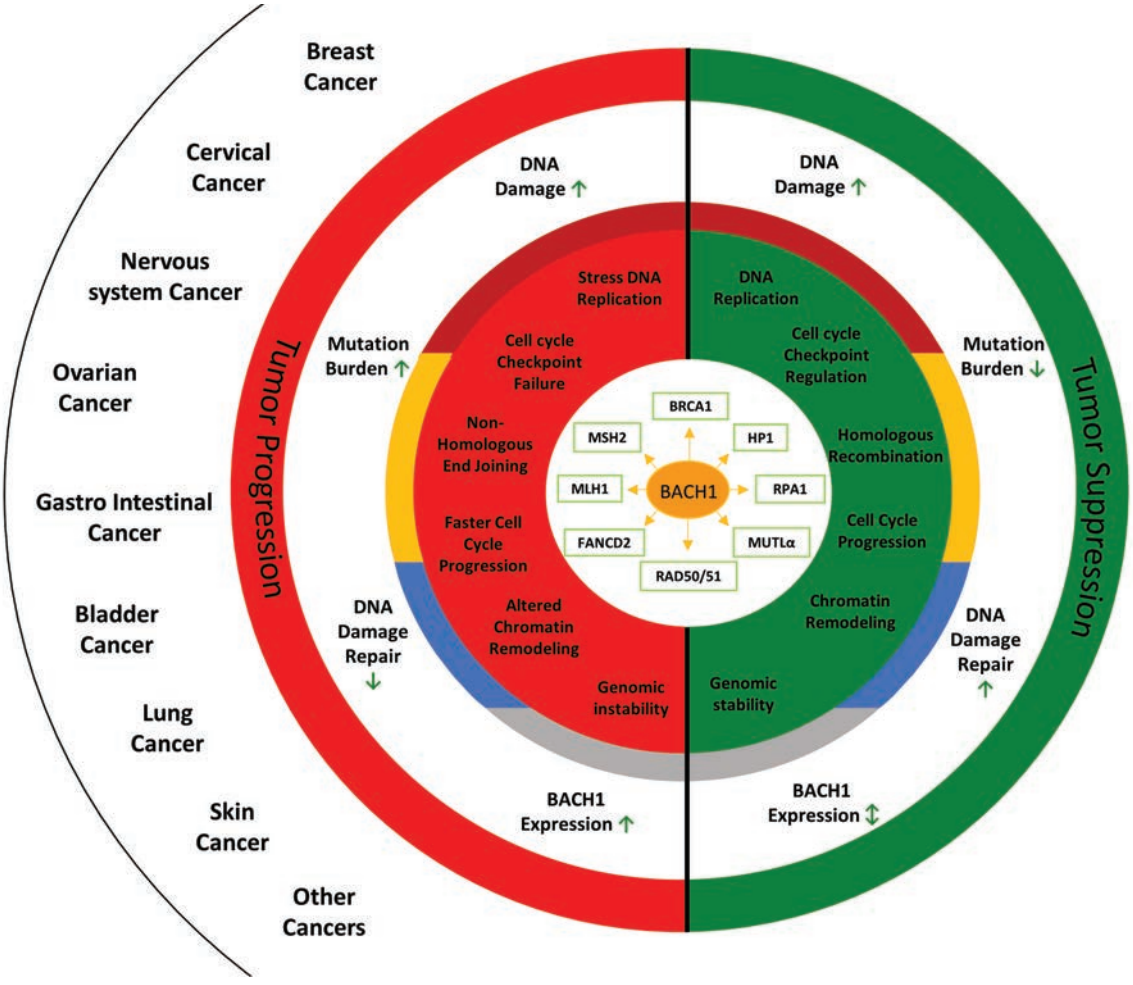

Figure 2. BACH1- a multifaceted protein. The schematic representation depicts the multi-functional role of BACH1. The inner circle (white) shows BACH1 and its interacting partners. The first ring represents various functions of BACH1 (half green ring) and altered function of aberrant BACH1 (half red ring). The second ring (multicolor) represents the group of functions and its correlation with different pathways where red represents DNA damage, blue represents mutation burden, yellow represents DNA damage repair and grey represents BACH1 expression. The third ring (white) represents the various pathways and its alterations, arrow represents ↑ increase, ↓ decrease and ↕ stable functional effects. The outermost colored ring represents the collective outcome of normal and aberrant BACH1 function in cancer formation. Left outermost arc represent various cancers with significant BACH1 aberrations.

the duplication of the genome within a defined period of time.[37] BACH1 alone is unable to unwind partial duplex DNA structures formed due to double-strand breaks, when the strands are bound by DNA double-strand break interacting proteins or blocking molecules.[8,38] Similarly, as happens during replication, the presence of RPA, stimulates BACH1/FANCJ for the displacement of the DNA interacting proteins resulting in unwinding of complex structures.[39] RPA also stimulates BLM1 to efficiently dislodge protein bound to duplex DNA to alleviate replication stress imposed by stalling of the replication forks.[8,36,40] So, during the formation of the secondary structures, these helicases, BACH1 and BLM1, displace proteins bound near double-stranded ends and resolve secondary structure or damaged DNA to enable error-free and kinetically efficient end-joining leading to the restoration of DNA replication.[25]

In conclusion, genomic integrity is maintained by the helicase and the phosphorylation property of BACH1. During diseased state with perturbed BRCA-BACH interaction due to dephosphorylation of BACH1, genomic instability develops by increased helicase activity and faster progression through S-phase. Accelerated S-phase leads to error-prone resolving of the secondary structures at the forks leading to genomic instability. BACH1 interacts with BRCA1, through the BRCT domain and contributes to the DNA repair function of BRCA1.[41] Loss in interaction also happens due to mutation in the interacting domains of the genes and so brings in less repair and helicase molecules at the damaged sites. As a result, the secondary structures form during the replication fail to resolve, resulting in more breaks and more damage to the DNA strands. High burden of damage leads to the activation of alternate repair pathways other than homologous recombination repair which results in accumulation of mutations followed by the development of cancer.[42,43]

BACH1 in DNA repair

The repair function of BACH1 along with its helicase activity maintains the genomic integrity. Unlike dephosphorylation of BACH1 for the helicase activity, the repair property is regulated through its acetylation. This acetylation of BACH1 dependent on the BRCA1-BACH1 interaction.[44] The BRCA1-BACH1 interaction ensures to suppress the mutation prone end-joining and promote double-strand DNA repair via the activation of homologous recombination.[1,45,46] Phosphorylated BACH1, interacts with BRCA1 and activates the G2/M checkpoint, results in stalled replication forks, which may signal for delayed entry into S phase which is shown in Figure 3.[6,27,29] On the other hand, delay in the S-phase leads to increased secondary structures and breaks resulting to activation of the DNA damage checkpoint.[6,47,48] This fine balance of BRCA1 interaction with phospho-BACH1 promotes a damage-free S-phase progression by activating the G2/M and damage checkpoints and ensuring error free HR repair mechanism.[44,45]

