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Roles of SWI/SNF Complex Genes in Breast Cancer

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1. Introduction

Cancer is a multifactorial genetic disease which is characterized by uncontrolled proliferation of the cells. Cells undergo mutational changes in a multistep process. Cancer developes from a tumor clone though the firstly mutated cell doesn't present all the features of a cancer cell. Accumulation of the mutations lead cells to display the properties of the cancer. The proliferating cells which have the capacity to survive and invade result in hyperplasia followed by dysplasia and invasion and metastasis at the end [1].

Breast cancer is the most common cancer type and one of the leading cause of cancer mortality in women. Various factors including estrogens and its signaling, EGFR signaling pathway, other oncogenes and tumor suppressor genes including chromatin remodeling factors contribute to development of breast cancer.

At molecular level two major group of genes are responsible for cancer development. These genes, proto- oncogenes and tumor suppressor genes (TSG) control cell growth together in cells at a balance. They are normally required for cell survival and have a direct role in carcinogenesis and cancer progression. When the balance is broken between oncogenes and TSGs due to activation of proto-oncogene or inactivation tumor suppressor genes, cancer develops (**Figure 1, 2**).

In cellular functions proto-oncogenes serve as growth factors, growth factor receptors, transcription factors and signal transduction elements. The mutated proto-oncogenes are named as oncogenes. An oncogene, when mutated or altered, contributes to conversion of a normal cell into a cancer cell. The activation of a proto-oncogene may occur during replication; by a translocation; by gene amplification or by the alterations in mRNA expression. TSGs are also normal cellular genes taking part in regulation of the cell cycle,

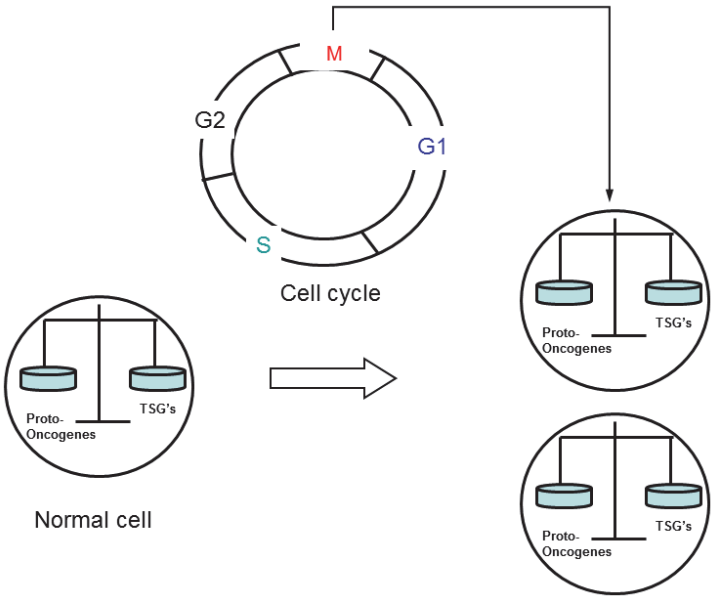

Fig. 1. In human cells proto-oncogenes and tumor suppressor genes are at a balance. There exists a controlled cell division and proliferation.

