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Review

Regulation of BS69 Expression in Cancers

YUN CHEN[1,2], YA-HUI TSAI[1,2] and SHENG-HONG TSENG[3]

[1]*Department of Surgery, Far Eastern Memorial Hospital, New Taipei, Taiwan, R.O.C.;*
[2]*Department of Chemical Engineering and Materials Science, Yuan Ze University, Taoyuan, Taiwan, R.O.C.;*
[3]*Department of Surgery, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan, R.O.C.*

Abstract. *BS69 is encoded by a gene located on chromosome 10, in a region frequently deleted in human cancers and BS69 expression is often down-regulated in human cancers. In addition, BS69 acts as a transcriptional repressor via interaction with transcriptional factors associated with tumorigenesis, such as cellular homolog of the avian myeloblastosis viral oncoprotein, v-ets erythroblastosis virus E26 oncogene homolog 2 oncoprotein, MYC-associated protein X gene-associated protein. Overexpression of BS69 can suppress proliferation of osteosarcoma, breast cancer and glioma cells in vitro; and inhibits tumor growth in xenograft models. Therefore, BS69 may act as a tumor suppressor, and may be a new target for cancer therapy. However, BS69 down-regulation has been found to be involved in cellular senescence and is associated with the reversion of the malignant phenotype of breast cancer cells. Therefore, additional studies are necessary to clarify the role of BS69 in tumor development.*

BS69 is a 74-KDa multidomain protein localized at chromosome 10p12.48 (1-3). It was originally identified as an adenovirus early gene 1A (E1A)-binding protein that inhibits the transactivation by the E1A oncoprotein (4-6). BS69 contains plant homeodomain (PHD), bromo, Pro-Trp-Trp-Pro (PWWP), and myeloid, Nervy, and DEAF-1 (MYND) domains, and it is also named as Zinc finger MYND domain-containing protein 11 (ZMYND11) (3, 7-9). PHD domain plays an indispensable role in the functions and sumoylation of BS69, and both PHD and MYND domains are important for the localization of BS69 (9). The PHD-bromo-PWWP (PBP) domains are histone "readers", and the PBP-containing proteins have various chromatin-related functions (7, 10). BS69 has three truncated isoforms that are formed through alternative splicing, and it may oligomerize through the binding of its C-terminus MYND domain (amino acids 516-561) to the PxLxO motif in various proteins (3, 9).

Histone marks affect chromatin's functions and structure in either an open or closed conformation (11). They are read and bound by chromatin remodeling complexes through highly conserved recognition domains (12). Active readers open chromatin by removing nucleosomes either completely or partly, allowing access to deoxyribonucleic acid (DNA), and this open chromatin is amenable to transcription by DNA polymerase (12). BS69 can associate with chromatin, and play an important role in chromatin remodeling (3, 13). It specifically recognizes H3K36 trimethyl mark (H3K36me3) and H3.3K36me3, and functions as transcriptional corepressor by modulating ribonucleic acid (RNA) polymerase II (Pol II) at the elongation stage and as RNA splicing regulator (7, 14). Deletion of any of the PBP domains, particularly the PWWP domain and bromodomain, abrogates the ability of BS69 to bind to H3K36me3 (12). Both H3K36me3 and H3.3K36me3 are bound to chromatin along with elongating Pol II, then BS69 is recruited to gene bodies after one or several rounds of transcription when sufficient H3.3K36me3 is accumulated (7, 12). Therefore, there is genome-wide co-localization of BS69 with H3K36me3 and H3.3K36me3 in gene bodies (7). BS69 represses gene expression by preventing the transition of Pol II to elongation, and BS69 depletion increases Pol II occupancy specifically on BS69-repressed genes (7). The specific recognition by BS69 establishes a unique state that defines the genomic distribution of BS69, offering a spatiotemporal control of gene expression for both normal and neoplastic growth (7). BS69 participates in transcriptional repressor complexes and represses the transcription by