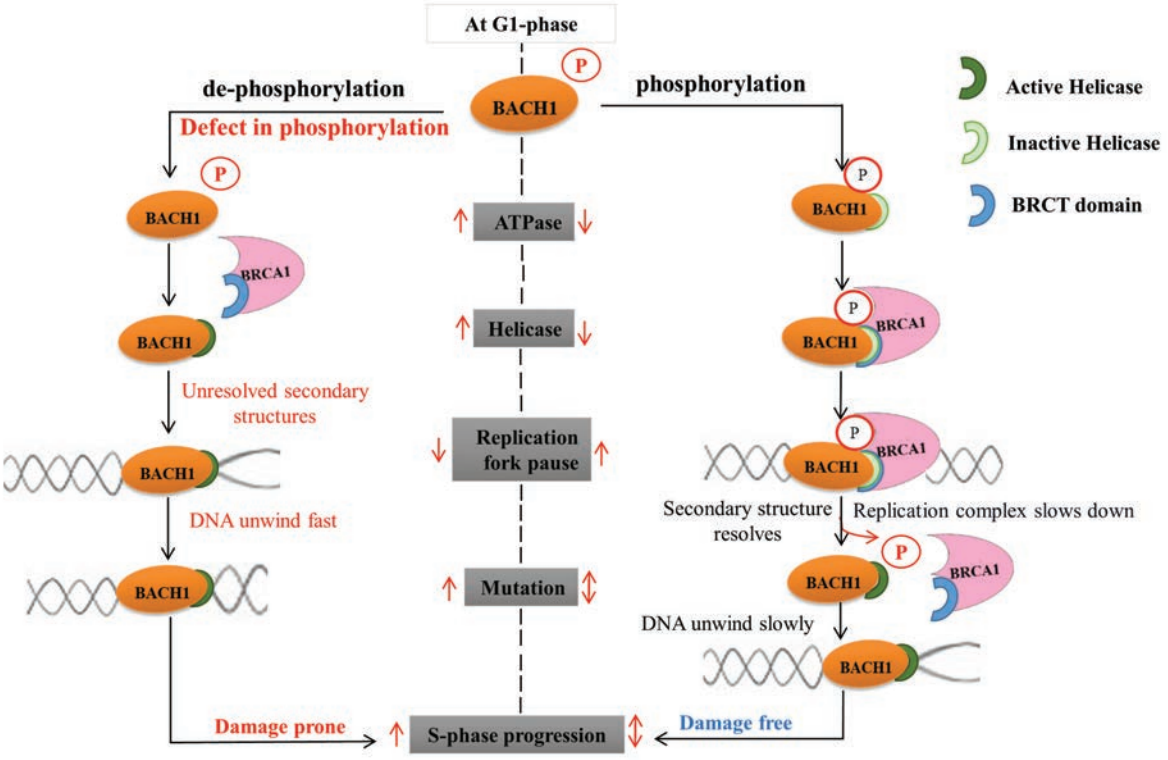

Figure 3. Mechanism of action of *BACH1* through its dual states. At G1-phase of the cell cycle, phosphorylated *BACH1* interacts with BRCA - complex to form the BRCA-BACH complex. This complex have low ATPase/helicase activity which results in slowdown in the S-phase progression enhancing the proof reading of the polymerase. The complex of BACH1/BRCA supports in resolving difficult structural motifs (right side of the figure). With de-phosphorylation or defect in phosphorylation, the BACH1/BRCA complex breaks down, leaving behind only BACH1 at the fork generating the space for the replication machinery to start replication. Dephosphorylated BACH1 regains the helicase activity to unwind the DNA for timely progression through S-phase (left side). Active helicase represented in dark green color, Inactive helicase-light green color and BRCT domain- blue color respectively. Arrow represents ↑ increase; ↓ decrease and ↕ stable functional effects.

Both BRCA1 and BACH1 are recruited to the site of damage depending on the type of damage.[9,11,31] Recruitment of BRCA1 to laser-induced DSBs or Psoralen (Pso) Interstrand Crosslink (ICLs) is dependent on BACH1 whereas the recruitment is independent when the damage is caused by exposure to IR. Also, the recruitment of BACH1 at the damage sites is dependent on the interactor proteins to the site of damage. For laser-induced DSBs but not Psoralen (Pso)-Interstrand Crosslink (ICLs), DNA double strand break repair proteins, MRE11 and its associated nuclease activity function with or in parallel to BRCA1 for efficient BACH1 recruitment at the sites of damage.[31] In absence of MRE11 exonuclease, loading of another *BRCA1* interactor, CTIP, to DSBs is also delayed. CTIP is another protein associated with BRCA1 and modulates BRCA1s functions in DNA repair and/or cell cycle checkpoint control.[49] BRCA1 deficient cells also leads to less localization of CTIP at damage sites. This indicates that at laser induced damage sites, FANCJ/ BACH1 join hands with CTIP to remove secondary structures and helps CTIP to efficiently repair DNA ends with the help of repair protein MRE11 after interacting with BRCA1.[50,51] At the site of Pso-ICLs, BACH1 is also localized with the help of another mismatch repair (MMR) protein MLH1.[10,33] In case of UV light induced DNA crosslink, both MLH1 and upstream MMR protein MSH2 along with BACH1 is required, hence preventing aberrant DNA damage response.[52] So, BACH1 helps in the repair of damaged DNA through homologous recombination. In any of the situations like, absence of *BACH1*, mutation in the *BACH1* or loss of BACH1-BRCA1 interaction, the repair of damage through HR is perturbed. As a result, the alternate error-prone repair pathways like non-homologous end-joining (NHEJ) gets activated. The error-prone repair leads to mutations, which promotes the development, progression, recurrence and metastasis of cancer.

BACH1 in chromatin remodeling

Chromatin remodeling is another important event, which takes place in and around the replication complex or the double-strand DNA breaks aiding in genomic stability, unperturbed replication and DNA repair.[53,54] The proteins involved in maintaining genomic integrity bind to replication forks and damaged sites through highly organized signaling pathways.[54,55] BACH1 belongs to the group of human XPD-like helicases, which include XPD, RTEL1 and CHLR1, which have a role in chromatin remodeling as well as repair and regulates replication at difficult sites.[56] Structural and biochemical studies have proved that the XPD like helicases have an affinity towards single stranded DNA and forked DNA and plays a vital role in their arrangements.[57-59] BACH1 has direct interaction with BRCA1 through its BRCT domain, and also to the DNA through histone H3. This justifies that these proteins may have a role in the remodeling of chromatin along with repair, that takes place in and around the region of DNA damage.[60] Among the XPD like helicases, BACH1 possesses a G-quadruplex specific recognition site.[13] The G- quadruplexes are proven as epigenetic modulators and chromatin remodelers.[15] The affinity between G4s and BACH1/FANCJ helicase strongly justify the involvement of FANCJ in chromatin remodeling through G4s.[12,13,15] FANCJ mostly recognizes the replication linked transient G4s which plays role in CpG island methylation maintenance as well as de novo CpG methylation control.[15] FANCJ binds to the G4s through G4-binding peptide sequence, *RHAU18* which unwinds the branched DNA structures by repeated rounds of stepwise G4-unfolding and refolding.[13] It specifically binds to the 5' flaps and D-loops facilitating the fork movement through replication barriers and helps in processing of the replication intermediates. This results in suppression of the heterochromatin spreading and proper maintenance of chromatin structure.[13,14] BACH1 also coordinates the functioning of polymerase REV1 and helicases WRN/BLM of opposite polarity near G4 DNA motifs to maintain epigenetic stability.[12] The *BACH1* sequence is significantly homologous to the DEAH helicase *CHLR1*.[1] CHLR1, which belongs to FANCJ helicase family also plays a role in heterochromatin organization.[3,16] This helicase affects epigenetic modification of the genetic content and chromatin organization in the mammalian nucleus. In absence of CHLR1, defects in localization and organization of the chromatin have been observed. Aberrant localization of pericentric heterochromatin accompanied by perturbed centromere clustering happens in absence of CHLR1, the homolog of BACH1.[16] Pericentric heterochromatin is loaded with chromatin binding proteins like heterochromatin-binding protein 1 (HP1) isoforms. Epigenetic modifications like histone methylation at sites H3K9 and H4K20 also takes place at the pericentric heterochromatin.[61,62] *CHLR1* plays a role in the chromatin association of HP1 at the pericentric regions but it does not affect the histone modifications resulting into no alteration in the level of heterochromatin marker H3K9me3. Interestingly at the telomere regions, the association of both HP1 and histone modification is affected with depletion of FANCJ helicase family. Therefore BACH1/FANCJ helicase family certainly do play a role in targeting HP1 to the correct genomic regions.[16] Proper localization and binding of HP1 protein are required for the global organization of heterochromatin and centromere clustering. Its presence at the constitutive heterochromatin forms an obstacle for DNA replication providing a regulation to it.[63,64] Epigenetic modification like methylation is severely impaired at the pericentric/heterochromatin regions in absence of CHLR1, whereas the centromere/kinetochore regions are unaffected with the absence of these FANCJ like helicase. So, BACH1/ChlR1/FANCJ plays a heterochromatin specific role in epigenetic events.[12,16] Heterochromatin organization and accessibility to replication is regulated by BACH1 through HP1.[28] FANCJ helicases might function in facilitating DNA replication at difficult sites, such as cohesion binding sites as well as condensed heterochromatic sites, stalled replication forks with secondary structures or at the DNA double strand breaks, by participating in both cohesion establishment and heterochromatin arrangement.[12-14] The *BACH1* interactor *BRCA1* is capable of functioning as a histone deacetylase.[65] So combination of epigenetic modifications like deacetylation and methylation at the heterochromatin or difficult to replicate regions lead to chromatin remodeling for accessibility of the DNA for repair and replication.[66,67] All these functions of BACH1 lead to the conclusion that *BACH1* has a role in heterochromatin organization during replication, regulation and repair of complex sites.