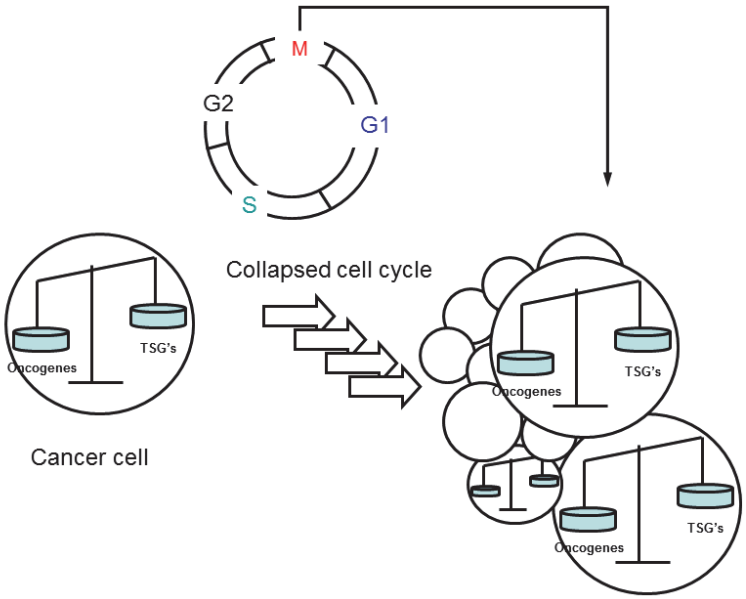

Fig. 2. In a cancer cell, over expression of oncogenes (activation) or low expression of TSGs (inactivation) leads cells to uncontrolled proliferation.

apoptosis, differentiation, surveillance of genomic integrity and repair of DNA errors, chromatin remodeling, signal transduction, and cell adhesion. The activation of the oncogenes and the inactivation of tumor suppressor genes lead cells to proliferate in an uncontrolled manner. Usually one mutation is sufficient for the activation mechanism of oncogenes whereas two hits are necessary for the inactivation of tumor suppressor genes [2,3]. However, a new class of tumor suppressor gene, in which one of the alleles is lost while the rest allele is kept, has recently been defined. Such a tumor suppressor gene is called as haploinsufficient and supposed to be in a cancer-prone state [4-6]. These patients develop cancer when they are exposed to the various carcinogens such as smoking, x-ray and chemicals.

In eukaryotic cells, genetic information encoded by DNA is packaged into chromatin and kept in the nucleus. Thus chromatin is composed of DNA and proteins. The primary proteins of chromatin are histones. A nucleosome, basic unit of chromatin, consists of 146 base-pairs of duplex DNA wrapped around a histone octamer composed of two of each of the conventional histone proteins: H2A, H2B, H3 and H4. Another histon, H1, provides compaction of neighboring nucleosomes by linking them. These compact situation of chromatin reversibly changes in an open and closed situation by various molecules such as histon acetyl transferases (HAT), histon deacetyl transferases (HDAC) and chromatin remodeling molecules, which then influence on transcriptional regulation of gene expression through accesibility of transcription factors by these molecules.

Transcription is an important step to control gene expression from the very early step of life to the end. To maintain transcription every human cell has to deal with the step of an access to DNA either through histone acetylases or chromating remodelling complexes. Many activator proteins of transcription use both of these mechanisms. Histone Acetyl Transferases (HATs) add acetyl groups to the tails of the histones that protrude out of nucleosomes which lead to the binding of the transcription factors. Chromatin remodeling complexes use ATP to open or close the chromatin (**Figure 3**).

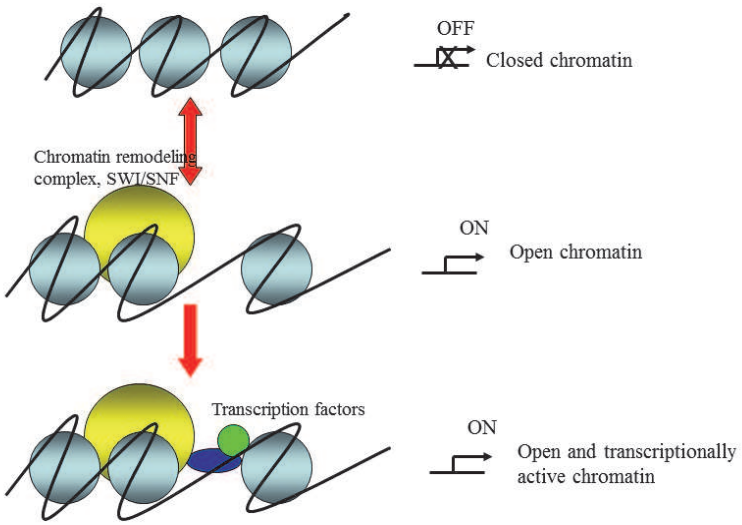

Fig. 3. The binding of chromatin remodeling complex changes conformationally closed chromatin to open chromatin that enables the transcription factors to bind and start transcription.

