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# Role of TSG101 in cancer

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## 1. ABSTRACT

The tumor susceptibility gene 101 (TSG101) encodes a multidomain protein that contains a UEV (ubiquitin e2 variant) domain at is N-terminus and a putative DNA-binding motif at its C-terminus. In addition to being a *bona fide* component of the ESCRT (endosomal sorting complexes required for transport) complex 1 and playing a critical role in endosomal sorting and trafficking, TSG101 has also been implicated in an array of cellular functions including, cytokinesis, protein ubiquitination, transcriptional regulation, cell cycle and proliferation, as well as viral budding. The major focus of this article is on the role of TSG101 in tumorigenesis.

## 2. INTRODUCTION: INITIAL DISCOVERY AND CONTROVERSY

TSG101, originally known as CC2, was initially identified as a putative coiled-coil domain-containing protein that interacts with stathmin in a yeast two-hybrid screen in 1995 (1). Shortly after, the full-length TSG101 was cloned and its initial function was revealed as a potential tumor suppressor from a controlled homozygous functional knockout screen. Inactivation of TSG101 in NIH3T3 mouse fibroblasts led to focus formation in monolayer cell cultures, anchorage independent growth in soft-agar, and *in vivo* tumor formation in nude mice. Interestingly, the same study also showed that

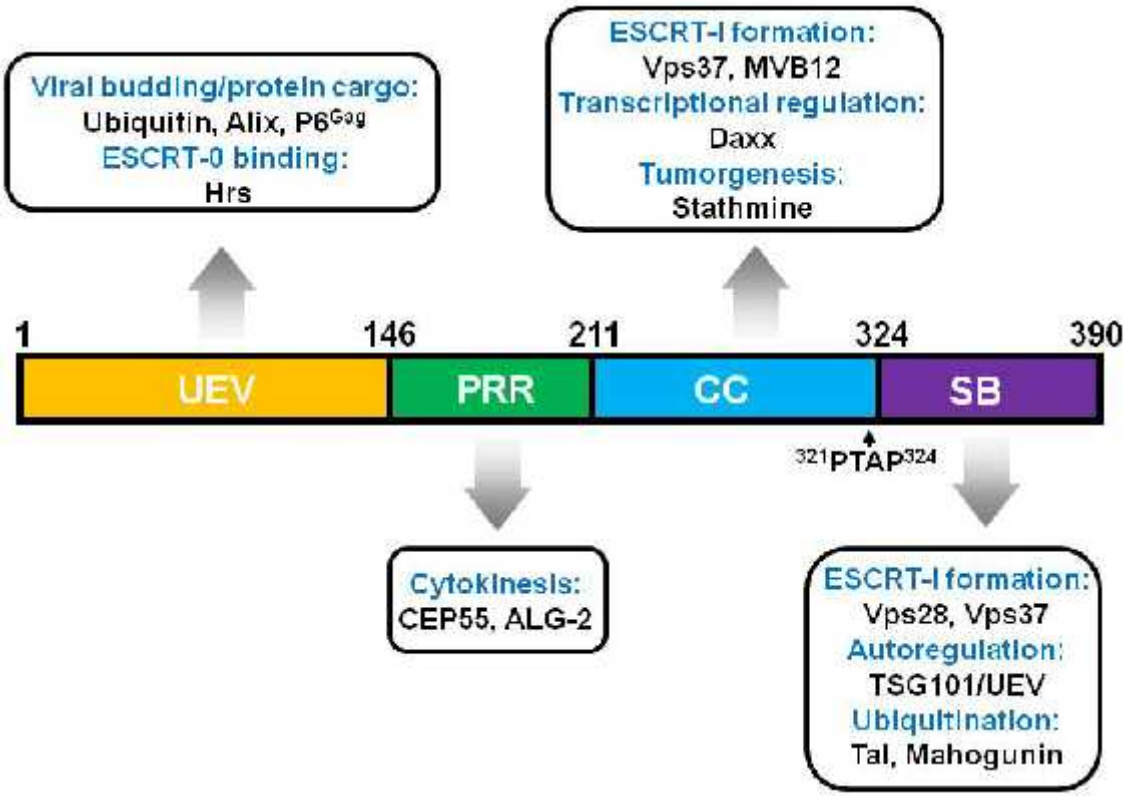


**Figure 1.** Major structural motifs and functions of TSG101. TSG101 contains four individual structural motifs: the N-terminal UEV domain, the protein-rich region (PRR), the coiled-coil (CC) region and the C-terminal α-helical/steadiness box (SB) domain, each interacts with different partners and exerts distinctive functions.

overexpression of the *TSG101* also resulted in cellular transformation as evident from focus formation and colony growth in soft agar (2). Subsequent studies mapped human TSG101 to *chromosome 11*, subbands p15.1–15.2, a region showing loss of heterozygosity (LOH) in a variety of human malignancies. Moreover, it was found that seven of the fifteen uncultured primary *human* breast *carcinomas* had intragenic TSG101 deletions, on the basis of the presence of truncated transcripts observed RT-PCR and Southern blot analysis of PCR products of genomic DNA, while no TSG101 *abnormalities* were observed in matched normal breast tissue from these breast cancer patients (3). Immediately after the original publication showing that TSG101 was often mutated in human breast cancers, several studies using larger numbers of tumor samples failed to detect intragenic TSG101 deletions. Lee and Feinberg analyzed 72 samples of primary breast cancer samples. Identical digestion patterns were observed for all tumors, matched and unrelated normal tissues by Southern hybridization of genomic DNA. Analysis of 46 breast-tumor samples and matched blood control samples, as well as multiple breast cancer cell lines, by Southern blot experiments, failed to confirm that TSG101 gene undergoes large rearrangements in a significant portion of breast tumors and breast cancer cell lines as originally suggested (4). Several additional follow-up studies, analyzing genomic DNA and mRNA isolated from cancer and normal samples, verified the occurrence of "aberrant TSG101 transcripts" but again failed to detect significant intragenic deletions, insertions or mutations of TSG101 (5-7). It was suggested that these apparently aberrant transcripts were the products of either PCR artifacts (7) or alternative/aberrant splicing variants and present in both cancer and normal tissues (6). However, further comparative analysis of human and mouse TSG101 genes revealed additional introns within the human TSG101 gene and determined that these shorter TSG101 transcripts were not aberrant splicing variants, but true alternative splicing variants generated exclusively by exon skipping (8). These convincing results called into question the existence of TSG101 mutants in breast cancer, as well as the role of TSG101 as a tumor suppressor, which led to the retraction of the original publication (9).

## 3. TSG101 STRUCTURE AND FUNCTION

Human TSG101 protein is 390 amino acid residues in length and contains four known structural motifs: the N-terminal UEV domain, followed by a proline-rich region (PRR), a coiled coil (CC) region, and a C-terminal α-helical/steadiness box (SB) domain. Each of these motifs possesses distinct structure and functionalities that render TSG101 versatile in cellular functions (Figure 1).

