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Review

Loss of Tumor Suppressor Gene Function in Human Cancer: An Overview

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Abstract
Cancer is a disease caused by the accumulation of genetic and epigenetic changes in two types of genes: tumor suppressor genes (TSGs) and proto-oncogenes. Extensive research has been conducted over the last few decades to elucidate the role of TSGs in cancer development. In cancer, loss of TSG function occurs via the deletion or inactivation of two alleles, according to Knudson's two-hit model hypothesis. It has become clear that mutations in TSGs are recessive at the level of an individual cell; therefore, a single mutation in a TSG is not sufficient to cause carcinogenesis. However, many studies have identified candidate TSGs that do not conform with this standard definition, including genes inactivated by epigenetic silencing rather than by deletion. In addition, proteasomal degradation by ubiquitination, abnormal cellular localization, and transcriptional regulation are also involved in the inactivation of TSGs. This review incorporates these novel additional mechanisms of TSG inactivation into the existing two-hit model and proposes a revised multiple-hit model that will enable the identification of novel TSGs that can be used as prognostic and predictive biomarkers of cancer.

Introduction

Many genetic studies in different cancers have identified a small number of genes that must be mutated or altered to promote the growth of malignant cells [1]. The two main properties of cancer cells, uncontrolled cell growth and the ability to invade other tissues, are the result of these genetic and epigenetic alternations. Genetic alternations include genetic mutations, genomic instability, loss of heterozygosity (LOH), and gene copy number variation

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(CNV). By contrast, epigenetic changes include histone modifications, DNA methylation, and loss of imprinting (LOI). These modifications regulate gene expression without altering the underlying nucleotide sequence [2-4].

In general, cancer-related genes can be divided into two broad classes, proto-oncogenes and tumor suppressor genes (TSGs). Proto-oncogenes are generally involved in pathways that promote cellular growth. These genes can cause normal cells to become cancerous when they are activated by mutations or alterations. Mutations in proto-oncogenes are typically dominant in nature, and the mutated versions of these genes are known as oncogenes [5]. TSGs is considered as another kind of crucial genes, which are involved in DNA damage repair, inhibition of cell division, induction of apoptosis, and suppression of metastasis. Therefore, loss of TSGs function would result in the onset and progression of cancer [6]. Previous study showed one copy of a TSG is sufficient to control cell proliferation; therefore, both alleles of a TSG must be permanently inactivated or lost to result in tumor development [7]. Additionally, some genes can act as both proto-oncogenes and TSGs, depending on context. TSGs are broadly classified into five types: 1) Genes encoding intracellular proteins, that control progression into a specific stage of the cell cycle (e.g., pRB and p16) [8]; 2) Genes encoding receptors or signal transducers for secreted hormones or developmental signals that inhibit cell proliferation [e.g., transforming growth factor (TGF)-β and adenomatous polyposis coli (APC)] [9]; 3) Genes encoding checkpoint-control proteins that trigger cell cycle arrest in response to DNA damage or chromosomal defects [e.g., breast cancer type 1 susceptibility protein (BRCA1), p16, and p14] [10]; 4) Genes encoding proteins that induce apoptosis (e.g., p53) [11]; and 5) Genes encoding proteins involved in repairing mistakes in DNA [e.g., p53 and DNA mismatch repair protein 2 (MSH2)] [12].

TSG inactivation is a common mechanism contributing to the development of cancer. Molecular studies show that inactivation of TSGs is commonly associated with cytogenetically undetectable microdeletions that were identified by demonstrating LOH of polymorphic markers that map within or near tumor suppressor loci [13]. Germline mutations in TSGs account for most known heritable forms of cancer, because somatic inactivation of one allele is usually compatible with normal development [14]. In addition, promoter methylation also contributes to the inactivation of TSGs [15, 16]. Most of the TSGs discovered to date follow the above Knudson paradigm (Table 1). These TSGs are recessive at the cellular level, and both alleles are deleted, mutated, or silenced by methylation in cancer. However, there is increasing evidence from studies of human tumor specimens that functional inactivation of TSGs by cellular mechanisms such as proteasomal degradation, abnormal cellular location, and transcriptional regulation can also contribute to tumorigenesis. This review provides

Table 1. Location and function of tumor suppressor genes

Gene	Familial cancer syndrome	Function	Chromosomal location
TP53	Li-Fraumeni syndrome	Cell cycle regulation, apoptosis	17p13.1
RB1	Familial retinoblastoma	Cell cycle regulation	13q14.1-q14.2
p16(INK4a)	Familial melanoma	Cell cycle regulation	9p21
p14(ARF)	Familial melanoma	Mdm2 antagonist	9p21
CHK 1/2	Li-Fraumeni syndrome	Protein kinase (G1 control)	22q12.1
KLF6	Unknown	Transcriptional regulation	10q21-q22
NF1	Neurofibromatosis type I	Catalysis of RAS inactivation	17q11.2
APC	Familial adenomatous polyposis	Inhibition of signal transduction	5q21-q22
TSC1	Tuberous sclerosis 1	Interaction with tuberin	9q34
DCC	Deleted in colorectal carcinoma	Transmembrane receptor	18q21.3
BRCA1	Familial breast cancer	Cell cycle, DNA repair	17q21
MSH2	HNPCC1	DNA mismatch repair	2p22-p21
MLH1	HNPCC2	DNA mismatch repair	3p21.3
PTEN	Cowden syndrome	PI-3 kinase signal transduction	10q23.3
LKB1	Peutz-Jeghers syndrome	Phosphorylation and activation of AMPK	19q13.3
CDH1	Familial diffuse gastric cancer	Cell-cell adhesion protein	16q22.1
TGF-R I	Unknown	Growth inhibition	9q22.33-q31.1
TGF-R II	Unknown	Growth inhibition	3p24.1
SMAD4	Familial juvenile polyposis syndrome	Regulation of TGF-β/BMP signaling	18q21.1
SMAD2	Juvenile polyposis	TGF-β signal transduction	18q21.1