By cooperation of members of these two classes of complexes, the structure of chromatin is dynamically regulated and thus they play important roles in the control of gene expression. ATP-dependent chromatin remodelers are divided into families according to the subunit composition and biochemical activity such as SWI/SNF, ISWI, INO80, SWR1 and NURD/Mi2/CHD complexes. Of these in particular, some of the members SWI/SNF complexes are emerging tumor suppressors, as genetic and epigenetic inactivation events in several SWI/SNF subunits have been detected in various human cancers [7-10].

2. Function of SWI/SNF family members

Transcription factor action and then the targeted gene expression are mainly regulated by SWI/SNF family of chromatin remodeling complexes. SWI/SNF complexes are large 2-MDa (1.14 MDa in yeast) multi-subunit conglomerates that are involved in either enhancement or suppression of the downstream genes [7-12]. SWI/SNF complex genes were identified through two screens in yeast Saccharomyces cerevisiae. The first identified gene that is required for the expression of SUC2 for sucrose metabolism (sucrose non-fermenting (SNF) mutants), and the second screen showed another gene required for the activation of HO for mating-type switching (switch (SWI) mutants [7, 13-15].

SWI/SNF complex is composed of three groups of subunits; 1) enzymatic (ATPase), 2) core subunits, and 3) accessory subunits [8,11]. Though the exact mechanisms for modification of chromatin structure by SWI/SNF complexes remain incompletely understood, current knowledge suggests that ATPase-dependent disruption of histone-DNA association and resultant nucleosome "sliding" is the main mechanism [8,12]. The mammalian genome encodes 29 different SWI/SNF-like ATPases [12]. Accordingly, each SWI/SNF complex consists of only one of two ATPases, BRM (Brahma) or BRG1 (Brahma-Related Gene 1), which show 74% homology.

SWI/SNF complexes are classified into two major classes as BAF (BRG1 or BRM-Associated Factor; also known as SWI/SNF-A) or PBAF (Polybromo-Associated BAF; also known as SWI/SNF-B) complexes (**Figure 4**). BAF complexes contain either BRG1 (also known as SMARCA4, SNF2b, BAF190) or BRM (also known as SMARCA2, SNF2a) and PBAF complexes include only BRG1 as ATPase subunit. Each ATPase is accompanied with 10 to 12 proteins as core and accessory subunits. The core subunits include BAF155 (also known as SWI3, SRG3, SMARC1), BAF170 (also known as SMARCC2), and SNF5 (also known as SMARCB1, BAF47, INI1). Accessory subunits consist of BAF45 (a,b,c,d; encoded gene names PHF10, DPF1, DPF2, DPF3), BAF53 (a,b; encoded gene names ACTL6A, ACTL6B), BAF57 (encoded gene name SMARCE1), BAF60 (a,b,c; encoded gene name SMARCD1, SMARCD2, SMARCD3), BAF180 (encoded gene name PBRM1), BAF200 (encoded gene name ARID2), BRD7 and BAF250 (a,b; a: also known as ARID1A, SMARCF1, OSA1; b: also known as ARID1B, OSA2) [7,8]. ARID1A (BAF250a) and ARID1B (BAF250b) subunits are mutually exclusive and exist only in BAF complexes. BAF180, BAF200 and BRD7 are exclusively present in PBAF complexes [7,8] [**Figure 4**].