### 3.1. The UEV domain

The UEV domain of human TGS101 encompasses the first 145 amino acid residues. It shows significant sequence homology to ubiquitin E2 ligases. While catalytically inactive as it lacks the active-site cysteine, replaced by a tyrosine residue (10, 11), TSG101 UEV domains retains the ability to bind ubiquitin, which is essential for TSG101's functions in sorting protein cargo into multivesicular bodies (MVBs) and late endosomal compartments and facilitating viral budding. The three-dimensional structure of the TSG101 domain has been solved by both NMR and X-ray crystallographic techniques (12, 13). The TSG101 UEV domain folds into a typical ubiquitin-conjugating (UBC)-like structure (E2 fold) with four α-helices packed against one side of a four stranded anti-parallel β-sheet. The X-ray crystal structure of TSG101 UEV-ubiquitin complex reveals that ubiquitin molecule binds to a concave surface on the other side of the β-sheet to form a highly solvated interface that buries a 1,250 $Å^2$ solvent accessible surface area (14). The crystal structures of the free and ubiquitin-bound TSG101 UEV are essentially identical, with an RMSD (root-mean-square deviation) of 2 Å that exclusively involves amino acid residues Asp45 and Asp46 in the β-hairpin formed by strand 1/2 (13).

In addition to binding ubiquitin, the TSG101 UEV domain also binds P(T/S)AP sequence motifs in both viral and cellular proteins. For example, interaction of TSG101 UEV with the PSAP motif located within an intrinsically flexible region of the Hrs subunit of ESCRT-0 is believed to responsible for the recruitment of the ESCRT-1 complex by ESCRT-0 (15). Again, both NMR and X-ray crystal structures of TSG101 UEV-PTAP peptide complexes are available (16, 17). The solution structure of TSG101 UEV domain in complex with a nine-residue PTAP peptide from the late domain of HIV-1 Gag protein shows that the PTAP peptide binds to a bifurcated groove independent of the ubiquitin surface with each of the PTAP residues making extensive contacts with the protein. Unlike the binding of ubiquitin, PTAP binding induces noticeable conformational changes in TSG101 UEV (16). While the crystal structure TSG101 UEV-PTAP complex qualitatively confirms the overall binding architecture of the peptide, detailed interactions between the peptide and the protein differs significantly between the two structures. The peptide backbone between P and T is flipped 180° between the crystal and the averaged NMR structure. The peptide connecting T and A is also in a sharply different orientation (17). At present, the causes of these structural differences are not entirely clear. Nonetheless, these structural data demonstrate that TSG101 UEV can simultaneously interact with both ubiquitin and the PTAP motif from different protein partners or from the same protein. These interactions are essential for TSG101 to participate in different cellular processes, such as the organization of the ESCRT complex, cargo recruitment, transcriptional regulation and cytokinesis (14, 18, 19).

### 3.2. The proline-rich region (PRR)

The proline-rich region of TSG101, spanning approximately 70 residues with a 30% Pro content, connects the UEV domain to the core of ESCRT-1 complex. Presumably, the TSG101 PRR is unstructured and not as well studied as the UEV domain. The function of the PRR was not revealed until recently (20, 21). It was reported that a proline-rich sequence, $^{154}$QATGPPNTSYMPG$^{166}$, within the PRR of TSG101 competes with a similar proline-rich sequence on ALIX (ALG-2-interacting protein X), an ESCRT associated protein, for binding to the central hinge region of CEP55A (21). CEP55A is a mid-body protein required for abscission (22). The presence of ESCRT-I and ALIX lead to further recruitment of the ESCRT-III complexes, which are believed to possess membrane scission activity and to be responsible for cell abscission during cytokinesis (19). Depletion of TSG101 and ALIX inhibits cell abscission, suggesting that both proteins are required for cytokinesis (20). In addition to CEP55A, TSG101 PRR also binds ALG-2 (apoptosis-linked gene 2), a dimeric $Ca^{2+}$-binding EF hand protein, in a $Ca^{2+}$-dependent manner (23). While the binding site for ALG-2 on ALIX has been mapped to overlaps with the CEP55-binding sequence described above (24), the corresponding sequence in TSG101 has not been mapped in detail. Nor has the function of TSG101-ALG2 interaction been determined.

### 3.3 The coiled-coil (CC) region

The CC region was initially identified in a yeast-hybrid screen for its ability to bind stathmin, a cytosolic phosphoprotein implicated in tumorigenesis (1). Crystallographic analyses of the yeast ESCRT-1 complex, which is conserved from yeast to humans, reveals that the CC region of Vps23, the yeast ortholog of TSG101, interacts with Vps37 and Mvb12 to form a 130 Å long, rigid stalk of triple coiled helices (25). These structural studies confirm that the CC region of TSG101 is essential for the structural integrity of the ESCRT-1 complex. In addition, it has been reported that the CC domain is essential for TSG101-mediated suppression of ligand-induced transactivation of estrogen receptor and other nuclear hormone receptors (26). Further studies have demonstrated that TSG101 CC interacts with Daxx, a Fas interacting protein and transcription regulator, and co-localizes with Daxx in the nucleus, where TSG101 and Daxx cooperatively repress glucocorticoid receptor-mediated transcriptional activity (27). Moreover, a TSG101 isoform without the CC resulted from alternative slicing has been shown to be expressed exclusively in Burkitt's lymphoma cells and non-Hodgkin's lymphomas, but not in normal cells (28, 29).

### 3.4. The C-terminal α-helical/steadiness box (SB) domain

The C-terminal α-helical/Steadiness box (SB) domain of Vps23/TSG101, the N-terminal half of Vps28, and the C-terminal half of Vps37 form the headpiece of the ESCRT-1 complex core (30, 31). The SB domain forms a hairpin structure consisting of two long antiparallel α helices. Despite a lack of detectable sequence similarity, the three subunits of the ESCRT-1 headpiece assume a strikingly similar overall structure and are arranged side-by-side at nearly identical ~30° angles with Vps23 in the middle making direct interactions with the Vps28 subunit

on one side and Vps37 subunit on the other. There is no direct contact between Vps28 and Vps37 (30, 31). These results suggest that the SB domain, along with the CC domain, plays an important role in maintaining ESCRT-1 stability.