an overview of the inactivation mechanisms of known TSGs that do not follow the classic Knudson two-hit hypothesis. Molecular analysis of these TSGs may reveal novel targets for specific sub-classes of cancer.

The ubiquitin-proteasome degradation pathway

Cellular levels of proteins encoded by TSGs and oncogenes must be critically regulated to prevent carcinogenesis and malignant progression. Levels of TSG products are often controlled by the ubiquitin-proteasome pathway, a specific cellular proteolysis mechanism. E3 ubiquitin ligases catalyze the polyubiquitination of their specific protein substrates by cooperation with the ubiquitin-activating enzyme E1 and the ubiquitin-conjugating enzyme E2, and then the modified substrates are degraded by the 26S proteasome [17]. Enhanced degradation of TSG products due to dysfunction of the ubiquitination-proteasome pathway or aberrant expression of E3 ligases may be associated with tumorigenesis. As an example, inactivation of TSG function via ubiquitin-proteasomal degradation is discussed below.

Inactivation of p53 TSG (TP53) by ubiquitin-proteasomal degradation

The p53 TSG (TP53) is inactivated in the majority of cancers [18, 19]. It negatively regulates the cell cycle and is involved in genomic stabilization and angiogenesis [18, 19]. Inactivation of *TP53* by homozygous deletion (HD), LOH, point mutations, and/or methylation has been frequently reported in human cancers (Table 2 – 9). In addition to these genetic inactivation mechanisms, the cellular p53 level is also regulated through ubiquitination-mediated degradation [20]. A number of RING finger domain-containing E3 ligases, including mouse double minute 2 homolog (MDM2), MDM4, herpesvirus-associated ubiquitin-specific protease (HAUSP), constitutively photomorphogenic 1 (COP1), Pirh2, and ARF-BP1, can ubiquitinate p53 [21-25]. However, MDM2 appears to be the dominant regulator, as the lethality of *MDM2* deficiency can be rescued by the loss of *TP53* [21, 26]. The E3 ligase activity of MDM2 towards p53 is significantly increased by heterodimerization with MDM4 [21, 26] . Gene amplification of *MDM2* was observed in approximately 10% of tumors [21, 26], most of which retained wild-type *TP53*. In some tumor cells, overexpression of MDM2 occur even in the absence of *MDM2* gene amplification [27]. Additionally, overexpression of

Table 2. The expression and inactivation mechanisms of tumor suppressor genes in leukemia and brain cancer. Note: "—"no report found; "HD" homozygosity deletion; "NS" no significant difference; the average percent was calculated using total case divide by positive case

	Leukemia				Brain cancer			
Genes	Expression (%)	LOH/HD (%)	Mutation (%)	Methylation (%)	Expression (%)	LOH/HD (%)	Mutation (%)	Methylation (%)
TP53	Dysregulated [18]	50 [91]	17.3 [92]	32 [93]	Dysregulated [94]	24-53% [95-97]	34 [96-98]	30-53% [99]
RB1	Low [100, 101]	30-55% [102, 103]	0% [102, 104]	—	—	0-25% [105]	0-30% [106]	21%[107]
p16(INK4a)	61% loss [100]	4-76% [101]	0-7% [101]	2-75% [101]	26% Low [100, 108]	31% [101, 109]	1-45% [101, 109]	3-19% [101, 109]
p14(ARF)	Low [110]	5% [111]	34 [112]	0-41% [112-114]	Low [115, 116]	HD 50% [117]	12% [117]	16-44% [115-117]
CHK 1/2	6% Loss [118]	0% [118]	0-2% [118, 119]	0% [118]	—	—	—	—
KLF6	Lower [120, 121]	—	—	—	80% Low [122]	43 [123]	0-5% [124, 125]	—
NF1	30.8% Downregulation [126]	Frequent [127]	0-33% [128, 129]	—	Loss [130, 131]	Rare [130, 131]	Rare [130, 131]	—
APC	Low [132]	—	—	48 [132]	NS [133]	58.8 [134]	—	0% [135]
TSC1	—	—	—	—	—	15 [136]	0% [136, 137]	—
DCC	27.6% loss [138]	8-68.4% [139-141]	—	Frequent	88% Low [142]	50 [143]	0% [143]	
BRCA1	Downregulation [144]	—	—	13 [145]	—	0% [146]	Rare [146]	0%[146]
MSH2	Low or undetectable [147]	—	—	85.7 [148]	Dysregulated [149]	—	14 [150]	
MLH1	Low	—	—	24 [151]	NS [149]	—	4 [150]	17 [152]
PTEN	Low [153]	0-20% [154-156]	NS [153]	Nil [153]	Loss [157]	53 [157]	20-40% [109, 157]	0-26% [135, 157]
LKB1	—	—	—	—	Loss [158]	19 [159]	0% [159]	—
CDH1	Loss [160]	2 [160]	—	48 [160]	Low [160]	31 [161]	0% [160]	57-66% [162]
TGF-R I	Downregulation [163]	—	—	—	NS [164]	—	Rare [165]	
TGF-R II	Low [166]	—	Rare [166, 167]	—	NS [164]	—	Rare-3% [165, 168]	—
SMAD4	Low [169]	—	Rare [169]	—	Low [164]		0% [170]	—
SMAD2	—	26 [171]	0% [172]	—	Low [164]		0% [170]	—