BACH1 - an important player in cancer biology

The very basic cause of cancer is the mutations in the genetic material. While mutations in tumorigenesis is very well characterized, but very little is known about the development of mutations that initiate tumorigenesis. In very simple terms cancer can develop due to genetic mutations transmitted through generations or it can be defined as a disease of ageing fueled by the accumulation of somatic mutations.[68,69] Mutations can develop by the variations or differential expression of the DNA damage repair molecules. Aberrations in the genetic material can also develop by the compromised proofreading activity of the replication machinery or inability to resolve the secondary structures at the difficult to repli-

cate site. In this era of cancer management, next generation sequence testing (NGS) and multi-gene '*panel*' germline mutation testing in different cancers have identified the increase in mutations.[70,71] There is a rise in the number of mutations that leads to variants of uncertain significance (VUS) and needs further characterization. Characterizing these VUS will help to identify additional genes associated with an increased risk of cancer. These mutations which are till date insignificant are mostly present in the genes which play a role in DNA damage repair or cell cycle regulation pathways. Mutations in genes affecting these type of signaling pathways can significantly affect the molecular pathogenesis of diseases like cancer. The helicase BACH1, which has a significant role in repair through homologous recombination, is instrumental in the molecular pathogenesis of cancer in different tissue types (Figure 2). Analysis from 2 different datasets, cBioPortal and COSMIC, shows a significant number of mutations in *BACH1* which are VUS. These VUS mutations significantly falls in the HBB domain, which has a role in DNA damage repair and BRCA1-BRCT interacting domain, which plays a role in helicase by considering cBioPortal and COSMIC datasets respectively

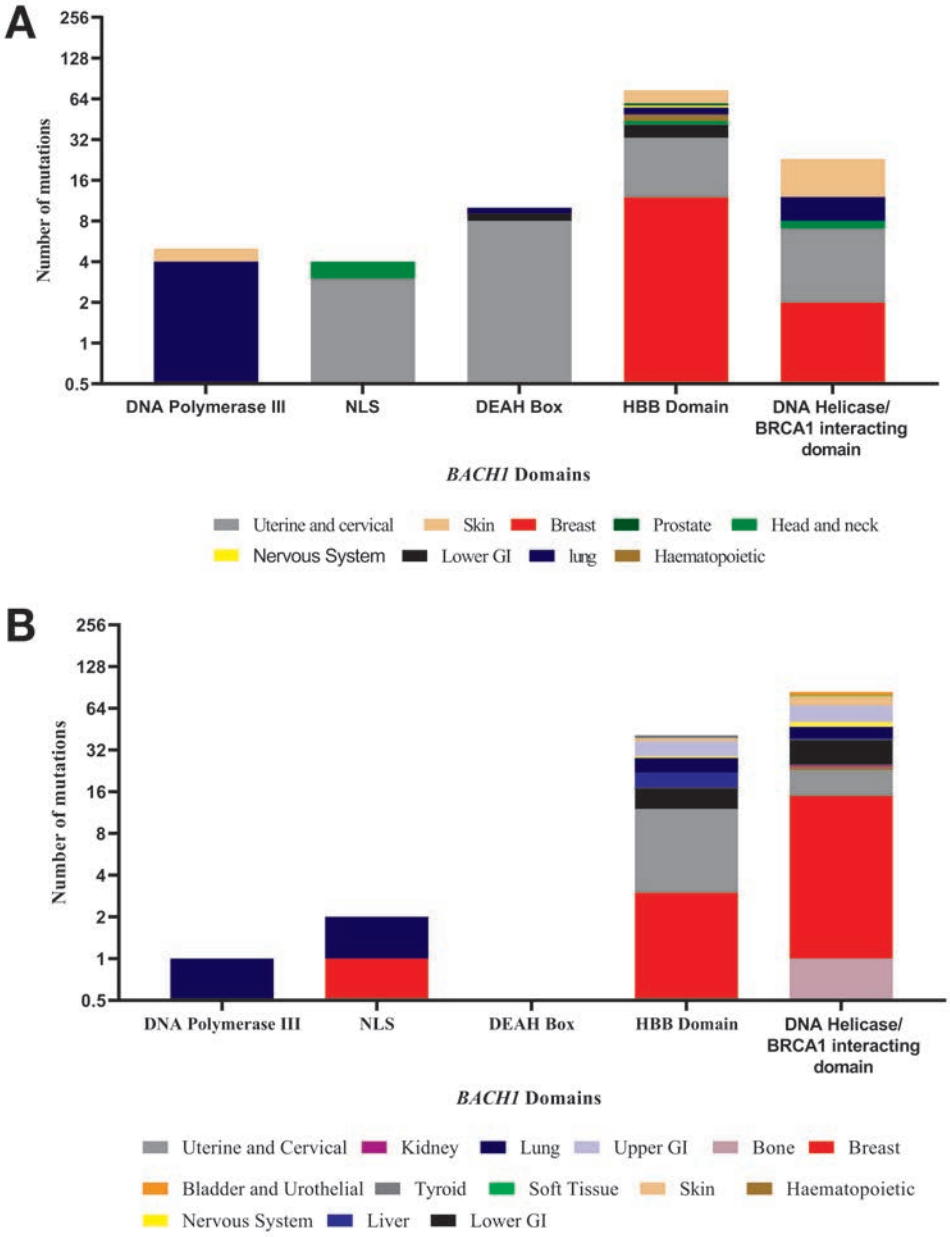

Figure 4. Mutation analysis of BACH1 variants of uncertain significance, predicting it's mutational hot spots. A) SNP's of *BACH1* gene were analyzed from cBioPortal. These mutations are variants of uncertain significance. The mutation position was mapped with the domains of *BACH1* respectively. X-axis represents *BACH1* domains and Y-axis represents number of mutations. Different color code is used to represent cancer types (Number of mutations= 611). B) SNP's of *BACH1* gene were analyzed from COSMIC. These mutations are variants of uncertain significance. The mutation position was mapped with the domains of *BACH1* respectively. X-axis represents *BACH1* domains and Y-axis represents number of mutations. Different color code is used to represent cancer types (Number of mutations= 560).