Besides being a critical structural component of the ESCRT-1 complex, the SB domain also plays an important role in maintaining the homeostasis of cellular levels of TSG101. Considering that both depletion and overexpression of TSG101 lead to oncogenic transformation and abnormal cell growth, it is not surprising that the levels of TSG101 are controlled within a narrow range in normal cells. Feng and colleagues report that the TSG101 protein is maintained at a steady-state level in cultured murine and human cells. Ectopic expression of TSG101 results in a down-regulation of endogenous TSG101. It is further revealed that the cellular level of TSG101 is controlled in an auto-regulatory manner through a posttranslational process involving a "steadiness box," located near TSG101's COOH-terminal end (32). Subsequent studies demonstrate a mechanism of TSG101 autoregulation that involves Tal (TSG101-associated ligase), a novel ring-finger containing E3 ubiquitin ligase (33). Tal contains an N-terminal leucine-rich repeat (LRR), followed by an ezrin-radixin-moezin (ERM) domain, a coiled-coil (CC) region, an α sterile alpha motif (SAM), and a C-terminal RING finger (RF), as well as a tandem PT(S)AP motif immediately N-terminal to the RF. Tal interacts with TSG101 in a bimodal fashion, while the PT(S)AP motif recognizes the UEV domain of TSG101 the central region of Tal binds to the SB domain. Monoubiquitination of TSG101 at multiple lysine residues at the C-terminal SB domain by Tal shuttles TSG101 from membrane bound fractions to cytoplasm and inactivates its cargo sorting activities such as receptor tyrosine kinase internalization and viral budding (34). Subsequent studies reveal additional Tal functions in controlling TSG101 protein stability, where Tal polyubiquitinates lysine residues in the C-terminus SB domain of TSG101, therefore targeting TSG101 for proteasome-mediated degradation (33). Complex formation with Vps28 or Vps37 as described above for the ESCRT-1 headpiece prevents Tal-mediated polyubiquitination presumably by blocking the access of the lysine residues within the SB domain. While essential for maintaining cellular homeostasis of TSG101 level, polyubiquitination of the SB domain by Tal does not seem to be important for other ESCRT related TSG101 functions (33). Another ring finger containing E3 ubiquitin ligase, Mahogunin, has been reported to interact with TSG101 in a similar fashion as Tal. Mahogunin binds to TSG101 UEV domain via its PSAP motif and catalyzes monoubiquitination of TSG101 at multiple lysine sites. However, it is not clear if Mahogunin and Tal target the same lysine residues located within the SB domain. In addition, Mahogunin does not polyubiquitinate TSG101, and ectopic expression of Mahogunin does not result in TSG101 degradation (35).

## 4. TSG101 ROLE IN CANCER

Since the initial discovery and debate of TSG101 as a candidate tumor suppressor gene, major efforts have been devoted to reexamine the role of TSG101 in tumorigenesis. While the subject remains controversial, significant amount of literature now describes TSG101 as a tumor progression enhancer in various types of cancers.

### 4.1. TSG101 and Breast Cancer

The involvement of TSG101 in cancer was initially reported in breast cancer, one of the most studied human cancer types. Li, *et al* in 1997 reported that abnormal truncation of the coiled-coil domain of TSG101 could be detected in 7 out of 15 breast cancer samples. This high frequency of coiled-coil domain deletion led to the proposal of TSG101 as a tumor suppressor (3), which seems to consistent with the fact that TSG101 gene is located on chromosome 11, subbands p15.1–15.2, a region associated with LOH in breast cancer (36). However, as discussed earlier, further studies failed to verify intragenic deletions, insertions or mutations of TSG101 in breast tumors (4-7). In fact, targeted deletion of *Tsg101* in mouse embryonic fibroblasts does not lead to increased proliferation and cellular transformation and actually results in growth arrest at G1/S transition and cell death (37). In addition, studies using mammary gland-specific knockout mice show that *Tsg101* is essential for the growth, proliferation, and survival of mammary epithelial cells and *Tsg101* deficient mice do not develop mammary tumors after a latency of 2 years (38). Results based on three double knock-out models (*Tsg101/p53, Tsg101/p21*, and *Tsg101/p19*$^{Arf}$) further reveal that *Tsg101* is essential for cell survival regardless of the status of p53, p21 and p19$^{Arf}$ (39). Taken together, these studies convincingly demonstrate that TSG101 is required for normal cell function of embryonic and adult tissues but not a tumor suppressor for breast cancer.

Further challenging the notion that TSG101 is a potential breast cancer tumor suppressor, it appears that the expression levels of TSG101 in primary human breast carcinomas are upregulated (40-42). On the other hand, gene silencing of TSG101 via RNAi in MDA-MB-31 cells resulted in growth inhibition and cell cycle arrest at the G1/S checkpoint. In addition, TSG101 downregulation also suppressed both colony formation potential and the migratory capability of the cancer cells (43). Similar results were recently reported using MCF-7 cells (44). To test if Tsg101 has oncogenic properties *in vivo*, Oh *et al.* generated transgenic mice that overexpressed Tsg101 in the developing mammary gland. While the mammary gland of females overexpressing exogenous Tsg101 developed normally throughout the reproductive cycle, the ectopic expression of Tsg101 led to increased levels of phosphorylation Erk1/2 and stat3, and slightly increased the susceptibility of mammary epithelia toward malignant transformation in aging females. These results suggest that Tsg101 protein possesses only weak oncogenic properties, i.e., instead of tumor initiation, Tsg101 is more likely playing a role in the progression of a subset of spontaneously arising breast cancers (41).

### 4.2. TSH101 and Ovarian Cancer

Ovarian cancer is another common gynecological tumor where deletion of both regions at 11p15.5-15.3 and 11p15.1 is strongly associated with high grade

nonmucinous epithelial ovarian cancer (45). Similar to breast cancer, truncated TSG101 transcripts of the TSG101 is frequently observed in ovarian cancer (46-48). Again, these truncated TSG101 transcripts most likely represent splice variants as there is no evidence of genomic deletions in the TSG101 gene in ovarian cancer (46, 47, 49).

Functional proteomic analysis of genetically-defined human ovarian cancer models reveals that TSG101 is up-regulated in human ovarian epithelial cells expressing oncogenic HRAS or KRAS (50, 51). Suppressing TSG101 by siRNA in ovarian cancer SKOV-3 cells led to $G_2$/M arrest, growth inhibition and cell death. The levels of hypoxia inducible factor 1α (HIF-1α) and CBP/p300-interacting transactivator with ED-rich tail 2 (CITED2), two closely related transcriptional factors important for cell growth and survival, were markedly reduced after TSG101 knockdown (50). Concurrent with down-regulation of CITED2 and HIF-1α, the mRNA and protein levels of the cyclin-dependent kinase inhibitor p21 are dramatically increased (52). When ectopically implanted in athymic nude mice, SKOV-3 cells transfected with TSG101 siRNA induced significantly smaller tumors *in vivo* than those from SKOV-3 cell treated with control non-specific siRNA (50).