Table 3. The expression and inactivation mechanisms of tumor suppressor genes in head and neck and Lung cancer. Note: "—"no report found; "HD" homozygosity deletion; "NS" no significant difference; the average percent was calculated using total case divide by positive case

	Head and Neck cancer				Lung cancer			
Gene	Expression (%)	LOH/HD (%)	Mutation (%)	Methylation (%)	Expression (%)	LOH/HD (%)	Mutation (%)	Methylation (%)
TP53	Dysregulated [173]	47-66% [174, 175]	47 [176]	—	57.3 – 63.3% [177, 178]	90 [179]	88 [180]	Hypo [181]
RB1	NS [182]	42-68% [182, 183]	0% [183]	16 [184]	Altered [185]	62.5 [186]	20 [186]	—
p16(INK4a)	68% Loss [100]	2-55% [101, 187]	1-45% [101]	3-47% [101, 187]	45% Loss [178]	29 [188]	0-70% [101]	51 [189]
p14(ARF)	15% Loss [190]	27-33% [187, 191-193]	HD (12%) [194]	16-44% [187, 191-193]	20.9 [195]	23-79% [196, 197]	23 [196]	0% [196, 197]
CHK 1/2	—	—	—	—	83% Low [198]	—	Low [198, 199]	Hyper [198]
KLF6	—	30 [200]	16 [201]	—	85% Low [202]	34 [202]	0% [202]	0% [202]
NF1	—	—	—	—	—	—	8 [203]	—
APC	30% Low [204]	13-35% [205-207]	0-2% [205, 206]	10-15% [207, 208]	—	44-81% [209]	3-5% [210]	59.0% [211]
TSC1	Low [212]	40 [212]	0% [212]	—	—	0 % [213]	10.6% [213]	—
DCC	—	38 [214]	—	54.2 - 59% [215, 216]	Low [217]	50% [217-219]	Rare [218]	—
BRCA1	67% Weak [220]	—	5.72 % Rare [221]	—	51.5 [222]	—	Rare [223]	18.6 [224]
MSH2	88% Low [225]	18 [225]	0-3% [225, 226]	50 [227]	36.9 [228]	33 [229]	0% [229]	28.6 [230]
MLH1	58% Low [225]	55 [225]	0% [225, 226]	28.6 [231]	59 [229]	53 [229]	0% [229]	55 [230]
PTEN	31.2 [232]	41-71% [232]	9-23% [232]	0% [191]	32.8 [233]	Rare [234]	1.6 – 9..8% [235]	26 [234]
LKB1	Low [236]	—	12.5% [236, 237]	—	Loss [238]	65 [239]	15-30% [240]	3 [241]
CDH1	Decreased [160]	0 – 7% [160]	4-24% [160]	43 [160]	Reduced [242]	36 [243]	0% [242]	30-66% [244, 245]
TGF-R I	83% Loss [246, 247]	—	Rare [248, 249]	62 [247]	31% Loss [250]	—	Rare [251, 252]	0% [250]
TGF-R II	Decreased [246]	—	Rare [248, 249]	—	Decreased [253]	Frequent [251]	Rare [251, 252]	Frequent [254]
SMAD4	12% Failed [255]	47 [256, 257]	3 [256, 258]	—	62.5% Loss [178]	38 [218]	0% [259]	—
SMAD2	38% Loss [260]		0% [260]	—	NS [261]	—	0% [262]	—

Table 4. The expression and inactivation mechanisms of tumor suppressor genes in cancer. Note: "—"no report found; "HD" homozygosity deletion; "NS" no significant difference; the average percent was calculated using total case divide by positive case