Correspondence to: Dr. Sheng-Hong Tseng, Department of Surgery, National Taiwan University Hospital, 7 Chung-Shan S. Rd., Taipei 100, Taiwan, R.O.C. Tel: +886 223123456 (ext. 65110), Fax: +886 289665567, e-mail: shenghongtseng@gmail.com

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interaction with the nuclear receptor corepressor (N-CoR) through MYND domain (3, 6). In addition to E1A, BS69 also interacts with a variety of viral and cellular proteins, such as Epstein-Barr virus (EBV)-encoded EBV nuclear antigen 2 (EBNA2), latent membrane protein 1 (LMP-1), MYC-associated protein X gene-associated protein (MGA), cellular homolog of the avian myeloblastosis viral oncoprotein homolog (c-MYB), and v-ets erythroblastosis virus E26 oncogene homolog 2 oncoprotein (ETS-2) (4, 5, 15-18).

BS69 can interact with tumor necrosis factor receptor-associated factors (TRAF) 1, 2, 3, 5, and 6 (19). It also interacts with LMP-1; it negatively regulates LMP-1-induced nuclear factor-kB (NF-kB) activation and positively regulates LMP-1-mediated activation of c-jun N-terminal kinase (JNK) pathway (17, 19). The regulation of the LMP-1-induced NF-kB activation is mediated through the interaction between BS69 and TRAF3 (19). Silencing of BS69 or TRAF3 using small interfering RNA (siRNA) enhances LMP-1-induced NF-kB activation in HeLa cells (19). Further, BS69 acts as a scaffold protein to bridge LMP-1 and TRAF6, and such recruitment and aggregation of BS69 is a prerequisite for the activation of the LMP-1-induced JNK pathway (17). Toll-like receptor 3 (TLR3, CD283) is a member of the TLR family which plays a fundamental role in the recognition of pathogens and activation of immunity (20). Toll-interleukin-1 (IL-1) receptor domain (TIR)-containing adaptor molecule-1 (TICAM-1), an adaptor for TLR3, can activate both the interferon (IFN)-regulatory factor (IRF)-3 and the IFN-β promoter (21). BS69 is a TICAM-1 binding protein and a member of TICAM-1 signalosome (21, 22). In HEK293T human embryonic kidney cells and HeLa cells, BS69 positively modulates the function of TICAM-1, and the activation of NF-kB/IRF-3 followed by cytokine production is augmented in the presence of BS69 overexpression (22). In contrast, knockdown of endogenous BS69 decreases IFN-β induction (22). These results indicate that BS69 is a positive regulator of the TLR3-TICAM-1 pathway (22). However, the positive activation of NF-kB by BS69 through the TLR3-TICAM-1 pathways is opposite to the negative regulation of LMP-1-activated NF-kB by BS69, which suggests that BS69 harbors dual modes of cytoplasmic NF-kB regulation (17, 22, 23). These findings suggest that BS69 has immunomodulatory function.