Consistent with the finding in genetically-defined human ovarian cancer models, Immunoanalysis using ovarian cancer samples and micro-tissue array containing 422 cases of primary ovarian cancer samples revealed elevated TSG101 levels in more than 70% of human ovarian carcinomas. While normal human ovarian surface epithelium did not show significant expression for TSG101, the expression of TSG101 was increasingly positive in borderline tumors, low grade and high grade carcinomas compared to normal human ovarian surface epithelium. Compared to other histotypes, serous carcinoma, poorly differentiated carcinomas and malignant mixed mullerian tumors expressed higher levels of TSG101. There is a positive correlation between the grade and stage of the cancer and the levels of TSG101 expression in EOC. Moreover, the levels of TSG101 expression have significant impacts on the prognostic outcomes. The 5-year survival rate for ovarian cancer patients with low TSG101 expression is about 53% while only 33% patients with high levels of TSG101 survive more than 5 years (52). Taken together, these results suggest that elevated TSG101 is associated with poor prognosis and a potential therapeutic target for ovarian cancer. Indeed, a recent study showed a time-dependent down-regulation of TSG101 in human ovarian cancer A2870 cells in response to Gleevec chemotherapeutic treatment, suggesting TSG101 expression level may represent an important index of drug efficacy for Gleevec in ovarian cancer (53)

**4.3. TSG101 Cervical Cancer**

Unlike that of breast cancer or ovarian cancer, the development of cervical cancer is strongly associated with human papillomavirus (HPV) infection (54). While HPV infection is a necessary factor in the development of almost all cases of cervical cancer (55), the development of cervical cancer is a rare event that requires additional genetic and epigenetic alterations. Similar to breast and ovarian cancers, LOH for alleles on chromosome 11 has been reported for cervical carcinoma (56, 57). Aberrant splicing of TSG101 was also detected in both primary cancer samples and immortalized cell lines (58-62). However, no mutation and intragenic deletion was observed in both normal and malignant cells, and there is no evidence of direct connection between truncated transcript and cancer progression (59, 61). On the other hand, a recent report suggests that the expression level of TSG101 is down-regulated in cervical cancer (63). This apparent down-regulation of TSG101 observed in cervical cancer is likely a direct consequence of HPV infection as decreased TSG101 levels are observed in non-tumor cervical cell infected by HPV16. Since HPV infection has been shown to cause epigenetic changes in cervical cancer (64), one possibility is that the promoter of TSG101 is hypermethylated to inhibit its expression. However, methylation analysis of TSG101 promoter suggests that TSG101 down-regulation in cervical cancer cells is not regulated by epigenetic events (63). Therefore, the mechanism of TSG101 down-regulation in cervical cancer remains unclear.

**4.4 TSG101 and Prostate Cancer**

As in breast and ovarian cancers, abnormal splicing variants of TSG101 were frequently observed (65, 66). For example, analysis of 15 cases of primary and metastatic prostate cancer led to the detection of transcripts with deletions in nine samples (65). Like breast cancer and ovarian cancer, prostate cancer is also sex hormone related. The development of this cancer type is closely associated with the functions of androgen and its receptor (AR). Sun and colleagues reported that TSG101 can interact with AR to suppress it ligand-induced transcriptional activation. Instead of a direct binding, interaction between AR and TSG101 was shown to be mediated by a transcription co-activator, CBP/p300, which is capable of binding to TSG101 both *in vitro* and *in vivo* (67). In contract to the initially reported role of AR transcription suppression, a more recent investigation revealed that TSH101 functioned as a coactivator of the AR by promoting it monoubiquitination (18). This is consistent with the finding that reduction of TSG101 protein has a negative impact on prostate tumor cell growth (43).

As a member of Vps protein family, TSG101 is an integral component of the prostasomes, exosome-like vesicles released by human prostate epithelial cells (68). Prostasomes have been implicated in playing roles in prostate cancer progression (69) and may be used as a biomarker for prostate tumor metastasis (70). Prostasomes released from prostate cancer cells contain high levels of protein kinases and concurrent lower ATPase activity which may affect interaction between cancer cell and its microenvironment through increased phosphorylation (71). While the exact role of TSG101 in prostasomes formation and secretion is not clear, a recent study shows that TSG101 is important for increased release of endosome-like vesicles in human prostate cancer cells response to radiation treatment. Moreover, these TSG101 containing exosome-like microvesicles were enriched in B7-H3 protein, a diagnostic marker for prostate cancer (72).

### 4.5. TSG101 and Lung Cancer

Aberrant splicing but no intragenic deletion of TSG101 is a common event in different cancer types, including lung cancer (46, 73). Normal and shortened TSG101 transcripts were detected in 89% of small cell lung carcinoma (SCLC) cell lines while only the full-length TSG101 transcript was detected in normal tissues, primary non-small cell lung carcinoma (NSCLC) specimens, and the majority of NSCLC cell lines. Single strand conformational polymorphism (SSCP) analysis and direct sequencing of TSG101 cDNAs failed to detect mutations or deletions, suggesting suggest that TSG101 is not mutated in lung cancer (74).

Contradicting results have been reported regarding the expression level of TSG101 in lung cancer (75, 76). TSG101 was identified from a cDNA library constructed from Anip973, a highly metastatic lung adenocarcinoma cell line, to be able to promote colony formation and anchorage-independent growth on soft agar when transfected in NIH3H3 cells. Further analysis reveals that TSG101 is overexpressed in all fifteen lung cancer cell lines and five lung cancer tissues examined as compared to matching normal lung tissue. Ectopic expression of TSG101 cDNA in A549, a lung adenocarcinoma cell line, resulted in an increased cell proliferation (75). These results suggest that TSG101 is unlikely a primary tumor suppressor gene, but is capable of promoting cell growth the malignant phenotype in NIH3T3 and lung cancer cells. However, Chang and colleagues reported that TSG101 level is decreased in human lung cancer samples (76, 77). Downregulation of TSG101 protein was correlated with the upregulation of Notch 3 receptor in lung cancer (78). The exact reason for this apparent discrepancy is not obvious. To understand the role of TSG101 in lung cancer, more careful studies with larger sample sizes are required.

## 5. Conclusion and Perspectives

TSG101 is a versatile protein that has been implicated in multiple cellular functions, including but not limited to, endosomal sorting and trafficking (79-82), transcriptional regulation (83, 84), cell cycle and proliferation (37, 38, 85-87), protein ubiquitination regulation (88, 89), and cytokinesis (20, 21, 90, 91). While initially discovered as negative regulator for tumorigenesis, accumulating evidence now describes TSG101 as a positive modulator of cancer progression. Consistent with this notion, overexpression of TSG101 has been reported in most cancer types, in addition to the five discussed above such as, colorectal carcinoma (92), gastric carcinoma (93), papillary thyroid carcinoma (94, 95), gallbladder adenocarcinoma (96), and multi-drug resistant human gastric adenocarcinoma cell (97). The ability of TSG101 to serve both positive and negative roles in cellular homeostasis places it alongside with an increasing family of proteins that can regulate cellular functions in apparently opposing manners under different physiological contexts. The challenge will be to define precisely how TSG101 exerts its oncogenic properties in cancer development. Important questions include: Which particular cellular function is critical for TSG101's role in cancer? Does TSG101 play a similar role in all cancer types or is its functions in cancer tissue-specific? What are the roles of TSG101 splicing variants and how are they regulated? Answers to these questions will not only clarify the current controversy within the field but may also provide new diagnostic and/or therapeutic tools for cancer.