(Figure 4). This picture of distribution of mutation becomes clear by analyzing the characterized mutation along with the VUS. Furthermore, Analysis of mutations (SNPs) which are characterized and predicted including VUS conclude that the HBB domain of *BACH1* is the most susceptible site of mutation in different cancer types followed by the BRCT interacting domain, which is the *BRCA1* binding site (Figure 5). This conclusion justifies that *BACH1*s repair activity significantly plays an independent role in the tumor biology of different cancer types apart from the *BRCA1* interaction. Mutational analysis reveals that the *BRIP1* locus is strongly associated with hepatocellular carcinoma (HCC) risk in patients with hepatitis B virus (HBV) and/or hepatitis C virus (HCV)-induced liver disease.[20] The variants of *BACH1* which are linked with viral cirrhosis have mutations in the domains which interacts with the DSB repair protein or DNA mismatch repair protein like MRE11 or MUTL α (Figure 2) [20]. Alternately, mutations in the mismatch repair proteins like MLH1 and MSH2, which regulate the localization of BACH1 at the DSBs has been recognized as bladder cancer driver genes.[72] SNPs in the *BRIP1* gene influences cervical cancer susceptibility by regulating the RHOA

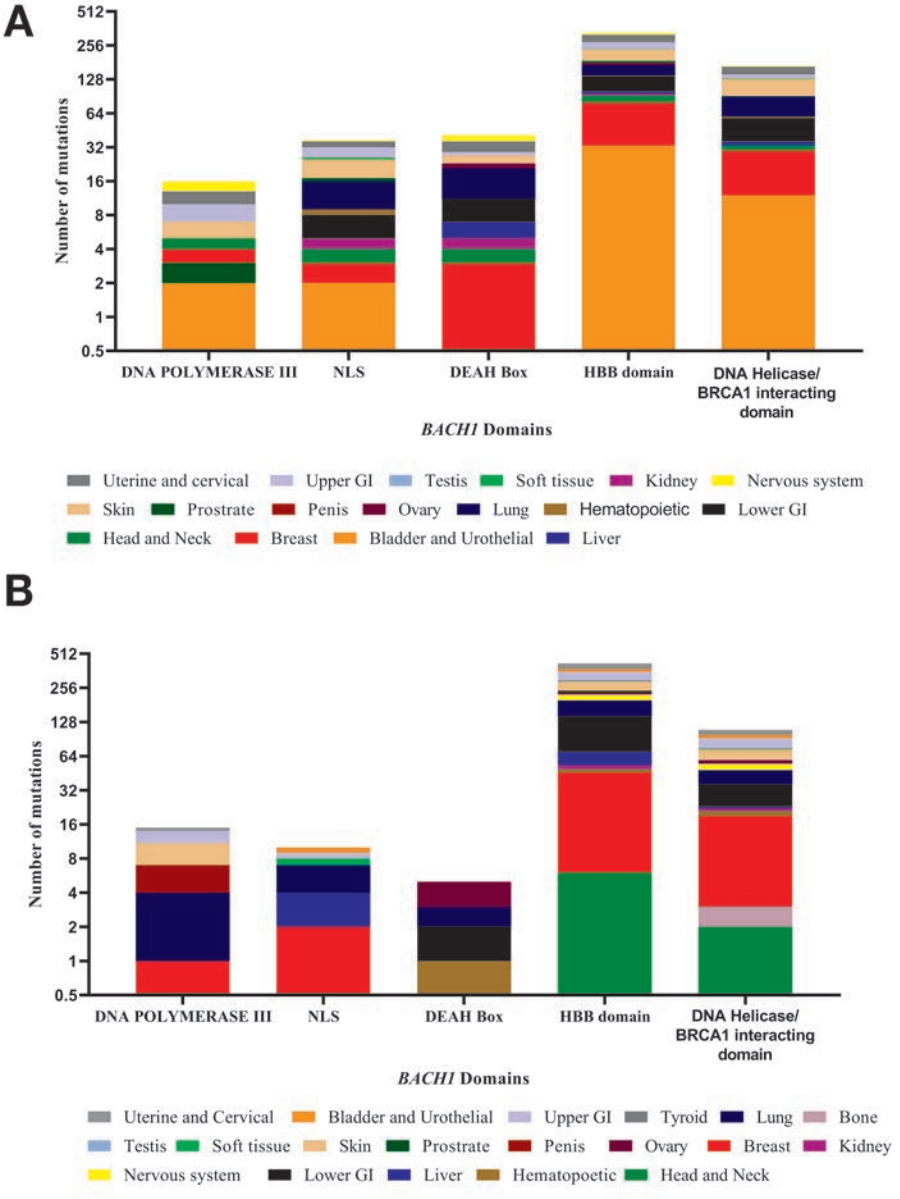

Figure 5. The bar graph represents the domain specific mutation in different cancers. A) SNP's of *BACH1* gene were analyzed from cBioPortal. These mutations are of clinical and non-clinical conditions like pathogenic, non-pathogenic and variants of uncertain significance. The mutation position was mapped with the domains of *BACH1* respectively. X-axis represents *BACH1* domains and Y-axis represents number of mutations. Different color code is used to represent cancer types (Number of mutations= 611). B) SNP's of *BACH1* gene were analyzed from COSMIC. These mutations are of clinical and non-clinical conditions like pathogenic, non-pathogenic and variants of uncertain significance. The mutation position was mapped with the domains of *BACH1* respectively. X-axis represents *BACH1* domains and Y-axis represents number of mutations. Different color code is used to represent cancer types (Number of mutations= 560).

GTPase activity, which is a player in cell proliferation, adhesion, apoptosis, cell polarity, invasion and metastasis (Figure 2).[73] Several somatic mutations are found in *FANCJ* which are associated with skin cancer also. Mutational analysis of the melanoma candidate genes and *BRIP1* gene justifies the role of DNA damage response as an important factor in melanoma etiology (Figure 2).[74] Very recent case studies confirm the role of *BRIP1* in colon cancer also. Germline mutations in *BRIP1* lead to its truncated variants, which have an association with the colon cancer predisposition (Figure 2).[75] A brief analysis of the somatic mutations present in different cancer obtained from different databases shows an increase in BACH1 mutation and its overexpression, confirming its involvement in different cancer type (Figure 6). Many evidences confirm the significant role of *BACH1* in the development and progression of lung cancer and most of the gynecological cancers, which are explained, in the following paragraphs.

BACH1 in breast cancer

BRCA1 gene is well established for its role in breast cancer (BC),[76] but recent scientific developments show that *BRCA1* interactor genes like *BRIP1 (BACH1/FANCJ), ATM, BRCC45, CTIP, MERIT40, NBS1, RAD50* and *TOPBP1* plays an important role as modifiers of breast cancer risk.[77] The meta-analysis study reveals that the *BACH1* polymorphism at the 919-serine position may reduce the danger of breast cancer in the Caucasian populations, mainly in postmenopausal females with a family history of breast cancer and without *BRCA1/2* mutations.[78] Literature shows that *BRCA1* and *TP53* are the major genetic players in case of Triple-Negative Breast Cancer (TNBC). Though there is no significant correlation between BRCA1 and TP53 expression in TNBCs but their expression have a high prognostic significance.[79] BRCA1+/TP53+ patients had better overall survival than BRCA1–/TP53–TNBC patients.[80] Further research would reveal the pathways and the associated players to provide the molecular explanation behind their interactions and role in disease pathology. Low expression of BRCA1 leads to loss of BRCA1 protein interaction resulting in more free BACH1 repair protein. Efficient repair is affected as BRCA1 interactor BACH1 cannot be loaded at the site of DNA damage. Also less damage sensing leads to less efficient homologous repair by BACH1 and the damage is repaired through some other pathways like NHEJ, with compromised proofreading activity developing mutations.[81,82] Accumulation of mutations leads to favorable condition for developing transformed tumor cells which are resistant to chemotherapy-induced apoptosis. This results in the recurrence of breast cancer, which would explain why negative BRCA1 expression is associated with poorer prognosis.[83] In case of TP53, the expression of the gene does not directly correlates with the proper function of the gene. Missense mutation of *TP53* yields a highly stable mutant TP53 protein that can give high TP53 expression, whereas TP53 proteins resulting from truncating *TP53* mutations are unstable and cannot be detected.[84] The prevalence of *TP53* mutation types varies among different breast cancer subgroups. There is a high prevalence of missense mutations in luminal tumors whereas the prevalence of truncated mutations are there in basal tumors.[85] Also truncated mutations are strongly associated with poor survival and these mutations are not easy to be detected. In other words, though the mutations in checkpoints are undetected they can lead to an increase in DNA damage, which will increase the activity of repair genes like *BACH1*. Increased