	Esophageal cancer				Gastric cancer			
Gene	Expression (%)	LOH/HD (%)	Mutation (%)	Methylation (%)	Expression (%)	LOH/HD (%)	Mutation (%)	Methylation (%)
TP53	41.9 [263]	67.5 [264, 265]	50 – 60 [266]	—	Overexpression [267]	0-83% [267]	0-77% [267, 268]	0% [267, 268]
RB1	6.5 [269]	34 [269]	9 [270]	44 [271]	NS [272]	29 [272]	—	—
p16(INK4a)	Loss [101]	17 - 22 [101, 273]	0-52% [101]	19 - 62% [101, 273]	Loss [101]	0-9% [101]	0-2% [101]	17 - 42% [101, 274, 275]
p14(ARF)	Loss [273, 276]	33 [273, 276]	0% [273, 276]	0-19% [273, 276]	Loss [277]	71.4 [275, 277]	0% [274]	24 - 33% [274, 277]
CHK 1/2	Loss	—	—	—	Overexpression [278]	—	2% [250, 279]	—
KLF6	—	—	Frequent [280]	—	48% Reduce [281]	43% [282]	5% [282]	—
NF1	—	80% [283]	—	—	NS [284]	—	—	—
APC	11% Low [285]	29% [285, 286]	10% [287]	68-78% [215, 288]	78% Loss [289]	37% [290, 291]	20% [292, 293]	84% [293]
TSC1	—	—	—	—	—	—	—	—
DCC	Low [294]	23% [295]	4% [295]	74% [294]	Loss [296]	35% [297, 298]	0% [296]	45% [296, 298]
BRCA1	88.6% [299]	—	—	—		40% [300]	—	—
MSH2	20% Low [301]	—	—	48.3% [302]	Low [303, 304]	—	17 % [305-307]	17% [307]
MLH1	27% [308]	—	—	60% [309]	Low [304]	—	21% [307]	4.6% [306, 307]
PTEN	NS [310]	9% [311]	3% [312]	18.9% [313]	Low [314]	4.4% [315]	18.7% [316]	39% [317]
LKB1	—	—	—	—	Low [318]	—	11% [318]	—
CDH1	59.6% [319]	68% [160]	2% [311]	97.9% [319]	Low [160]	10-24% [160]	0-41% [160]	49-75% [160]
TGF-R I	54% Low [320]	—	Rare [321]	—	82% Low [322]	—	—	12.5-50% [323, 324]
TGF-R II	29% Low [320]	—	Rare [321]	—	42% Loss [325]	33% [324, 326]	10% [324, 326]	
SMAD4	68% Loss [327]	46% [328]	5.9% [287]	70% [329]	40% Loss [75]	29-41% [75, 330]	rare	5% [75]
SMAD2	Low [331]	35% [331]	0% [254]	—	Low [75, 330]	Frequent [332]	0% [333]	—

MDM4 has been found in approximately 10% of all tumors and in 65% of retinoblastomas [21, 28]. Viruses may also promote the degradation of p53. The human papilloma virus E6 protein forms a complex with the homologous to the E6 carboxyl terminus (HECT) domain of E3 ubiquitin ligase, which results in the ubiquitination and degradation of p53 [21, 29, 30]. These findings are consistent with the idea that the ubiquitin-proteasome pathway promotes tumorigenesis through the loss of p53 function.

Table 5. The expression and inactivation mechanisms of tumor suppressor genes in cancer. Note: "—"no report found; "HD" homozygosity deletion; "NS" no significant difference; the average percent was calculated using total case divide by positive case

	Colorectal cancer				Pancreatic Cancer			
Gene	Expression (%)	LOH/HD (%)	Mutation (%)	Methylation (%)	Expression (%)	LOH/HD (%)	Mutation (%)	Methylation (%)
TP53	Overexpression [334]	66% [335-338]	45% [334]	—	Overexpression [339]	-	43% [340-342]	—
RB1	NS [343]	50% [344]	—	—	NS [345]	6% [346]	—	—
p16(INK4a)	27% Loss [101]	81% [347]	—	10-53% [101]	85% Loss [100, 101]	30% [101]	17-38% [101]	13% [101]
p14(ARF)	Loss [348]	—	—	4-28% [349-351]	53% Loss [352]	—	Rare [353]	0-14% [354, 355]
CHK 1/2	50% decreased [356]	Frequent [357]	—	Rare [358]	Overexpression [359]	—	—	—
KLF6	37% Loss [360, 361]	29-52% [361, 362]	17-45% [361-363]	—	—	0% [364]	0% [364]	—
NF1	Overexpression [365]	14-57% [344, 365, 366]	3-8% [366, 367]	—	—	—	—	—
APC	Low [368, 369]	30-47.8 % [338, 370, 371]	26.7-83% [371, 372]	10-50% [369, 373]	Loss [374]	Rare [375, 376]	40% [375, 376]	10-45% [354]
TSC1	—	—	—	—	—	—	—	—
DCC	40% decreased [377, 378]	64.3% [338, 344, 378]	17% [378]	82.7% [379]	59% Loss [346, 380]	50% [381]	—	—
BRCA1	Decreased [382]	39.8% [383, 384]	—	—	Down-regulation [300]	—	Rare [385]	—
MSH2	33.3% reduced [386, 387]	Frequent [388]	Rare [389, 390]	10% [387]	14% Loss [391]	—	0% [392]	—
MLH1	50% reduced [386, 387]	Frequent [388]	Rare [389, 390]	18-39% [350, 351]	NS [391]	—	0%[392]	4%[393, 394]
PTEN	34.3% Loss [395]	9% [157]	2-8% [157, 395]	27.3% [394, 395]	Decreased [396, 397]	35% [398]	0% [398]	Frequent [396]
LKB1	—	13-52.6%[399, 400]	0-53.8% [399, 400]	8%[400]	7% Loss [401]	32% [402]	4-6%[402]	—
CDH1	Reduce [160]	13%[160]	0%[160]	20,46% [160, 403]	45% reduce [404]	—	—	29%[405]
TGF-R I	Down-regulation [406]	—	—	—	NS [407]	—	Rare [408]	—
TGF-R II	Down-regulation [406]	—	10-30% [409, 410]	0% [409]	Overexpression [407]	—	Rare [408]	—
SMAD4	38% Loss[381]	35%[411]	6-16% [411, 412]	0% [413]	55% Loss [414]	30-37% [69, 415]	16-44% [415]	-
SMAD2	Loss [416]	10% [417]	0% [417]	—	Overexpression [418]	—	—	—