## 6. ACKNOWLEDGEMENTS

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## 7. REFERENCES

1. A. Maucuer, J. H. Camonis, and A. Sobel: Stathmin interaction with a putative kinase and coiled-coil-forming protein domains. Proc Natl Acad Sci U S A 92, 3100-3104 (1995)

2. L. Li and S. N. Cohen: Tsg101: a novel tumor susceptibility gene isolated by controlled homozygous functional knockout of allelic loci in mammalian cells. Cell 85, 319-329 (1996)

3. L. Li, X. Li, U. Francke, and S. N. Cohen: The TSG101 tumor susceptibility gene is located in chromosome 11 band p15 and is mutated in human breast cancer. Cell 88, 143-154 (1997)

4. P. Steiner, D. M. Barnes, W. H. Harris, and R. A. Weinberg: Absence of rearrangements in the tumour susceptibility gene TSG101 in human breast cancer. Nat Genet 16, 332-333 (1997)

5. Q. Zhong, C. F. Chen, Y. Chen, P. L. Chen, and W. H. Lee: Identification of cellular TSG101 protein in multiple human breast cancer cell lines. Cancer Res 57, 4225-4228 (1997)

6. C. F. Xu, J. Greenman, and E. Solomon: Truncated TSG101 transcripts are present in peripheral blood from both familial breast cancer patients and controls. Eur J Cancer 34, 1077-1080 (1998)

7. M. Hampl, J. Hampl, J. Plaschke, G. Fitze, G. Schackert, H. D. Saeger, and H. K. Schackert: Evidence that TSG101 aberrant transcripts are PCR artifacts. Biochem Biophys Res Commun 248, 753-760 (1998)

8. K. U. Wagner, P. Dierisseau, E. B. Rucker, III, G. W. Robinson, and L. Hennighausen: Genomic architecture and transcriptional activation of the mouse and human tumor susceptibility gene TSG101: common types of shorter transcripts are true alternative splice variants. Oncogene 17, 2761-2770 (1998)

9. L. Li, U. Francke, and S. N. Cohen: Retraction. The TSG101 tumor susceptibility gene is located in chromosome 11 band p15 and is mutated in human breast cancer. Cell 93, following-(1998)

10. E. V. Koonin and R. A. Abagyan: TSG101 may be the prototype of a class of dominant negative ubiquitin regulators. Nat Genet 16, 330-331 (1997)

11. C. P. Ponting, Y. D. Cai, and P. Bork: The breast cancer gene product TSG101: a regulator of ubiquitination? J Mol Med 75, 467-469 (1997)

12. O. Pornillos, S. L. Alam, R. L. Rich, D. G. Myszka, D. R. Davis, and W. I. Sundquist: Structure and functional interactions of the Tsg101 UEV domain. EMBO J 21, 2397-2406 (2002)

13. A. Palencia, J. C. Martinez, P. L. Mateo, I. Luque, and A. Camara-Artigas: Structure of human TSG101 UEV domain. Acta Crystallogr D Biol Crystallogr 62, 458-464 (2006)

14. W. I. Sundquist, H. L. Schubert, B. N. Kelly, G. C. Hill, J. M. Holton, and C. P. Hill: Ubiquitin recognition by the human TSG101 protein. Mol Cell 13, 783-789 (2004)

15. X. Ren, D. P. Kloer, Y. C. Kim, R. Ghirlando, L. F. Saidi, G. Hummer, and J. H. Hurley: Hybrid structural model of the complete human ESCRT-0 complex. Structure 17, 406-416 (2009)

16. O. Pornillos, S. L. Alam, D. R. Davis, and W. I. Sundquist: Structure of the Tsg101 UEV domain in complex with the PTAP motif of the HIV-1 p6 protein. Nat Struct Biol 9, 812-817 (2002)

17. Y. J. Im, L. Kuo, X. Ren, P. V. Burgos, X. Z. Zhao, F. Liu, T. R. Burke, Jr., J. S. Bonifacino, E. O. Freed, and J. H. Hurley: Crystallographic and functional analysis of the ESCRT-I /HIV-1 Gag PTAP interaction. Structure 18, 1536-1547 (2010)

18. S. Burgdorf, P. Leister, and K. H. Scheidtmann: TSG101 interacts with apoptosis-antagonizing transcription factor and enhances androgen receptor-mediated transcription by promoting its monoubiquitination. J Biol Chem 279, 17524-17534 (2004)

19. N. Elia, R. Sougrat, T. A. Spurlin, J. H. Hurley, and J. Lippincott-Schwartz: Dynamics of endosomal sorting complex required for transport (ESCRT) machinery during cytokinesis and its role in abscission. Proc Natl Acad Sci U S A 108, 4846-4851 (2011)

20. E. Morita, V. Sandrin, H. Y. Chung, S. G. Morham, S. P. Gygi, C. K. Rodesch, and W. I. Sundquist: Human ESCRT and ALIX proteins interact with proteins of the midbody and function in cytokinesis. EMBO J 26, 4215-4227 (2007)

21. H. H. Lee, N. Elia, R. Ghirlando, J. Lippincott-Schwartz, and J. H. Hurley: Midbody targeting of the ESCRT machinery by a noncanonical coiled coil in CEP55. Science 322, 576-580 (2008)

22. M. Fabbro, B. B. Zhou, M. Takahashi, B. Sarcevic, P. Lal, M. E. Graham, B. G. Gabrielli, P. J. Robinson, E. A. Nigg, Y. Ono, and K. K. Khanna: Cdk1/Erk2- and Plk1-dependent phosphorylation of a centrosome protein, Cep55, is required for its recruitment to midbody and cytokinesis. Dev Cell 9, 477-488 (2005)

23. K. Katoh, H. Suzuki, Y. Terasawa, T. Mizuno, J. Yasuda, H. Shibata, and M. Maki: The penta-EF-hand protein ALG-2 interacts directly with the ESCRT-I component TSG101, and Ca2+-dependently co-localizes to aberrant endosomes with dominant-negative AAA ATPase SKD1/Vps4B. Biochem J 391, 677-685 (2005)

24. H. Suzuki, M. Kawasaki, T. Inuzuka, M. Okumura, T. Kakiuchi, H. Shibata, S. Wakatsuki, and M. Maki: Structural basis for Ca2+ -dependent formation of ALG-2/Alix peptide complex: Ca2+/EF3-driven arginine switch mechanism. Structure 16, 1562-1573 (2008)

25. M. S. Kostelansky, C. Schluter, Y. Y. Tam, S. Lee, R. Ghirlando, B. Beach, E. Conibear, and J. H. Hurley: Molecular architecture and functional model of the complete yeast ESCRT-I heterotetramer. Cell 129, 485-498 (2007)

26. M. Watanabe, Y. Yanagi, Y. Masuhiro, T. Yano, H. Yoshikawa, J. Yanagisawa, and S. Kato: A putative tumor suppressor, TSG101, acts as a transcriptional suppressor through its coiled-coil domain. Biochem Biophys Res Commun 245, 900-905 (1998)