SWI/SNF complexes were found to be based on their roles in the transcription activation. However, studies show that mammalian SWI/SNF complexes have function to both repression and activation of the targeted genes. For development of mammalian T lymphocyte, BRG1 and BAF57 are necessary both for silencing CD4 and activating CD8 expression [7,16,17]. Specific combinations of individual SWI/SNF components were reported to generate sub-complexes with specialized functions that are involved in

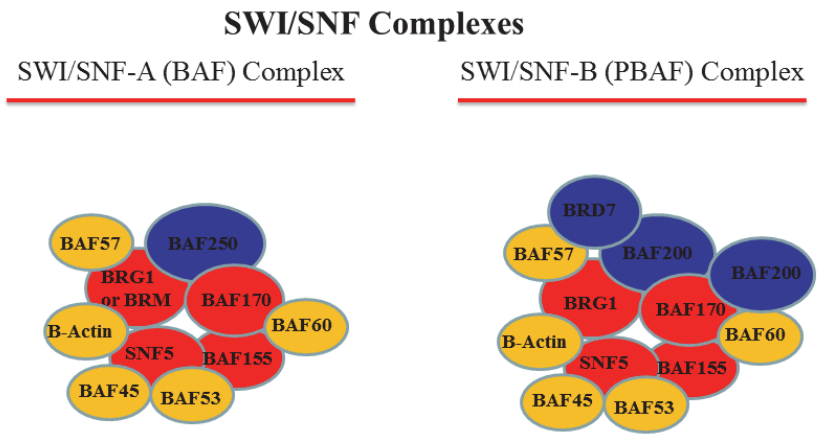

Fig. 4. SWI/SNF complexes are classified into two major classes as BAF (SWI/SNF-A) or PBAF (SWI/SNF-B) complexes. BAF complexes contain either BRG1 or BRM and PBAF complexes include only BRG1 as ATPase subunit. The core subunits include BAF155, BAF170, and SNF5. Accessory subunits consist of BAF45, BAF53, BAF57, BAF60, BAF180, BAF200, BRD7 and BAF250. BAF250a and BAF250b subunits are mutually exclusive and exist only in BAF complexes. BAF180, BAF200 and BRD7 are exclusively present in PBAF complexes.

sequential stages of muscle-gene activation--i.e., initial displacement of the nucleosome followed by the loading of the complete myogenic transcriptosome that promotes gene transcription [18]. Immunoprecipitation analysis of osteocalcin promoter showed that BRM- and BRG1-containing complexes have different roles on it. BRG1 complexes were associated with the promoter induction, while BRM-specific complexes were present only on the repressed promoter and were required for association of the co-repressor HDAC1 [19]. In embryonic stem (ES) cells, BRG1 was reported to act as a repressor to inhibit programmes that are associated with differentiation. On the other hand, it also facilitates the expression of core pluripotency programmes [20,21]. Loss of *Snf5* in murine fibroblasts results in more genes being activated such as E2F targeted genes than repressed [22]. Another example of repression of gene expression is recruitment histone deacetylases (HDACs), which remove activating acetyl marks from histone tails, by SWI/SNF complexes. By this mechanism, SNF5 suppresses cyclin expression in an HDAC1-dependent manner [23]. In conclusion, mammalian SWI/SNF complexes are composed of dynamic units with essential roles in regulating both the activation and the repression of gene expression programmes.

3. Roles of SWI/SNF proteins in cancer

Findings of abnormalities at genetic, epigenetic as well as protein levels of SWI/SNF complexes in various cancers provide a link between chromatin remodelling and tumour suppression. Tumor suppressor role of SWI/SNF complexes was first demonstrated with loss of BRG1 and BRM expression in many cancer cell lines and arrest of growth or slower growth after introduction of BRG1 or hBRM [24]. Brg mutant mice die at early embryonic days due to growth arrest of the inner cell mass and trophoblast [25,26]. Mice with Brg 1

heterozygosity develop mammary adenocarcinomas, suggesting an occurrence of cancer prone state due to haploinsufficiency of Brg1. On the other hand, the mouse with inactivation of BRM by homologous recombination (BRM-/- mice) is born alive and develops normally. Adult mutant mice were approximately 15% heavier than control littermates. This phenomenon was suggested to be caused by increased cell proliferation, because a higher mitotic index was detected in mutant livers and it was further supported by the observation that mutant embryonic fibroblasts were significantly deficient in their ability to arrest in the G0/G1 phase of the cell cycle in response to cell confluency or DNA damage. These studies suggested that BRM plays a role in the regulation of cell proliferation in adult mice and have some defects in control of cellular proliferation [27].