Tumor Suppression Effects of BS69

EBV has been found to be related to the development of multiple malignancies, including post-transplant lymphoma, Hodgkin disease and nasopharyngeal carcinoma (2, 19). LMP-1, a well-known oncogenic protein, is expressed in many EBV-associated tumor cells and is responsible for most of the altered cellular growth properties in these tumor cells (2, 19). BS69 can interact with LMP-1 to negatively regulate the LMP-1-mediated NF-kB activation, therefore, BS69 is considered to play a role in the EBV-associated malignancies (19, 23). In addition, treatment with follicle-stimulating hormone (FSH), a probable risk factor for the development of ovarian cancers, induces BS69 down-regulation in MCV152 ovarian surface epithelial cells (24). Further, the up-regulated genes in BS69-knockdown U2OS osteosarcoma cells are also enriched in small cell lung cancers, which suggests that BS69 knockdown favors tumor growth (7). Melanoma-associated antigen (MAGE) family has been found to play a role in tumorigenesis and cancer cell viability, and it can enhance p53 degradation in an ubiquitin-proteasome dependent pathway (2). Cancer-testis antigen HCA587 (MAGE-C2), belonging to the type 1 MAGE gene family, is active in hepatocellular carcinoma, melanoma, sarcoma, lung cancer, bladder cancer and breast cancer and silent in normal tissues except in male germ-line cells (2). HCA587 is a negative regulator of BS69 in human embryonic kidney cells; overexpression of HCA587 promotes ubiquitylation and proteasomal degradation of BS69, whereas knockdown of endogenous HCA587 increases protein levels of BS69 in human embryonic kidney cells and malignant melanoma cells (2). Furthermore, BS69 acts as a transcriptional repressor *via* interaction with a variety of transcriptional factors closely associated with the tumorigenic process including c-MYB, ETS2, MGA, as well as the breast cancer type 2 susceptibility protein (BRCA2)-interacting transcriptional repressor (EMSY) (5, 9, 18). High expression of c-MYB is associated with oncogenic activity and poor prognosis in T-cell leukemia, acute myelogenous leukemia, colorectal tumors, and adenoid cystic carcinomas (2, 25-27). ETS-2 is an activator modulated by ras-dependent phosphorylation, and increased ETS-2 expression is associated with initiation and progression of various cancers (2, 18). Amplification of the BRCA2 repressor EMSY contributes to the initiation and progression of breast cancer and ovarian cancers (2, 28). As BS69 is a corepressor of these transcriptional factors, it may have tumor suppression effects (2).

The gene locus encoding BS69 at chromosome 10p12.48 is a region frequently deleted in human cancers, implying that BS69 may have tumor suppressor-like properties (1, 2, 29, 30). BS69 is often down-regulated in several human cancers and leukemia (7, 8, 31). Deletion of BS69 occurs in 19.3% of acute myelogenous leukemia samples, in more than 36.1% of acute lymphoblastic leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, multiple myeloma and myelodysplastic syndrome (31). In addition, overexpression of wild-type BS69 inhibits tumor cell growth, whereas H3.3K36me3 binding-deficient BS69 mutants show severe defects in suppressing cell proliferation in both U2OS osteosarcoma cells and invasive MDA-MB231 breast cancer cells *in vitro* (7). In mouse xenograft produced by MDA-

MB231 breast cancer cells, tumor formation is strongly suppressed in mice injected with cells expressing wild type BS69, whereas H3.3K36me3-binding deficient mutant W294A cells are severely impaired in suppressing tumor growth *in vivo* (7). D307N substitution-missense mutation (position 307, D→N) diminishes BS69 binding to H3.3K36me3 and decreases the tumor suppressor function of BS69 in the MDA-MB231 breast cancer cells xenograft model (7). Further, low BS69 expression in breast cancer patients correlates with worse disease-free survival (7). These results indicate that BS69 suppresses tumorigenesis of breast cancer cells *in vitro* and *in vivo* in a manner that depends on its H3.3K36me3-binding activity (7).

Children and young adults with glioblastoma multiforme (GBM) have been noted to have mutations in the gene encoding the histone H3.3 variant H3F3A, occurring either at or close to key residues marked by methylation for regulation of transcription (K27M, lysine to methionine; and G34V/R, glycine to valine or arginine) (32-34). The H3.3 mutation results in amino acid substitution at K27 or G34 at or near residues targeted by key post-transcriptional modifications that regulate H3.3's activity (34). The G34V/R mutations drive a distinct expression signature of certain genes through differential genomic binding to the K36 trimethylation mark (H3K36me3) and this transcriptional program involves numerous markers of stem-cell maintenance, cell-fate decisions, and self-renewal (32, 35). H3F3A G34 mutations cause profound up-regulation of v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog (MYCN), a potent oncogene that can cause GBMs when expressed in the correct developmental context (32). The G34V/R mutations also impair BS69 binding to the H3.3K36me3 peptide (7), which may thus inhibit the repression effect of BS69. BS69 expression has also been found to be remarkably decreased in GBM tissues from 20 cases and U87 glioma cell line compared to normal brain tissue from 10 cases (8). BS69 up-regulation significantly suppresses U87 glioma cell proliferation and invasion, induces cell cycle arrest and apoptosis *in vitro*, and inhibits the tumor growth in a xenograft model *in vivo* (8). Further, BS69 is a direct and functional target of microRNA-196a-5p (miR-196a-5p) in U87 glioma cells and there is a negative correlation between miR-196a-5p and BS69 in U87 cells and GBM tissues (8). Down-regulation of miR-196a-5p and BS69 using siRNA increases significantly the proliferative and invasive ability, and decreases apoptosis of U87 cells, as compared with miR-196a-5p knockdown alone (8). These results suggest that decreased expression of BS69 could reverse the suppressive effect of down-regulated miR-196a-5p on U87 cells, which indicates that BS69 is a functional downstream target of miR-196a-5p in regulating GBM biological behavior (8).