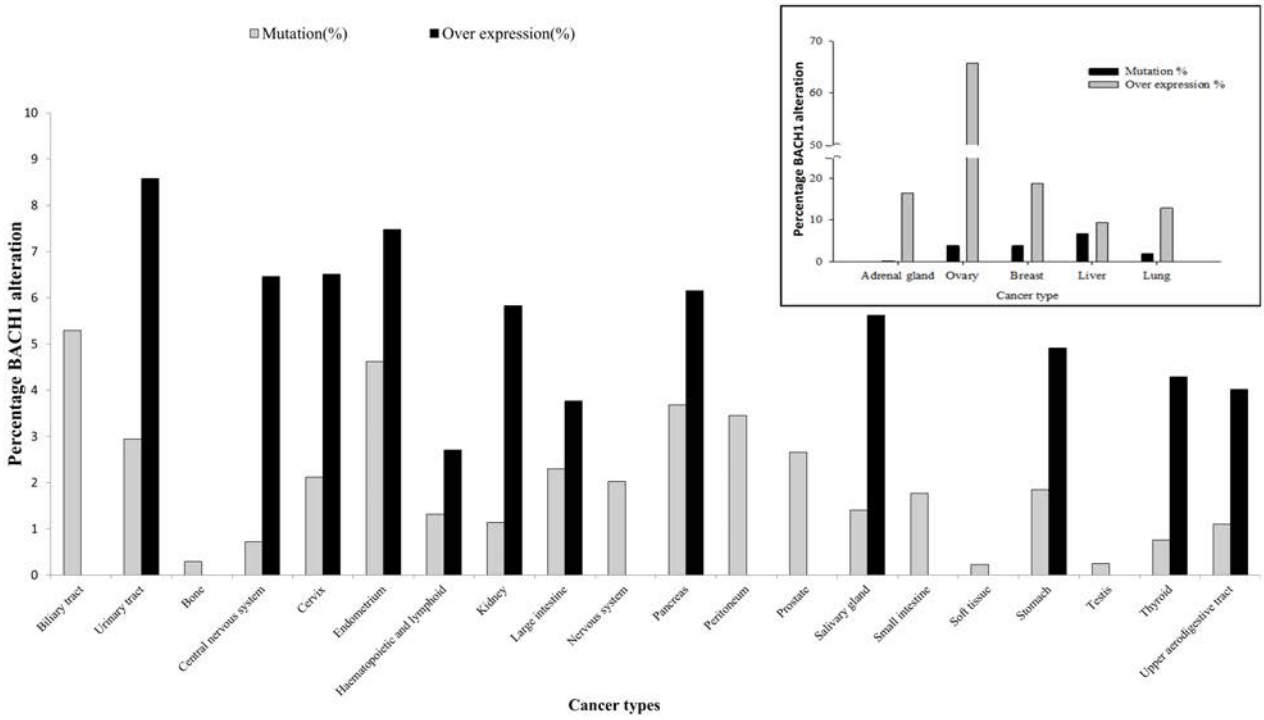

Figure 6. Mutation and overexpression of BACH1 in different cancer types. The schematic bar graph represents the total percentage of samples with mutated *BACH1* and the total percentage of the sample with overexpressed BACH1 in different cancer types. X-axis represents the type of cancer and Y-axis represents the percentage(%) of BACH1 alteration. The data was extracted from COSMIC data base.

BACH1 transcript levels were found in tumors with an estrogen receptor-negative, progesterone receptor-negative or HER-2-positive status. BRIP1/BACH1 overexpression is also detected in primary invasive breast carcinomas.[86] The 2014 COSMIC data on breast cancer and case studies reports overexpression of BACH1 is 18.75% of patient samples and the mutation rate is around 3.8%, confirming the role of *BACH1* in breast cancer biology (Figure 6). The appearance of *BACH1* and its target genes was correlated to an increased risk of breast cancer reappearance in patients.[87] Mutations in exon 20 of *BRCA1* are identified in BC patient which alter the stability of the BRCT domain at the binding site of *BACH1*.[88] The male breast cancer patients are generally identified to be normal for *BRCA1/2* gene but silent mutations are found on *BACH1* tumor suppressor gene and DNA helicase.[89] Susceptibility towards breast cancer also develops in carriers of the C47G polymorphism and Pro-Ser genotype of *BACH1* in premenopausal women.[90] Deletion mutations in *BRIP1* are also identified in early-onset of breast cancer.[91] In conclusion, these data from different research group justifies that *BRIP1/BACH1* is a genuine target gene for breast cancer disease pathology.

BACH1 in ovarian cancer

Cancer in ovary is the leading cause of cancer associated mortality among woman.[92] Reproductive factors such as high parity, use of oral contraceptive, breastfeeding, removal of the uterus and tubal ligation are few ways to protect against ovarian cancer,[93] whereas infertility and endometriosis are the major risk factors.[94] The mechanism for the development of this cancer at the molecular level is not well studied and understood, but inflammation-related oxidative stress has been proposed as a unifying theory by which these risk factors could cause genomic damage leading to the development of tumorigenesis in the ovary.[95] In other words, the efficacy of the DNA damage repair pathway may play a major role in ovarian carcinogenesis.[96] The above statement is supported by the COSMIC data, which shows that in a sample size of 266 patients the percentage of BACH1 overexpression, DNA damage repair gene, is 65.75 and in 1268 patients the percentage of BACH1 mutation is 3.84 (Figure 6). Several evidences link DNA repair with ovarian cancer- most of the ovarian cancer susceptible genes, like *BRCA1* and *BRCA2* have been identified to regulate DNA repair. *TP53* is another susceptible gene, which plays a role in maintaining genomic integrity via several mechanisms including induction of cell cycle arrest in response to DNA damage, DNA repair and regulation of apoptosis.[97] Statistical analysis from a population-based North Carolina Ovarian Cancer Study (NCOCS) support for strong associations between ovarian cancer and polymorphisms in the repair genes. They identified two SNPs in *CHEK2*, two SNPs in *TP53*, and one SNP each in *BACH1* and *LIG4* repair genes. Few weak targets like *NBS1*, *MSH6*, *RAD52*, *XRCC5* and *GADD45B* are also identified by some other group.[98] As *BACH1* is a major player in HR repair pathway, it will be of great diagnostics and prognostic value to find the exact role and the underlying molecular mechanism of *BACH1* in ovarian cancer, which remains unclear. The bioinformatics data indicates that the *BACH1* SNP found in ovarian cancer patients is predicted to affect splicing and also mi-RNA binding site.[99] These findings reflects that *BRCA1-BACH1* interaction plays an important role in the etiology of ovarian cancer.