Chromosome transfer studies mapped tumor suppressor gene(s) at 19p13 chromosome locus [28,29]. Studies with microsatellite analysis and functional as well as cancer tissue examination for abnormalities of candidate tumor suppressor gene indicated that chromosome 19p13 locus includes at least two putative tumor suppressor genes namely STK11/LKB1 and BRG1 [30]. STK11 maps about 8.5 Mb distally from BRG1. Loss of heterozygosity of 19p13 was reported in various cancers including thyroid cancer, sex cord stromal tumors, breast cancer, oral carcinoma, prostate cancer, pancreas carcinoma, brain tumors, colorectal carcinoma, gynecological tumors, lung cancers and ovarian carcinoma [31-46]. Some of the studies included genetic analysis of STK11/LKB1 and showed mutation in a subset of tumors especially related with Peutz-Jeugher Syndrome such as breast, colorectal, lung, pancreatic, biliary and ovarian cancer [41-49]. On the other hand, quite a lot of studies reported mutations and/or loss or various alterations of BRG1 in human cancer lines and primary tumors [50-61]. Thus genes at this chromosomal locus may involve in various type cancer exclusively or in cooperation in some cancer types. It should be also noticed that some studies showed only LOH without alteration of either one of these genes. In this situation, each of them can still be involved in carcinogenesis due to haploinsufficiency. At least haploinsufficiency of BRG1 is recognized [25-27,62], while further studies are necessary whether such a role exists for STK11/LKB1 or not. Similar to BRG1, abnormalities of BRM in various cancers have been reported [58-61,63-69].

Though the early studies of cell lines and animal models strongly suggested subunits of SWI/SNF proteins as tumor suppressor, the first definitive evidence that members of these complexes function as tumor suppressive was shown by Versteege and colleagues. They demonstrated occurrence of LOH of BAF47 (SNF5) in almost all cases of pediatric rhabdoid sarcoma, in which the other allele was mutated or silenced by methylation [70]. Inactivation of SNF5 subunit of SWI/SNF is via biallelic mutations, including deletion, nonsense, missense and frameshift mutations was also shown by other studies, supporting SNF5 as a strong tumor suppressor gene at least in this kind of tumors [71-73].

SNF5 alterations have also been shown in other types of tumors though it is much rare as compared to malignant rhabdoid tumors. In a recent study, the effects of Ini1 haploinsufficiency (loss of one allele) on cell growth and immortalization in mouse embryonic fibroblasts were examined. Their results revealed that heterozygosity for Ini1 up-regulated cell growth and immortalization and that exogenous Ini1 down-regulated the growth of primary cells in a Rb-dependent manner. Furthermore, loss of Ini1 was redundant with loss of Rb function in the formation of pituitary tumors in Rb heterozygous mice and gave rise to the formation of large, atypical Rb(+/-) tumor cells lacking adrenocorticotropic hormone expression, confirming in vivo the relationship between Rb and Ini1 in tumor suppression [74]. Mutations and alterations of SNF5 were also reported in familial

schwannomatosis and other cancer types [75-84]. Germ line mutations of SNF5 were detected in brain tumors and rhabdoid tumors, suggesting its link with familial cancers [85-88]. In some other tumors, no alteration of SNF was detected [89,90].