27. R. Muromoto, K. Sugiyama, T. Yamamoto, K. Oritani, K. Shimoda, and T. Matsuda: Physical and functional interactions between Daxx and TSG101. Biochem Biophys Res Commun 316, 827-833 (2004)

28. M. Ferrer, S. Lopez-Borges, and P. A. Lazo: Expression of a new isoform of the tumor susceptibility TSG101 protein lacking a leucine zipper domain in Burkitt lymphoma cell lines. Oncogene 18, 2253-2259 (1999)

29. M. Ferrer, S. Hernandez, E. Campo, and P. A. Lazo: Loss of the TSG101 leucine zipper domain in aggressive non-Hodgkin's lymphomas. Leukemia 14, 2014-2016 (2000)

30. H. Teo, D. J. Gill, J. Sun, O. Perisic, D. B. Veprintsev, Y. Vallis, S. D. Emr, and R. L. Williams: ESCRT-I core and ESCRT-II GLUE domain structures reveal role for GLUE in linking to ESCRT-I and membranes. Cell 125, 99-111 (2006)

31. M. S. Kostelansky, J. Sun, S. Lee, J. Kim, R. Ghirlando, A. Hierro, S. D. Emr, and J. H. Hurley: Structural and functional organization of the ESCRT-I trafficking complex. Cell 125, 113-126 (2006)

32. G. H. Feng, C. J. Lih, and S. N. Cohen: TSG101 protein steady-state level is regulated posttranslationally by an evolutionarily conserved COOH-terminal sequence. Cancer Res 60, 1736-1741 (2000)

33. B. McDonald and J. Martin-Serrano: Regulation of Tsg101 expression by the steadiness box: a role of Tsg101-associated ligase. Mol Biol Cell 19, 754-763 (2008)

34. I. Amit, L. Yakir, M. Katz, Y. Zwang, M. D. Marmor, A. Citri, K. Shtiegman, I. Alroy, S. Tuvia, Y. Reiss, E.

Roubini, M. Cohen, R. Wides, E. Bacharach, U. Schubert, and Y. Yarden: Tal, a Tsg101-specific E3 ubiquitin ligase, regulates receptor endocytosis and retrovirus budding. Genes Dev 18, 1737-1752 (2004)

35. B. Y. Kim, J. A. Olzmann, G. S. Barsh, L. S. Chin, and L. Li: Spongiform neurodegeneration-associated E3 ligase Mahogunin ubiquitylates TSG101 and regulates endosomal trafficking. Mol Biol Cell 18, 1129-1142 (2007)

36. R. Winqvist, A. Mannermaa, M. Alavaikko, G. Blanco, P. J. Taskinen, H. Kiviniemi, I. Newsham, and W. Cavenee: Refinement of regional loss of heterozygosity for chromosome 11p15.5 in human breast tumors. Cancer Res 53, 4486-4488 (1993)

37. A. Krempler, M. D. Henry, A. A. Triplett, and K. U. Wagner: Targeted deletion of the Tsg101 gene results in cell cycle arrest at G1/S and p53-independent cell death. J Biol Chem 277, 43216-43223 (2002)

38. K. U. Wagner, A. Krempler, Y. Qi, K. Park, M. D. Henry, A. A. Triplett, G. Riedlinger, E. B. Rucker III, and L. Hennighausen: Tsg101 is essential for cell growth, proliferation, and cell survival of embryonic and adult tissues. Mol Cell Biol 23, 150-162 (2003)

39. M. J. Carstens, A. Krempler, A. A. Triplett, Lohuizen M. Van, and K. U. Wagner: Cell cycle arrest and cell death are controlled by p53-dependent and p53-independent mechanisms in Tsg101-deficient cells. J Biol Chem 279, 35984-35994 (2004)

40. Y. F. Lo, T. C. Chen, S. C. Chen, and C. C. Chao: Aberrant expression of TSG101 in Taiwan Chinese breast cancer. Breast Cancer Res Treat 60, 259-266 (2000)

41. K. B. Oh, M. J. Stanton, W. W. West, G. L. Todd, and K. U. Wagner: Tsg101 is upregulated in a subset of invasive human breast cancers and its targeted overexpression in transgenic mice reveals weak oncogenic properties for mammary cancer initiation. Oncogene 26, 5950-5959 (2007)

42. G. Zhu, L. Reynolds, T. Crnogorac-Jurcevic, C. E. Gillett, E. A. Dublin, J. F. Marshall, D. Barnes, C. D'Arrigo, P. O. Van Trappen, N. R. Lemoine, and I. R. Hart: Combination of microdissection and microarray analysis to identify gene expression changes between differentially located tumour cells in breast cancer. Oncogene 22, 3742-3748 (2003)

43. G. Zhu, R. Gilchrist, N. Borley, H. W. Chng, M. Morgan, J. F. Marshall, R. S. Camplejohn, G. H. Muir, and I. R. Hart: Reduction of TSG101 protein has a negative impact on tumor cell growth. Int J Cancer 109, 541-547 (2004)

44. Y. Zhang, M. Song, Z. S. Cui, C. Y. Li, X. X. Xue, M. Yu, Y. Lu, S. Y. Zhang, E. H. Wang, and Y. Y. Wen: Down-regulation of TSG101 by small interfering RNA inhibits the proliferation of breast cancer cells through the MAPK/ERK signal pathway. Histol Histopathol 26, 87-94 (2011)

45. K. H. Lu, J. N. Weitzel, S. Kodali, W. R. Welch, R. S. Berkowitz, and S. C. Mok: A novel 4-cM minimally deleted region on chromosome 11p15.1 associated with high grade nonmucinous epithelial ovarian carcinomas. Cancer Res 57, 387-390 (1997)

46. S. A. Gayther, P. Barski, S. J. Batley, L. Li, K. A. de Foy, S. N. Cohen, B. A. Ponder, and C. Caldas: Aberrant splicing of the TSG101 and FHIT genes occurs frequently in multiple malignancies and in normal tissues and mimics alterations previously described in tumours. Oncogene 15, 2119-2126 (1997)

47. M. E. Carney, G. L. Maxwell, J. M. Lancaster, C. Gumbs, J. Marks, A. Berchuck, and P. A. Futreal: Aberrant splicing of the TSG101 tumor suppressor gene in human breast and ovarian cancers. J Soc Gynecol Investig 5, 281-285 (1998)

48. V. Balz, H. B. Prisack, H. Bier, and H. Bojar: Analysis of BRCA1, TP53, and TSG101 germline mutations in German breast and/or ovarian cancer families. Cancer Genet Cytogenet 138, 120-127 (2002)

49. N. A. Bennett, R. A. Pattillo, R. S. Lin, C. Y. Hsieh, T. Murphy, and D. Lyn: TSG101 expression in gynecological tumors: relationship to cyclin D1, cyclin E, p53 and p16 proteins. Cell Mol Biol (Noisy -le-grand) 47, 1187-1193 (2001)