BACH1 in lung cancer

Lung cancer is the most commonly diagnosed cancer and it is one of the reasons for cancer death worldwide. Approximately 1.6 million case results in deaths per year.[100] The molecular mechanisms which play the role in malignancy are unknown. The important genes which have a role in lung cancer are the cell cycle and the repair genes like *TP53*, *RB*, *BRD7*, *PCNA* and *NFKB1*.[101] *BRIP1* is found to be overexpressed in lung cancer (COSMIC data, 2014, Figure 6). Homozygous deletions are observed in lung adenocarcinoma in the *BRIP1* gene (3%). Also, BRCAness, *i.e.* HR defects in absence of any germline mutation in *BRCA*, is usually seen in non-small cell lung cancer (NSCLC).[102] High transcript level expression of BRCA1 is a helpful tool for choosing NSCLC patients for individualized chemotherapy, as it is the only independent prognostic variable for NSCLC patients.[103] The findings of Zhang group highlights that the integrity of the FA-BRCA pathway is a determinant of sensitivity/resistance to DNA crosslinking agents in lung cancer cells and may represent a mechanism underlying the resistance to chemotherapy of DNA crosslinking agents.[104] Ubiquitous type of mutation having *BRIP1* variants are identified from tumor and blood sample obtained from NSCLC patients.[105] In lung cancer, germline mutations are observed in the *CHK1* gene which is involved in Fanconi anemia and *BRCA1/2* signaling pathways.[106] Methylation in *FANCF* promoter is a significant predictor for poor survival in adenocarcinoma of the lung, so inactivation of *FANC-BRCA* pathways may result in the poorer survival rate of patients with lung cancer.[107] These findings justify the important role played by *FANC/BACH1* in cancer metabolism of lungs.

Concluding remarks and future perspective

Our current understanding indicates that BACH1 nuclear protein differentially participate in complex networks that regulate cell growth, cell cycle, DNA replication, DNA repair, mitotic chromatin dynamics, and also epigenetic modifications at the specific heterochromatin sites. *BACH1* functions in the replication of the difficult sites and during stress, damage and secondary structures, because of its characteristics as a helicase, repair gene and as chromatin remodeler. Cancer mutation data (COSMIC) shows the widespread mutation of this gene in different cancer types. The overexpression of this gene in different cancer types clearly explains the increase in damage in the process of tumorigenesis and the proper repair activity is highly abrogated leading to accumulation of mutations. High mutation burden provides a favorable environment for the development, progression and recurrence of tumor. Further analysis reveals that the HBB domain of *BACH1* is the most affected domain and the hot spot for characterized as well as uncharacterized mutations, explaining its role in cancer biology. Since the HBB domain has no link with BRCA1 interaction, so the effect conferred by this domain in different cancer types is independent of the *BRCA1* function. The BRCA1 binding domain or the DNA helicase comes as the second most affected region of BACH1. The analysis of variants with uncertain significance also shows HBB domain as the most susceptible sites in *BACH1* which justifies the emerging role of DNA repair through *BACH1* in cancer biology. A deep insight into the functional aspect of the HBB domain along with *BRCA1* interaction will open new avenues in the treatment of most of the deep-rooted cancers. Mutations or defect in this gene affects major molecular pathways that regulates and maintains the genomic integrity of the cells. With an aberration

in the genetic integrity tumorigenesis develops. So, *BACH1/BRIP1/FANCJ/ChlR1* gene has high potentials of transforming a normal cell into a tumor cell if compromised under certain circumstances, thus justified to be named as an oncogene. Even-though *BACH1* has a substantial role in cancer biology and has a major role to play in different types of cancer, very few studies have been completed towards understanding the mechanism of how the proteins interact among themselves. In few of the cancers, BACH1 is analyzed as the major interactor protein of BRCA1, so, a detailed analysis of the interaction study is required to identify its role in tumorigenesis and metastasis. Current literature and our ongoing studies indicate that *BRCA1-BACH1* interaction is lost due to diseased condition or a mutation at the interactor domain results in downregulation of DNA proofreading activity leading to more mutations, and hence increasing the risk of tumorigenesis. So, to understand *BACH1*, it is essential to explore this protein, its functional and interacting domains and critically evaluate its involvement to physiology and identify the potential roles in human pathologies, such as cancer.

References

1. Cantor SB, Bell DW, Ganesan S, et al. BACH1, a novel helicase-like protein, interacts directly with BRCA1 and contributes to its DNA repair function. Cell 2001;105:149-60.
2. Hall JM, Lee MK, Newman BM, et al. Linkage of early-onset familial breast cancer to chromosome 17q21. Science 1990;250:1684-9.
3. Hirota Y, Lahti JM. Characterization of the enzymatic activity of hChlR1, a novel human DNA helicase. Nucleic Acids Res 2000;28:917-24.
4. Cantor S, Drapkin R, Zhang F, et al. The BRCA1-associated protein BACH1 is a DNA helicase targeted by clinically relevant inactivating mutations. PNAS 2004;101:2357-62.
5. Levran O, Attwooll C, Henry RT, et al. The BRCA1-interacting helicase BRIP1 is deficient in Fanconi anemia. Nat Genet 2005;37:931-3.
6. Kumaraswamy E, Shiekhattar R. Activation of BRCA1/BRCA2-associated helicase BACH1 is required for timely progression through S phase. Mol Cell Biol 2007;27:6733-41.
7. Brosh Jr RM. DNA helicases involved in DNA repair and their roles in cancer. Nat Rev Cancer 2013;13:542-58.
8. Gong Z, Kim JE, Leung CC, et al. BACH1/FANCJ acts with TopBP1 and participates early in DNA replication checkpoint control. Mol Cell 2010;37:438-46.
9. Peng M, Litman R, Jin Z, et al. BACH1 is a DNA repair protein supporting BRCA1 damage response. Oncogene 2006;25:2245-53.
10. Cantor SB, Xie J. Assessing the link between BACH1/FANCJ and MLH1 in DNA crosslink repair. Environ Mol Mutagen 2010;51:500-7.
11. Brosh Jr RM, Cantor SB. Molecular and cellular functions of the FANCJ DNA helicase defective in cancer and in Fanconi anemia. Front Genet 2014;5:372-14.
12. Sarkies P, Murat P, Phillips LG, et al. FANCJ coordinates two pathways that maintain epigenetic stability at G-quadruplex DNA. Nucleic Acids Res 2012;40:1485-98.
13. Wu CG, Spies M. G-quadruplex recognition and remodeling by the FANCJ helicase. Nucleic Acids Res 2016;44:8742-53.
14. Schwab RA, Nieminuszczy J, Shin-ya K, Niedzwiedz W. FANCJ couples replication past natural fork barriers with maintenance of chromatin structure. J. Cell Biol 2013;201:33-48.
15. Varizhuk A, Isaakova E, Pozmogova G. DNA G−quadruplexes (g4s) modulate epigenetic (Re) programming and chromatin remodeling. BioEssays 2019;41:1900091-101.
16. Inoue A, Hyle J, Lechner MS, Lahti JM. Mammalian ChlR1 has a role in heterochromatin organization. Exp Cell Res 2011;317:2522-35.
17. Wu Y, Brosh Jr RM. FANCJ helicase operates in the Fanconi Anemia DNA repair pathway and the response to replicational stress. Curr Mol Med 2009;9:470-82.
18. Alter BP. Diagnosis, genetics, and management of inherited bone marrow failure syndromes. Am J Hematol 2007;2007:29-39.
19. Seal S, Thompson D, Renwick A, et al. Truncating mutations in the Fanconi anemia J gene BRIP1 are low-penetrance breast cancer susceptibility alleles. Nat Genet 2006;38:1239-41.
20. Oussalah A, Avogbe PH, Guyot E, et al. BRIP1 coding variants are associated with a high risk of hepatocellular carcinoma occurrence in patients with HCV-or HBV-related liver disease. Oncotarget 2017;8:62842-57.
21. Peng M, Litman R, Xie J, et al. The FANCJ/MutLα interaction is required for correction of the cross−link response in FA−J cells. EMBO J 2007;26:3238-49.
22. Williams SA, Wilson JB, Clark AP, et al. Functional and physical interaction between the mismatch repair and FA-BRCA pathways. Hum Mol Genet 2011;20:4395-410.
23. Yeom G, Kim J, Park CJ. Investigation of the core binding regions of human Werner syndrome and Fanconi anemia group J helicases on replication protein A. Sci Rep 2019;9:1-10.
24. Estep KN, Brosh Jr RM. RecQ and Fe-S helicases have unique roles in DNA metabolism dictated by their unwinding directionality, substrate specificity, and protein interactions. Biochem Soc Trans 2018;46:77-95.
25. Awate S, Brosh Jr RM. Interactive roles of DNA helicases and translocases with the single-stranded DNA binding protein RPA in nucleic acid metabolism. Int J Mol Sci 2017;18:1-25.
26. Dhar S, Brosh RM. BLM's balancing act and the involvement of FANCJ in DNA repair. Cell Cycle 2018;17:2207-20.
27. Yu X, Chini CC, He M, et al. The BRCT domain is a phosphoprotein binding domain. Science 2003;302:639-42.
28. Wu W, Togashi Y, Johmura Y, et al. HP1 regulates the localization of FANCJ at sites of DNA double−strand breaks. CANCER Sci 2016;107:1406-15.
29. Yarden RI, Pardo-Reoyo S, Sgagias M, et al. BRCA1 regulates the G2/M checkpoint by activating Chk1 kinase upon DNA damage. Nat Genet 2002;30:285-9.
30. Greenberg RA, Sobhian B, Pathania S, et al. Multifactorial contributions to an acute DNA damage response by BRCA1/BARD1-containing complexes. Genes Dev 2006;20:34-46.
31. Suhasini AN, Sommers JA, Muniandy PA, et al. Fanconi anemia group J helicase and MRE11 nuclease interact to facilitate the DNA damage response. Mol Cell Biol 2013;33:2212-27.
32. Shakya R, Reid LJ, Reczek CR, et al. BRCA1 tumor suppression depends on BRCT phosphoprotein binding, but not its E3 ligase activity. Science 2011;334:525-8.
33. Zhang X, Guo J, Wei X, et al. Bach1: function, regulation, and involvement in disease. Oxid Med Cell Longev 2018;1-8.
34. Atkinson J, McGlynn P. Replication fork reversal and the maintenance of genome stability. Nucleic Acids Res 2009;37:3475-92.
35. Wu Y, Shin-ya K, Brosh RM. FANCJ helicase defective in