Complete loss of Snf5 in genetically engineered mouse leads to early embryonic death. However, heterozygote mice with haploinsufficient Snf5 (snf5+/-) develop tumors similar to malignant rhabdoid tumors in about one third of the animals [91-93]. On the other hand, conditional biallelic inactivation of Snf5 (Snf5-/- mice) resulted in tumors including lymphomas and rhabdoid tumors in 100% of mice [94]. Onset of these tumors occurred in a median period of 11 weeks for a single gene inactivation. When compared to this period with most commonly mutated genes in human cancer i.e. p53 and RB1, p53 loss gave rise to lymphomas and sarcomas at 20 weeks and RB1 heterozygosity together with p53 deficiency resulted in similar tumors and other cancers at 16 weeks [95]. Thus shorter onset time for tumor occurrence in Snf5 inactivation as compared to other well-known tumor suppressors indicates strong tumor suppressor character of this gene. Tumor formation in the absence of SNF5 has been supposed to be due to loss of function of the SWI/SNF complex. However, this view has been challenged by several findings of a recent research. Using both human cell lines and mouse models, Wang et al. [96] showed that cancer formation in the absence of SNF5 does not result from SWI/SNF inactivation but rather that oncogenesis is dependent on continued presence of BRG1 activation than tumor suppressor loss. Thus Snf5 loss would lead to effects more frequently associated with oncogene activation than tumor suppressor loss.

Other than BRG1 and SNF5, alterations of other member of SWI/SNF complexes have been reported in various cancer types. For example mutations of BAF180 (PBRM1) were identified in 41% of renal cell carcinomas, making this gene as the second most frequently mutated gene in these cancers after VHL50 [97]. The ARID1A subunit of SWI/SNF complexes was also recently shown to have mutation or loss of protein in primary human cancers including ovarian clear cell carcinomas, low and high grade endometrioid carcinomas [98-101].ARID1A was also rarely mutated in medulloblastoma, breast and lung cancer [102,103].

4. Alterations and roles of SWI/SNF proteins in breast cancer

Breast cancer is among the most common tumors affecting women. It is characterized by a number of genetic aberrations. Some 5-10% of cases are thought to be inherited. Estrogen plays an important role in normal physiology and malignancy of breast tissue. Biological functions of estrogen are mediated by estrogen receptor (ER). ER controls transcription of ER targeted genes by binding to estrogen responsive elements in their promoters. ATP-dependent chromatin remodeling complexes also influence this signaling pathway by changing the chromatin open/close state. In this respect, heterozygous state of a SWI/SNF subunit, Brg1 in mice leads to mammary carcinomas, indicating roles of SWI/SNF proteins in breast cancer [25]. On the other hand, BRCA1 and BRCA2 genes are already known to have roles both in familial and sporadic breast cancers [104-106]. Breast tumors of patients with germ-line mutations in the BRCA1 and BRCA2 genes have more genetic defects than sporadic breast tumors.

Bochar et al. [107] isolated a predominant form of a multiprotein BRCA1-containing complex from human cells displaying chromatin-remodeling activity using a combination of affinity- and conventional chromatographic techniques. Mass spectrometric sequencing of components of this complex proved that BRCA1 is associated with a SWI/SNF-related complex. They also demonstrated that BRCA1 directly interacts with the BRG1 subunit of

the SWI/SNF complex. Furthermore, p53-mediated stimulation of transcription by BRCA1 was completely abrogated by either a dominant-negative mutant of BRG1 or the cancer-causing deletion in exon 11 of BRCA1, revealing that BRCA1 has a direct function in transcriptional control through modulation of chromatin structure [107].

To investigate abnormalities SWI/SNF complex subunits in breast cancer, Decristofaro et al. [108] determined the protein status of the core subunits of BAF170, BAF155, BAF57, BAF53a, and BAF47 in 21 breast cancer cell lines. The authors also determined the protein status of the BRM, BRG1 as well as two other proteins found in human SWI/SNF complexes, BAF180 and BAF250. A breast cancer cell line negative for the BAF57 protein was identified [108].