50. T. W. Young, F. C. Mei, D. G. Rosen, G. Yang, N. Li, J. Liu, and X. Cheng: Up-regulation of tumor susceptibility gene 101 protein in ovarian carcinomas revealed by proteomics analyses. Mol Cell Proteomics 6, 294-304 (2007)

51. X. Cheng, T. W. Young, and F. C. Mei: Proteomics analyses of ovarian cancer using genetically defined human ovarian cancer models. Front Biosci 12, 5166-5174 (2007)

52. T. W. Young, D. G. Rosen, F. C. Mei, N. Li, J. Liu, X. F. Wang, and X. Cheng: Up-regulation of tumor susceptibility gene 101 conveys poor prognosis through suppression of p21 expression in ovarian cancer. Clin Cancer Res 13, 3848-3854 (2007)

53. B. B. Patel, Y. A. He, X. M. Li, A. Frolov, L. Vanderveer, C. Slater, R. J. Schilder, Mehren M. von, A. K. Godwin, and A. T. Yeung: Molecular mechanisms of action of imatinib mesylate in human ovarian cancer: a proteomic analysis. Cancer Genomics Proteomics 5, 137-149 (2008)

54. F. X. Bosch, M. M. Manos, N. Munoz, M. Sherman, A. M. Jansen, J. Peto, M. H. Schiffman, V. Moreno, R. Kurman, and K. V. Shah: Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International biological study on cervical cancer (IBSCC) Study Group. J Natl Cancer Inst 87, 796-802 (1995)

55. J. M. Walboomers, M. V. Jacobs, M. M. Manos, F. X. Bosch, J. A. Kummer, K. V. Shah, P. J. Snijders, J. Peto, C. J. Meijer, and N. Munoz: Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 189, 12-19 (1999)

56. E. S. Srivatsan, B. C. Misra, M. Venugopalan, and S. P. Wilczynski: Loss of heterozygosity for alleles on chromosome II in cervical carcinoma. Am J Hum Genet 49, 868-877 (1991)

57. A. B. Mitra, V. V. Murty, R. G. Li, M. Pratap, U. K. Luthra, and R. S. Chaganti: Allelotype analysis of cervical carcinoma. Cancer Res 54, 4481-4487 (1994)

58. R. Klaes, M. Kloor, F. Willeke, P. Melsheimer, Doeberitz M. von Knebel, and R. Ridder: Significant increase of a specific variant TSG101 transcript during the progression of cervical neoplasia. Eur J Cancer 35, 733-737 (1999)

59. J. G. Chang, T. H. Su, H. J. Wei, J. C. Wang, Y. J. Chen, C. P. Chang, and C. J. Jeng: Analysis of TSG101 tumour susceptibility gene transcripts in cervical and endometrial cancers. Br J Cancer 79, 445-450 (1999)

60. J. D. O'Boyle, M. L. Proctor, K. M. Fong, W. M. Lin, D. S. Miller, and C. Y. Muller: Role of TSG101 in uterine cervix cancer. Gynecol Oncol 75, 401-405 (1999)

61. T. H. Su, J. G. Chang, L. I. Perng, C. P. Chang, H. J. Wei, N. M. Wang, and C. H. Tsai: Mutation analysis of the putative tumor suppressor gene PTEN/MMAC1 in cervical cancer. Gynecol Oncol 76, 193-199 (2000)

62. C. P. Matthews, K. Shera, N. Kiviat, and J. K. McDougall: Expression of truncated FHIT transcripts in cervical cancers and in normal human cells. Oncogene 20, 4665-4675 (2001)

63. J. Broniarczyk, A. K. Olejnik-Schmidt, M. W. Luczak, M. T. Schmidt, M. Dabrowski, A. Jozefiak, W. Kedzia, A. Kwasniewska, and A. Gozdzicka-Jozefiak: Analysis of expression and structure of the TSG101 gene in cervical cancer cells. Int J Mol Med 25, 777-783 (2010)

64. A. Duenas-Gonzalez, M. Lizano, M. Candelaria, L. Cetina, C. Arce, and E. Cervera: Epigenetics of cervical cancer. An overview and therapeutic perspectives. Mol Cancer 4, 38-(2005)

65. Z. Sun, J. Pan, G. Bubley, and S. P. Balk: Frequent abnormalities of TSG101 transcripts in human prostate cancer. Oncogene 15, 3121-3125 (1997)

66. A. P. Stubbs, P. D. Abel, M. Golding, G. Bhangal, Q. Wang, J. Waxman, G. W. Stamp, and E. N. Lalani: Differentially expressed genes in hormone refractory prostate cancer: association with chromosomal regions involved with genetic aberrations. Am J Pathol 154, 1335-1343 (1999)

67. Z. Sun, J. Pan, W. X. Hope, S. N. Cohen, and S. P. Balk: Tumor susceptibility gene 101 protein represses androgen receptor transactivation and interacts with p300. Cancer 86, 689-696 (1999)

68. A. Llorente, Deurs B. van, and K. Sandvig: Cholesterol regulates prostasome release from secretory lysosomes in PC-3 human prostate cancer cells. Eur J Cell Biol 86, 405-415 (2007)

69. G. Ronquist and B. O. Nilsson: The Janus-faced nature of prostasomes: their pluripotency favours the normal reproductive process and malignant prostate growth. Prostate Cancer Prostatic Dis 7, 21-31 (2004)

70. A. Larsson, G. Ronquist, C. Wulfing, E. Eltze, O. Bettendorf, L. Carlsson, B. O. Nilsson, and A. Semjonow: Antiprostasome antibodies: possible serum markers for prostate cancer metastasizing liability. Urol Oncol 24, 195-200 (2006)

71. A. A. Babiker, G. Ronquist, B. Nilsson, and K. N. Ekdahl: Overexpression of ecto-protein kinases in prostasomes of metastatic cell origin. Prostate 66, 675-686 (2006)

72. B. D. Lehmann, M. S. Paine, A. M. Brooks, J. A. McCubrey, R. H. Renegar, R. Wang, and D. M. Terrian: Senescence-associated exosome release from human prostate cancer cells. Cancer Res 68, 7864-7871 (2008)

73. B. Trink, S. I. Pai, S. L. Spunt, V. Raman, P. Cairns, J. Jen, E. Gabrielson, S. Sukumar, and D. Sidransky: Absence of TSG101 transcript abnormalities in human cancers. Oncogene 16, 2815-2818 (1998)

74. Y. Oh, M. L. Proctor, Y. H. Fan, L. K. Su, W. K. Hong, K. M. Fong, Y. S. Sekido, A. F. Gazdar, J. D. Minna, and L. Mao: TSG101 is not mutated in lung cancer but a shortened transcript is frequently expressed in small cell lung cancer. Oncogene 17, 1141-1148 (1998)