Fanconia anemia and breast cancer unwinds G-quadruplex DNA to defend genomic stability. Mol Cell Biol 2008;28:4116-28.
36. Wu W, Rokutanda N, Takeuchi J, et al. HERC2 facilitates BLM and WRN helicase complex interaction with RPA to suppress G-quadruplex DNA. Cancer Res 2018;78:6371-85.
37. Cantor SB, Nayak S. FANCJ at the FORK. Mutat Res 2016;788:7-11.
38. Gupta R, Sharma S, Sommers JA, et al. Analysis of the DNA substrate specificity of the human BACH1 helicase associated with breast cancer. J Biol Chem 2005;280:25450-60.
39. Gupta R, Sharma S, Sommers JA, et al. FANCJ (BACH1) helicase forms DNA damage inducible foci with replication protein A and interacts physically and functionally with the single-stranded DNA-binding protein. Blood 2007;110:2390-8.
40. Sommers JA, Banerjee T, Hinds T, et al. Novel function of the Fanconi anemia group J or RECQ1 helicase to disrupt protein-DNA complexes in a replication protein A-stimulated manner. J Biol Chem 2014;289:19928-41.
41. Schwartz MF, Duong JK, Sun Z, et al. Rad9 phosphorylation sites couple Rad53 to the Saccharomyces cerevisiae DNA damage checkpoint. Mol Cell 2002;9:1055-65.
42. Xie J, Litman R, Wang S, Peng M, et al. Targeting the FANCJ-BRCA1 interaction promotes a switch from recombination to polη-dependent bypass. Oncogene 2010;29:2499-508.
43. Davis AJ, Chen DJ. DNA double strand break repair via non-homologous end-joining. Transl. Cancer Res. 2013;2:130-43.
44. Xie J, Peng M, Guillemette S, et al. FANCJ/BACH1 acetylation at lysine 1249 regulates the DNA damage response. PLoS Genet 2012;8:1-14.
45. Savage KI, Harkin DP. BRCA1, a 'complex'protein involved in the maintenance of genomic stability. The FEBS J 2015;282:630-46.
46. Dohrn L, Salles D, Siehler SY, et al. BRCA1-mediated repression of mutagenic end-joining of DNA double-strand breaks requires complex formation with BACH1. Biochem J 2012;441:919-28.
47. Wang X, Lui VC, Poon RT, et al. DNA damage mediated S and G2 checkpoints in human embryonal carcinoma cells. Stem Cells 2009;27:568-76.
48. Willis N, Rhind N. Regulation of DNA replication by the S-phase DNA damage checkpoint. Cell Division 2009;4:1-10.
49. Yu X, Baer R. Nuclear localization and cell cycle-specific expression of CtIP, a protein that associates with the BRCA1 tumor suppressor. J Biol Chem 2000;275:18541-9.
50. Anand R, Ranjha L, Cannavo E, Cejka P. Phosphorylated CtIP functions as a co-factor of the MRE11-RAD50-NBS1 endonuclease in DNA end resection. Mol Cell 2016;64:940-50.
51. Wang H, Li Y, Truong LN, et al. CtIP maintains stability at common fragile sites and inverted repeats by end resection-independent endonuclease activity. Mol Cell 2014;54:1012-21.
52. Peng M, Xie J, Ucher A, et al. Crosstalk between BRCA−Fanconi anemia and mismatch repair pathways prevents MSH2−dependent aberrant DNA damage responses. The EMBO J 2014;33:1698-712.
53. House N, Koch MR, Freudenreich CH. Chromatin modifications and DNA repair: beyond double-strand breaks. Front Genet 2014;5:1-18.
54. Lai W, Li H, Liu S, Tao Y. Connecting chromatin modifying factors to DNA damage response. Int J Mol Sci 2013;14:2355-69.
55. Osley MA, Shen X. Altering nucleosomes during DNA double-strand break repair in yeast. Trends Genet 2006;22:671-7.
56. White MF. Structure, function and evolution of the XPD family of iron-sulfur-containing 5'–>3' DNA helicases. Biochem Soc Trans 2009;37:547-51.
57. Wolski SC, Kuper J, Hanzelmann P, et al. Crystal structure of the FeS cluster-containing nucleotide excision repair helicase XPD. PLoS Biol 2008;6:e149.
58. Fan L, Fuss JO, Cheng QJ, et al. XPD helicase structures and activities: insights into the cancer and aging phenotypes from XPD mutations. Cell 2008;133:789-800.
59. Liu H, Rudolf J, Johnson KA, et al. Structure of the DNA repair helicase XPD. Cell 2008;133:801-12.
60. Wu W, Nishikawa H, Fukuda T, et al. Interaction of BARD1 and HP1 is required for BRCA1 retention at sites of DNA damage. Cancer Res 2015;75:1311-21.
61. Magaraki A, van der Heijden G, Sleddens-Linkels E, et al. Silencing markers are retained on pericentric heterochromatin during murine primordial germ cell development. Epigenetics Chromatin 2017;10:1-20.
62. Muramatsu D, Singh PB, Kimura H, et al. Pericentric heterochromatin generated by HP1 protein interaction-defective histone methyltransferase Suv39h1. J Biol Chem 2013;288:25285-96.
63. Yi Q, Chen Q, Liang C, et al. HP 1 links centromeric heterochromatin to centromere cohesion in mammals. EMBO reports 2018;19:1-13.
64. Saksouk N, Simboeck E, Déjardin J. Constitutive heterochromatin formation and transcription in mammals. Epigenetics Chromatin 2015;8:1-7.
65. Yarden RI, Brody LC. BRCA1 interacts with components of the histone deacetylase complex. PNAS 1999;96:4983-8.
66. Groth A, Rocha W, Verreault A, Almouzni G. Chromatin challenges during DNA replication and repair. Cell 2007;128:721-33.
67. Liu J, Kim J, Oberdoerffer P. Metabolic modulation of chromatin: implications for DNA repair and genomic integrity. Front Genet 2013;4:1-11.
68. Kennedy SR, Zhang Y, Risques RA. Cancer-associated mutations but no cancer: insights into the early steps of carcinogenesis and implications for early cancer detection. Trends Cancer 2019;5:531-40.
69. Risques RA, Kennedy SR. Aging and the rise of somatic cancer-associated mutations in normal tissues. PLoS Genet 2018;14:1-12.
70. Tate JG, Bamford S, Jubb HC, et al. COSMIC: the catalogue of somatic mutations in cancer. Nucleic Acids Res 2019;47:1-7.
71. Gao J, Aksoy BA, Dogrusoz U, et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal 2013;6:1-19.
72. Abbosh PH, Plimack ER. Molecular and clinical insights into the role and significance of mutated dna repair genes in bladder cancer. Bladder Cancer 2018;4:9-18.
73. Zou W, Ma X, Hua W, et al. BRIP1 inhibits the tumorigenic properties of cervical cancer by regulating RhoA GTPase activity. Oncol Lett 2015;11:551-8.
74. Guillemette S, Branagan A, Peng M, et al. FANCJ localization by mismatch repair is vital to maintain genomic integrity after UV irradiation. Cancer Res 2014;74:932-44.
75. Ali M, Delozier CD, Chaudhary U. BRIP-1 germline mutation and its role in colon cancer: presentation of two case reports and review of literature. BMC Med Genet 2019;20:1-5.
76. Karami F, Mehdipour P. A comprehensive focus on global