Deficiency of p270 protein (ARID1A) was shown in a subset of breast cancer. BAF180, a subunit of the PBAP type SWI/SNF chromatin remodeling complex maps to 3p21, in a region where frequent allele loss has been detected in various cancers. A study which used screening for tumor suppressor genes in breast cancer revealed multiple truncating mutations of PB1, which encodes the BAF180 subunit and the mutation was associated with loss of heterozygosity of the wild-type allele [109]. Functional studies showed binding of endogenous wild-type BAF180 to the p21 promoter, which was required for proper p21 expression and G1 arrest after transforming growth factor-beta and gamma-radiation treatment, making BAF180 as a physiologic mediator of p21 expression [109].

In a study, Wang et al. [110] examined the role of BAF57 in breast cancer using the cell line, BT549, which is an invasive human breast carcinoma cell line that lacks expression of BAF57 [111]. They prepared a BT549 stable cell line with expression of the full-length BAF57 protein. The results showed that BT549 clones expressing BAF57 revealed remarkable phenotypic changes, slow growth kinetics, and restoration of contact inhibition. Moreover, microarray analysis showed that BAF57-mediated cell death was associated with up-regulation of proapoptotic genes including the tumor suppressor familial cylindromatosis (CYLD). CYLD was found to be a direct target of BAF57 by chromatin immunoprecipitation analysis. Increased expression of CYLD in BT549 cells induced apoptosis, while its suppression by small interfering RNA inhibited cell death in BAF57 expressing BT549 cells, suggesting the crucial role of BAF57 in cell growth regulation and provided a novel link between hSWI/SNF chromatin remodeling factors and apoptosis [112]. P270 subunit of SWI/SNF complexes was found to be essential for normal cell cycle arrest, providing a direct biological basis to support the implication from tumor tissue screens that deficiency of p270 plays a causative role in carcinogenesis [113]. In a separate study, BAF57 was found to be an ER subtype-selective modulator that specifically regulates ERalpha-mediated transcription, linking ER with SWI/SNF proteins [114].

Harte et al. [115] identified BRD7 as a novel binding partner of BRCA1 with a yeast two-hybrid screen using a BRCA1 bait composed of amino acids 1 to 1142. To determine the functional consequences of the BRCA1-BRD7 interaction, they examined the role of BRD7 in BRCA1-dependent transcription with microarray-based expression profiling. A variety of target genes such as ERalpha was found to be coordinately regulated by BRCA1 and BRD7 complex [115]. In a recent study, two novel mutations were found in one out of 95 breast cancer samples by sequencing BAF57 gene [116].

5. Conclusion and future aspects

Important function of subunits of SWI/SNF complexes arises from their roles in chromatin remodeling and trancription regulation. Mutation and other alterations of these proteins

lead to cancer development. Researches on roles of SWI/SNF subunits in development and cancer are increasingly performed yet much work is necessary for clarifying the exact functions of these genes to provide therapy for various human cancers. Promising results are noticed at the moment for usability of some of these genes as a therapeutic and diagnostic target. Thus progress on the knowledge of functions of subunits of SWI/SNF complexes as well as the relationship with other breast cancer-related molecules such as BRCA1-2 and p53 will clarify their roles in human cancer including breast cancer, which will result in their uses in cancer diagnostics as well as therapy in near future.

6. References

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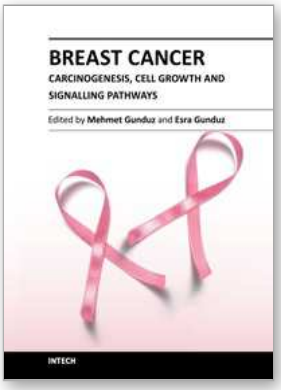

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Cancer is the leading cause of death in most countries and its consequences result in huge economic, social and psychological burden. Breast cancer is the most frequently diagnosed cancer type and the leading cause of cancer death among females. In this book, we discussed various aspects of breast cancer carcinogenesis from clinics to its hormone-based as well as genetic-based etiologies for this deadly cancer. We hope that this book will contribute to the development of novel diagnostic as well as therapeutic approaches.

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