75. F. Liu, Y. Yu, Y. Jin, and S. Fu: TSG101, identified by screening a cancer cDNA library and soft agar assay, promotes cell proliferation in human lung cancer. Mol Biol Rep 37, 2829-2838 (2010)

76. C. Cai, D. Zhang, P. Lu, Y. Gao, and J. Chang: [Expression and its significance of TSG101 in lung cancer tissue and lung cancer cell lines.]. Zhongguo Fei Ai Za Zhi 11, 172-177 (2008)

77. P. Lu, D. Zhang, Y. Gao, and C. Hu: [Expression and significance of TSG101, P21 and P300/CBP in squamous cell carcinoma and adenocarcinoma of the lung.]. Zhongguo Fei Ai Za Zhi 10, 197-202 (2007)

78. J. Chang, P. Lu, C. Cai, F. Li, Z. Zhong, and D. Zhang: [The Relationship between TSG101 Protein and Notch3 Receptor in Lung Cancer.]. Zhongguo Fei Ai Za Zhi 12, 111-116 (2009)

79. M. Babst, G. Odorizzi, E. J. Estepa, and S. D. Emr: Mammalian tumor susceptibility gene 101 (TSG101) and the yeast homologue, Vps23p, both function in late endosomal trafficking. Traffic 1, 248-258 (2000)

80. J. E. Garrus, U. K. von Schwedler, O. W. Pornillos, S. G. Morham, K. H. Zavitz, H. E. Wang, D. A. Wettstein, K. M. Stray, M. Cote, R. L. Rich, D. G. Myszka, and W. I. Sundquist: Tsg101 and the vacuolar protein sorting pathway are essential for HIV-1 budding. Cell 107, 55-65 (2001)

81. Q. Lu, L. W. Hope, M. Brasch, C. Reinhard, and S. N. Cohen: TSG101 interaction with HRS mediates endosomal trafficking and receptor down-regulation. Proc Natl Acad Sci U S A 100, 7626-7631 (2003)

82. K. G. Bache, A. Brech, A. Mehlum, and H. Stenmark: Hrs regulates multivesicular body formation via ESCRT recruitment to endosomes. J Cell Biol 162, 435-442 (2003)

83. M. Watanabe, Y. Yanagi, Y. Masuhiro, T. Yano, H. Yoshikawa, J. Yanagisawa, and S. Kato: A putative tumor suppressor, TSG101, acts as a transcriptional suppressor through its coiled-coil domain. Biochem Biophys Res Commun 245, 900-905 (1998)

84. A. B. Hittelman, D. Burakov, J. A. Iniguez-Lluhi, L. P. Freedman, and M. J. Garabedian: Differential regulation of glucocorticoid receptor transcriptional activation via AF-1-associated proteins. EMBO J 18, 5380-5388 (1999)

85. Q. Zhong, Y. Chen, D. Jones, and W. H. Lee: Perturbation of TSG101 protein affects cell cycle progression. Cancer Res 58, 2699-2702 (1998)

86. W. Xie, L. Li, and S. N. Cohen: Cell cycle-dependent subcellular localization of the TSG101 protein and mitotic and nuclear abnormalities associated with TSG101 deficiency. Proc Natl Acad Sci U S A 95, 1595-1600 (1998)

87. J. Ruland, C. Sirard, A. Elia, D. MacPherson, A. Wakeham, L. Li, J. L. de la Pompa, S. N. Cohen, and T. W. Mak: p53 accumulation, defective cell proliferation, and early embryonic lethality in mice lacking tsg101. Proc Natl Acad Sci U S A 98, 1859-1864 (2001)

88. C. P. Ponting, Y. D. Cai, and P. Bork: The breast cancer gene product TSG101: a regulator of ubiquitination? J Mol Med (Berl) 75, 467-469 (1997)

89. E. V. Koonin and R. A. Abagyan: TSG101 may be the prototype of a class of dominant negative ubiquitin regulators. Nat Genet 16, 330-331 (1997)

90. J. G. Carlton and J. Martin-Serrano: Parallels between cytokinesis and retroviral budding: a role for the ESCRT machinery. Science 316, 1908-1912 (2007)

91. Y. Yanagida-Ishizaki, T. Takei, R. Ishizaki, H. Imakagura, S. Takahashi, H. W. Shin, Y. Katoh, and K. Nakayama: Recruitment of Tom1L1/Srcasm to endosomes and the midbody by Tsg101. Cell Struct Funct 33, 91-100 (2008)

92. X. R. Ma, U. H. Edmund Sim, B. Pauline, L. Patricia, and J. Rahman: Overexpression of WNT2 and TSG101 genes in colorectal carcinoma. Trop Biomed 25, 46-57 (2008)

93. N. Koon, R. Schneider-Stock, M. Sarlomo-Rikala, J. Lasota, M. Smolkin, G. Petroni, A. Zaika, C. Boltze, F. Meyer, L. Andersson, S. Knuutila, M. Miettinen, and W. El-Rifai: Molecular targets for tumour progression in gastrointestinal stromal tumours. Gut 53, 235-240 (2004)

94. R. T. Liu, C. C. Huang, H. L. You, F. F. Chou, C. C. Hu, F. P. Chao, C. M. Chen, and J. T. Cheng: Overexpression of tumor susceptibility gene TSG101 in human papillary thyroid carcinomas. Oncogene 21, 4830-4837 (2002)

95. S. F. Hsu, Y. G. Goan, H. Y. Tsai, Y. R. Lin, R. T. Liu, and J. T. Cheng: An upstream regulatory element confers orientation-independent enhancement of the TSG101 promoter activity in transformed cells. Mol Biol Rep 39, 517-525 (2012)

96. D. C. Liu, Z. L. Yang, and S. Jiang: Identification of PEG10 and TSG101 as Carcinogenesis, Progression, and Poor-Prognosis Related Biomarkers for Gallbladder Adenocarcinoma. Pathol Oncol Res (2011)

97. Y. Zhao, H. You, F. Liu, H. An, Y. Shi, Q. Yu, and D. Fan: Differentially expressed gene profiles between multidrug resistant gastric adenocarcinoma cells and their parental cells. Cancer Lett 185, 211-218 (2002)

**Abbreviations:** ALG-2: apoptosis-linked gene 2; ALIX: ALG-2-interacting protein X; AR: androgen receptor; CC: coiled coil; CITED2: CBP/p300-interacting transactivator with ED-rich tail; ESCRT: endosomal sorting complexes required for transport; HIF-1α: hypoxia inducible factor 1α; HPV: human papillomavirus; LOH: loss of heterozygosity; MVBs: multivesicular bodies; PRR: proline-rich region; SB; steadiness box; TSG101: tumor susceptibility gene 101; Tal: TSG101-associated ligase; UBC: ubiquitin conjugating; UEV: ubiquitin E2 variant; Vps: vacuolar protein sorting.

**Key Words:** TSG101, Cancer, Tumorigenesis, Endosomal Sorting, Ubiquitination, Cytokinesis, Cell Proliferation, Review

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