Table 6. The expression and inactivation mechanisms of tumor suppressor genes in cancer. Note: "—"no report found; "HD" homozygosity deletion; "NS" no significant difference; the average percent was calculated using total case divide by positive case

	Hepatocellular cancer				Bladder cancer			
Gene	Expression (%)	LOH/HD (%)	Mutation (%)	Methylation (%)	Expression (%)	LOH/HD (%)	Mutation (%)	Methylation (%)
TP53	Overexpression [419]	16% [420-422]	51% [420-422]	20% [423, 424]	Overexpression [425]	73% [426]	23-61% [425, 427, 428]	—
RB1	Loss [424, 429]	33-50% [429, 430]	15%[429]	0-26% [424, 431]	—	12.5-29% [432, 433]	27% [434]	28% [435]
p16(INK4a)	46% Loss [436]	7% [436-438]	0%[436-438]	24-84% [436-438]	Loss [100, 439, 440]	32% [100, 101, 439, 440]	0-7% [100, 101, 439, 440]	23% [100, 101, 439, 440]
p14(ARF)	NS [441]	69% [438, 441, 442]	4% [441, 442]	0-39% [441, 442]	—	22% [443]	—	42% [444, 445]
CHK 1/2	High [446]	—	—	—	10% Reduce [447]	6% [448]	3% [447, 448]	—
KLF6	Loss [449]	39% [450]	0-5% [450, 451]	1% [452]	—	—	—	—
NF1	Rare	—	—	—	Decreased [453]	31% [454, 455]	Rare [456]	—
APC	Reduce [457]	14% [458, 459]	3% [424, 458, 460]	53-82% [457, 461]	NS [462]	6-10% [462, 463]	0% [462]	35% [464]
TSC1	—	—	16.2%[465]	—	—	32.4% [466]	7-11% [466-468]	—
DCC	—	14% [459]	—	Rare [469]	—	36% [463]	—	NS [470]
BRCA1	—	12% [459]	—	0% [438]	—	—	—	—
MSH2	18% Reduce [471]	20% [472]	34% [473, 474]	68% [475]	Loss [476, 477]	4% [477]	0-73% [478, 479]	—
MLH1	38% Reduce [471]	20%[472]	—	13.2% [475]	Loss [476, 477]	2% [477]	0% [480]	Rare [481]
PTEN	35% Loss [482]	—	3% [398]	0% [438]	53% decreased [483]	24% [398]	2% [398]	—
LKB1	Overexpressed [484]	22% [485]	1% [485]	4.2% [486]	NS [487]	—	—	—
CDH1	Reduce [160]	46% [160]	0% [160]	41%[160]	Reduce [160]	14% [160]	3% [160]	43% [160]
TGF-R I	Reduce [488]	—	—	—	NS [489]	—	5% [490]	—
TGF-R II	Reduce [488]	—	0% [491]	—	Reduce [489]	—	—	—
SMAD4	Overexpression [492]	—	3% [493, 494]	—	68% Reduce [495]	84% [495]	—	—
SMAD2	Reduce [482]	—	Rare [493, 494]	—	34% Reduce [495]	—	—	—

Inactivation of INK4A/ARF via ubiquitin-proteasomal degradation

$p16^{INK4A}$ and $p14^{ARF}$ are well-studied pro-apoptotic proteins due to their critical role in cell cycle arrest and cellular senescence, and their consequent association with malignancy [31-33]. Numerous studies have investigated the mechanism of inactivation of the *INK4A/ARF* locus in human cancers (Table 2 –9). Like p53, $p14^{ARF}$ is a direct target of polyubiquitination and proteasomal degradation. $p14^{ARF}$ specifically binds to MDM2, which has E3 ligase activity and induces the proteasomal degradation of MDM2. Thus, $p14^{ARF}$ stabilizes transcriptionally

Table 7. The expression and inactivation mechanisms of tumor suppressor genes in cancer. Note: "—"no report found; "HD" homozygosity deletion; "NS" no significant difference; the average percent was calculated using total case divide by positive case