spectrum of BRCA1 and BRCA2 mutations in breast cancer. Biomed Res Int 2013;1-21.
77. Rebbeck TR, Mitra N, Domchek SM, et al. Modification of BRCA1-associated breast and ovarian cancer risk by BRCA1-interacting genes. Cancer Res 2011;71:5792-805.
78. Shi J, Tong J, Cai S, et al. Correlation of the BACH1 Pro919Ser polymorphism with breast cancer risk: A literature based meta analysis and meta regression analysis. Exp Ther Med 2013;6:435-44.
79. Yadav BS, Chanana P, Jhamb S. Biomarkers in triple negative breast cancer: a review. World J Clin Oncol 2015;6:252-63.
80. Kim MC, Choi JE, Lee SJ, Bae YK. Coexistent loss of the expressions of BRCA1 and p53 predicts poor prognosis in triple-negative breast cancer. Ann Surg Oncol 2016;23:3524-30.
81. Saha J, Davis AJ. Unsolved mystery: the role of BRCA1 in DNA end-joining. J Radiat Res 2016;57:i18-i24.
82. Jackson SP. Sensing and repairing DNA double-strand breaks. Carcinogenesis 2002;23:687-96.
83. Thangaraju M, Kaufmann SH, Couch FJ. BRCA1 facilitates stress-induced apoptosis in breast and ovarian cancer cell lines. J Biol Chem 2000;275:33487-96.
84. Biganzoli E, Coradini D, Ambrogi F, et al. P53 status identifies two subgroups of triple-negative breast cancers with distinct biological features. Jpn J Clin Oncol 2011;41:172-9.
85. Dumay A, Feugeas JP, Wittmer E, et al. Distinct tumor protein p53 mutants in breast cancer subgroups. Int J Cancer 2013;132:1227-31.
86. Eelen G, Bempt IV, Verlinden L, et al. Expression of the BRCA1-interacting protein Brip1/BACH1/FANCJ is driven by E2F and correlates with human breast cancer malignancy. Oncogene 2008;27:4233-41.
87. Gupta I, Ouhtit A, Al-Ajmi A, et al. BRIP1 overexpression is correlated with clinical features and survival outcome of luminal breast cancer subtypes. Endocr Connect 2018;7:65-77.
88. Chakraborty A, Katarkar A, Chaudhuri K, Mukhopadhyay A. Detection of a novel mutation in exon 20 of the BRCA1 gene. Cell Mol Biol Lett 2013;18:631-8.
89. Venkateshwari A, Clark DW, Nallari P, et al. BRIP1/FANCJ mutation analysis in a family with history of male and female breast Cancer in India. J Breast Cancer 2017;20:104-7.
90. Pabalan N, Jarjanazi H, Ozcelik H. Association between BRIP1 (BACH1) polymorphisms and breast cancer risk: a meta-analysis. Breast Cancer Res 2013;137:553-8.
91. De Nicolo A, Tancredi M, Lombardi G, et al. A novel breast cancer–associated BRIP1 (FANCJ/BACH1) germ-line mutation impairs protein stability and function. Clin Cancer Res 2008;14:4672-80.
92. Momenimovahed Z, Tiznobaik A, Taheri S, Salehiniya H. Ovarian cancer in the world: epidemiology and risk factors. Int J Womens Health 2019;11:287-99.
93. Moorman PG, Calingaert B, Palmieri RT, et al. Hormonal risk factors for ovarian cancer in premenopausal and postmenopausal women. Am J Epidemiol 2008;167:1059-69.
94. Ness RB, Cramer DW, Goodman MT, et al. Infertility, fertility drugs, and ovarian cancer: a pooled analysis of case-control studies. Am J Epidemiol 2002;155:217-24.
95. Su KM, Wang PH, Yu MH, et al. The recent progress and therapy in endometriosis-associated ovarian cancer. J Chin Med Assoc 2020;83:227-32.
96. Gee ME, Faraahi Z, McCormick A, Edmondson RJ. DNA damage repair in ovarian cancer: unlocking the heterogeneity. J Ovarian Res 2018;11:1-12.
97. Chen CC, Feng W, Lim PX, et al. Homology-directed repair and the role of BRCA1, BRCA2, and related proteins in genome integrity and cancer. Annu Rev Cancer Biol 2018;2:313-36.
98. Schildkraut JM, Iversen ES, Wilson MA, et al. Association between DNA damage response and repair genes and risk of invasive serous ovarian cancer. PLoS One 2010;5:1-9.
99. Song H, Ramus SJ, Kjaer SK, et al. Tagging single nucleotide polymorphisms in the BRIP1 gene and susceptibility to breast and ovarian cancer. PLoS One 2007;2:1-7.
100. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87-108.
101. Gao Y, Wang B, Gao S. BRD7 acts as a tumor suppressor gene in lung adenocarcinoma. PLoS One 2016;11:1-9.
102. Waqar SN, Devarakonda SH, Michel LS, et al. BRCAness in non-small cell lung cancer (NSCLC). J Clin Oncol 2014;32:11033-.
103. Bartolucci R, Wei J, Sanchez JJ, et al. XPG mRNA expression levels modulate prognosis in resected non-small-cell lung cancer in conjunction with BRCA1 and ERCC1 expression. Clin Lung Cancer 2009;10:47-52.
104. Zhang J, Wang X, Lin CJ, et al. Altered expression of FANCL confers mitomycin C sensitivity in Calu-6 lung cancer cells. Cancer Biol Ther 2006;5:1632-6.
105. Jamal-Hanjani M, Wilson GA, Horswell S, et al. Detection of ubiquitous and heterogeneous mutations in cell-free DNA from patients with early-stage non-small-cell lung cancer. Ann Oncol 2016;27:862-7.
106. Haruki N, Saito H, Tatematsu Y, et al. Histological type-selective, tumor-predominant expression of a novel CHK1 isoform and infrequent in vivo somatic CHK2 mutation in small cell lung cancer. Cancer Res 2000;60:4689-92.
107. Marsit CJ, Liu M, Nelson HH, et al. Inactivation of the Fanconi anemia/BRCA pathway in lung and oral cancers: implications for treatment and survival. Oncogene 2004;23:1000-4.