BS69 and Cancer Reversion/Cellular Senescence

Although BS69 is considered a candidate tumor suppressor, the data of several reports do not support this viewpoint. A 22.8% of acute myelogenous leukemia (AML) has been found to be associated with amplification of BS69 (8). Furthermore, when human primary breast cancer cells are cocultured with normal mammary fibroblasts in three-dimensional collagen-I gels their malignant behavior is reversed (36). In the reverted breast cancer cells, BS69 was down-regulated to 3.8 folds as compared to the non-reverted breast cancer cells (36). Further, knockdown of BS69 using lentivirus-mediated short hairpin RNAs in untransformed primary human diploid fibroblasts IMR90 can inhibit cell proliferation and induce cell-cycle arrest in G1 phase, decrease bromodeoxyuridine (BrdU) incorporation, elevate p21 levels and the levels of several senescent markers, including enhanced senescence-associated β-galactosidase activity and formation of senescence-associated heterochromatin foci (37). Knockdown of p53 or p21 allows cells to bypass premature senescence that is induced by BS69 knockdown (37). Knockdown of BS69 in U2OS osteosarcoma cells (with wild type p53 alleles) also increases p21 expression and the percentage of cells arrested in G1, and decreases BrdU incorporation; however, no such effects are observed in p53-defective HeLa cells (37). Therefore, down-regulation of BS69 is involved in cellular senescence mainly through the p53-p21 pathway (37), and these data do not support the tumor suppressor effect of BS69 mentioned above.

Conclusion

BS69 gene is located in a region of chromosome 10 frequently deleted in human cancers and is often down-regulated in several human cancers and leukemia (1, 2, 5-7, 15, 30). The expression of BS69 has been noted to be negatively correlated with the expression of various oncoproteins (2, 7, 19, 24). In addition, BS69 acts as a transcriptional repressor in association with a variety of transcriptional factors that are closely associated with tumorigenic processes (5, 9, 18). Overexpression of BS69 can inhibit the proliferation of cancer cells *in vitro*; and exert tumor suppression effects on breast cancer and glioma xenograft models (7, 8). All these data suggest BS69 may act as a tumor suppressor, and manipulation of BS69 expression might modulate the behavior of cancer cells to provide a new strategy for cancer therapy. However, BS69 down-regulation is involved in cellular senescence and is associated with the reversion of malignant phenotype of breast cancer cells (36, 37). The reasons for such inconsistent data are unclear, and might be related to different cancer cell types and tumor microenvironments. Therefore, additional studies in different cancer cell types and various *in vitro* and *in vivo* models are mandatory to clarify the role of BS69 in malignancies.

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Conflicts of Interest

The Authors declare that no conflicts of interest exist in regard to this report.

Authors' Contributions

Yun Chen and Ya-Hui Tsai conducted the systemic literature search. Yun Chen wrote the first draft and Ya-Hui Tsai contributed to important intellectual content and revised the manuscript. Sheng-Hong Tseng contributed to the intellectual content, conducted critical revision and assembled the final manuscript of the work.

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