Renal cancer				Prostate cancer		
Expression (%)	LOH/HD (%)	Mutation (%)	Methylation (%)	Expression (%)	LOH/HD (%)	Mutation (%)
Overexpression [496]	20-48% [426, 497-499]	0-33% [498-500]	NS [501]	Overexpression [496, 502]	32-39% [502-504]	6-13% [502, 503, 505]
Weak [506]	60% [497, 507]	Rare [508]	NS [445]	Loss [509, 510]	5-60% [509-511]	16% [512]
52.9% Weak [506, 514]	2-16% [101]	NS [515]	10-35% [101, 514, 516, 517]	Loss [100]	4% [101]	0-6%[101]
Reduce [519]	23.5-83% [519, 520]	-	0- 17% [516, 520]	Loss [521]	4% [521]	—
—	—	—	—	—	NS [523]	1.2% [524]
—	—	5% [525]	—	Loss [526, 527]	19% [526, 528]	55% [526]
—	—	Rare [456]	—	—	—	—
Loss [529]	14-43% [507, 529, 530]	3% [529]	14-29% [516, 517]	—	20%[531]	3-10% [511, 532]
—	7-18% [525, 534]	0% [534]	—	—	—	—
Reduce [535]	7% [497, 536]	—	—	Reduce [537]	26-29% [531, 537]	Rare [538]
Moderate [539]	0% [539]	—	—	Reduce [540]	17% [541]	Rare [541, 542]
Loss [544, 545]	—	—	Frequent [545]	Reduce [546]	—	83% [547, 548]
Loss [544, 545]	35% [481]	—	0% [481, 549]	Reduce [546]	—	—
Overexpression [550]	27% [398]	5-7% [398, 525]	—	Reduce	33% [398]	15% [398]
—	—	—	—	—	—	—
67%Lacked [551]	7.5% [530]	—	11-67% [516, 517]	Reduce [160]	38% [160]	0% [160]
—	—	5% [490]	—	Reduce [552]	—	—
Reduce [553]	—	—	—	Reduce [552]	—	12% [554]
Reduce [556]	13% [557]	0%[490]	—	Loss [558]	10% [559]	Rare [559]
NS [561]	—	—	—	NS [562]	—	0% [562]

Table 8. The expression and inactivation mechanisms of tumor suppressor genes in Breast and Ovarian cancer. Note: "—"no report found; "HD" homozygosity deletion; "NS" no significant difference; the average percent was calculated using total case divide by positive case

	Breast cancer				Ovarian cancer			
Gene	Expression (%)	LOH/HD (%)	Mutation (%)	Methylation (%)	Expression (%)	LOH/HD (%)	Mutation (%)	Methylation (%)
TP53	Overexpression [563]	49% [564-566]	8-39% [505]	11.5% [567]	Low/High [568, 569]	44 -63% [570-572]	20.7-23% [572, 573]	51.5% [574]
RB1	Loss / reduced [575, 576]	26-47% [577, 578]	Nil [576]	Nil [576]	83% Loss [579]	61% [580]	67% [581]	—
p16(INK4a)	48.9% Low [100, 582]	0-10% [101, 583]	3-5%[101]	17-38.3% [101, 582]	Reduced [100, 584]	0-14% [101]	0 -11% [101]	0-43% [101, 584, 585]
p14(ARF)	Overexpression /Loss [586]	21% [583, 586]	0% [583]	24% [583]	Absent [587]	—	—	0-18% [588, 589]
CHK2	Reduce [590, 591]	44% [358]	Rare [590, 592, 593]	Nil [592]	23% Negative [358]	54% [358]	2.3% [593, 594]	Rare [358]
KLF6	Reduce [595, 596]	—	Rare [595]	—	Reduce [597]	59% [597]	—	—
NF1	—	Frequent [598]	0-27.7% [598, 599]	—	Reduce [600]	56% [601]	0-14.5% [602, 603]	—
APC	41% Reduce [604, 605]	23-38% [606-608]	0-6% [607, 608]	30.6% [609]	Absent [610]	50% [611-613]	0-89% [613, 614]	16-22% [585, 615]
TSC1	Reduce [616]	—	—	Frequent [616]	—	—	—	—
DCC	56% Reduce [604, 617]	31% [605, 618]	—	—	59% Loss [619, 620]	38% [621]	—	—
BRCA1	Loss [622]	21-42% [623]	3.9% [624]	11-31% [609, 625]	72% Decreased [626]	66% [626]	15% [627]	31% [626]
MSH2	28% Reduce [628]	Frequent [629, 630]	9% [631]	16% [629]	38% Loss [632]	12.5% [633]	0.18% [634]	—
MLH1	Reduce [635]	Frequent [630]	25% [631]	31-44% [631]	56% Loss [636]	47% [637]	8.2% [573]	12.5% [638]
PTEN	55.1% Reduce [639, 640]	31-63.3% [398, 640]	2-5% [398, 641]	48% [641]	37.5% Reduce [642]	39% [398]	8%[398]	12.5% [643]
LKB1	Low / Overexpression [644, 645]	31.5% [646]	Nil [647]	Rare [648]	54% Loss [649]	24% [650]	4% [650]	—
CDH1	Loss [651]	73% [606]	22% [606]	41% [606]	Reduce [652]	—	Rare [160]	13-26% [160, 585]
TGF-R I	Overexpression [653]	—	—	—	NS [654]	—	31% [655]	—
TGF-R II	Overexpression [653]	—	0-24% [656]	—	Reduce [654]	—	25% [655, 657]	—
SMAD4	Loss [658]	Frequent [659]	—	—	NS [660]	42% [661]	3.8% [662]	—
SMAD2	Reduce [663]	Frequent [663]	—	—	28%loss[674]	46% [661]	37.5% [655]	—

active p53 by inducing the degradation of MDM2 [34, 35]. Similarly, MDM2 overexpression in several cancer cell line causes p14ARF degradation via proteasome [36]. Thus, p14ARF-mediated disruption of p53 pathway mechanisms have been found in number of carcinomas [37].

Table 9. The expression and inactivation mechanisms of tumor suppressor genes in cervical and endometrial cancer. Note: "—"no report found; "HD" homozygosity deletion; "NS" no significant difference; the average percent was calculated using total case divide by positive case

Cervical cancer				Endometrial cancer		
Expression (%)	LOH/HD (%)	Mutation (%)	Methylation (%)	Expression (%)	LOH/HD (%)	Mutation (%)
Over/Low [664, 665]	20% [666, 667]	Rare [667, 668]	12% [669]	Over /Low [670-672]	19-32% [673-675]	14-22% [672, 675-677]
Low [679, 680]	62.8% [679, 681]	—	4.8% [669]	NS [682]	33% [683]	—
Overexpression [665, 684]	17% [681, 685]	15% [685]	6.5-36% [685, 686]	18% Loss [100]	8-13% [687, 688]	13% [687, 688]
Overexpression [684]	—	—	8.8% [686]	Low [690]	—	—
2.4% Expression [691]	—	—	—	Reduce [692]	—	Nil [692]
Altered [693]	—	—	—	—	—	—
—	—	—	—	—	—	9% [694]
Increased [695]	30% [696]	—	32% [697]	Reduced [698, 699]	24.3-60% [699, 700]	Nil [700]
—	—	—	—	Loss [701]	—	2% [694]
Reduce [702]	40% [703]	—	0-39.8% [704]	Loss [705]	14-30% [705]	—
Downregulation [706]	5-9% [707]	—	6% [706]	Loss [708]	24% [674]	3% [709, 710]
32% Loss [711]	—	9.7% [712]	—	Loss [713, 714]	Low [715]	Low [716]
Overexpression [718]	—	5.5% [712]	5.7% [719]	Loss [713, 714]	Frequent [720]	10-20% [720]
Downregulation [722, 723]	36% [398]	4% [398]	62% [723]	43% Loss [670, 701]	50% [398]	45% [398, 694]
Loss [724]	—	20% [725]	—	Loss [701]	—	Nil [726]
Reduce [160]	15% [160]	4% [160]	28% [160, 727]	Reduce [728]	—	Rare [729]
Overexpression [731]	—	43% [732]	—	Reduce [733]	—	2.6% [734]
NS [731]	60% [735]	6% [732]	—	Reduce [733]	—	17% [734]
24% Loss [737, 738]	10-37% [330, 737]	Rare [737]	0% [673]	Reduce [739]	21.4% [739]	22%HD [739]
Reduce [738]	10-37% [330, 740]	Nil [330]	—	Reduce [741, 742]	15% [743]	—

Inactivation of TGF-β family genes via ubiquitin-proteasomal degradation

Members of the TGF-β family are multifunctional proteins that are critically involved in many cellular process, including cell growth, survival, differentiation, migration, and apoptosis [38]. Alterations in their downstream signaling pathways are associated with a wide range of diseases, including cancer [38]. Among the TGF-β pathway members, TGF-β receptor I, TGF-β receptor II, SMAD4, and SMAD2 are considered to be classic TSGs. In certain cancers, TGF-β signaling is disrupted due to the somatic mutations in components of the TGF-β signaling pathway (Table 2 – 9). E3 ubiquitin ligases play an important role in the recognition and degradation of TGF-β family target proteins by the 26S proteasome. Ubiquitination of SMADs regulates the TGF-β signaling; SMAD ubiquitin regulatory factor (Smurf1, Smurf2), a HECT-type E3 ubiquitin ligases and ROC1-SCF^{Fbw1a}, a RING finger-type E3 ubiquitin ligase, have all been participate in the proteasomal degradation of TGF-β signaling members [39, 40]. Smurf1 and Smurf2 bind to TGF-β family receptors through the inhibitory SMADs, SMAD6 and SMAD7, to induce their ubiquitin-dependent protein degradation. Thus, dysregulation in E3 ubiquitin ligases that regulate tumor suppressors of the TGF-β family may lead to carcinogenesis and malignant progression of various cancers. Therefore, knowing the status of TGF-β and/or its downstream signaling mediators creates an opportunity for the use of selective inhibitors.

Mislocalization of tumor suppressor proteins

Tumor suppressor proteins are regulated by multiple events to avoid abnormal cellular proliferation, promote apoptosis, or both. Translocation of tumor suppressor proteins provides an efficient means of transducing signals between specific cellular compartments. Certain tumor suppressor proteins show different patterns of localization in normal and

cancer cells, and impaired spatiotemporal dynamics of tumor suppressor protein signaling has been shown to be involved in carcinogenesis and malignant progression [41, 42]. Next, we discuss several examples of how the mislocalization of tumor suppressor proteins can lead to tumorigenesis.

Inactivation of RB1 by mislocalization

RB1 is considered a classical TSG. The protein encoded by this gene is a negative regulator of the cell cycle. Inactivation of *RB1* through somatic mutation, deletion, or epigenetic silencing in various cancers is summarized in Table 2 – 9. Hypophosphorylated pRB binds to and represses the transcriptional activity of E2F family members, which control the expression of genes necessary for cell cycle progression [43]. By contrast, pRB that is serine-phosphorylated by cyclin-dependent kinase 3 (CDK3)/cyclin-C has been shown to facilitate re-entry into the cell cycle by G0-arrested cells. pRB that is cytoplasmically mislocalized by exportin 1-mediated nuclear export may also promote tumor formation [44, 45]. In addition, some pRB-related proteins can also affect its subcellular localization. A-type nuclear lamins (lamin A/C), core components of the nuclear matrix, can tether pRB and lead to cell cycle arrest [46]. By contrast, co-expression of cyclin E and simian vacuolating virus 40 (SV40) large T antigen inactivates pRB by disrupting its nuclear accumulation [47]. Another report reveals that pRB export from nucleus is regulated by its association with exportin-1, which is dependent on CDK-mediated phosphorylation of pRB at C-terminal phosphoresidues [48]. These data imply that nucleocytoplasmic mislocalization of pRB could be effectively reversed by inhibition of CDK activity. Thus, CDK inhibitors have tremendous clinical potential and promise in human cancer.

Inactivation of TP53 by mislocalization

p53 is a transcription factor (TF) that activates stress response genes involved in cell cycle checkpoints or cell death in response to DNA damage [49, 50]. However, in several types of cancer (including colon cancer, breast cancer, ovarian cancer, retinoblastoma, and neuroblastoma), wild-type p53 is inactivated due to abnormal subcellular localization [51]. In these situations, the function and activity of p53 remains intact. p53 contains a nuclear import/localization signal (NLS) and a nuclear export signal (NES) that mediate p53 translocation into the nucleus via nuclear transport receptors. For example, the function of p53 is also regulated by promyelocytic leukemia-nuclear bodies (PML-NBs) at the subnuclear level [52]. The PML protein forms a stable complex with p53 and cyclic AMP response element-binding protein (CREB) within PML-NBs and promotes p53 acetylation, which promotes apoptosis [53]. Loss of PML has been reported in many human cancers, so it is possible that functional inactivation of p53 could result from abnormal subcellular location induced by disruption of PML-NBs. In addition, several post-translational modifications of p53, such as sumoylation, glycosylation, neddylation, and ribosylation, also regulate p53 subcellular location [54]. p53 accumulation in the nucleus results in cell cycle arrest, senescence, and apoptosis. Thus, recent cancer treatment strategies attempted to induce wild type p53 nuclear retention or accumulation of p53 protein as a result of enhanced stabilization, resulting in apoptosis [55, 56].

Inactivation of BRCA1 by mislocalization

The familial breast cancer susceptibility gene *BRCA1* encodes a 220 kDa phosphorylatable TF with tumor suppressor activity. BRCA1 plays an important role in multiple biological pathways, including transcriptional regulation, proper genomic repair, cell proliferation, and apoptosis [57]. Reports of misregulation of *BRCA1* through somatic mutation, deletion, or epigenetic silencing in various cancers are summarized in Table 2 – 9. In addition, the subcellular localization of BRCA1 plays an important role in its tumor suppressor function. Many breast and ovarian cancer cell lines and primary tumors exhibit high levels of cytosolic BRCA1. The RING finger element of BRCA1 mediates nuclear import by association with its binding partner, BRCA1-associated RING domain protein 1 (BARD1) [58]. The structure of

the BRCA1/BARD1 heterodimer predicts that the BRCA1 NES lies within the RING finger domain that mediates shuttling of BRCA1 into the cytoplasm [59]. This raised the possibility that BARD1 binding masks the NES at the N-terminus of BRCA1 and prevents association with chromosome region maintenance protein 1 (CRM1), thereby causing nuclear retention of BRCA1 [59]. Specifically, cancer-associated germline mutations in the C-terminus of BRCA1 restrict it to the cytosol and repress its nuclear function, particularly in response to DNA damage [57, 59, 60]. Furthermore, it is not known whether other RING finger domain-binding proteins such as BRCA1-associated protein 1 (BAP1) also interact with BRCA1 to inhibit its control of cell growth. In the context of cancer, studies into how the intracellular shuttling of BRCA1 and its misregulation by somatic mutations alter its activity could provide insights into novel clinical applications.

Inactivation of APC by mislocalization

Loss of APC from mutation, epigenetic silencing, or hypermethylation of the promoter has been reported in many human cancers (Table 2 – 9). This tumor suppressor is generally localized within the cytoplasm of healthy cells but has been shown to localize to the nucleus of human cancer cells [61], where it binds to and exports the oncogenic product β-catenin [62]. APC contains two classical NLSs and two functional NESs near the N-terminus that mediate shuttling between the nucleus and the cytoplasm by association with exportin-1 [63, 64]_ENREF_58. Direct regulation of APC during cell proliferation comes from casein kinase-2 (CK2), which binds to and phosphorylates APC at the N-terminus, resulting in its nuclear translocation [65],[66]. In addition, the subcellular localization of APC is regulated by its binding partners. Other nuclear binding partners for APC are the protein tyrosine phosphatase PTP-BL, the TF activator protein-2α (AP-2α), and the nuclear export factor exportin-1 [66]. Recent research in mouse models revealed that nuclear APC regulates epithelial cell proliferation by inhibiting canonical WNT signaling in intestinal tissue, suggesting that the subcellular distribution of APC plays an important role in cancer progression [67]. Several therapeutic treatment approaches aimed at restoring APC localization and its function in Wnt/β-catenin signaling have been developed.

Inactivation of SMAD4 by mislocalization

Mothers against decapentaplegic homolog 4 (*SMAD4*) is a TSG associated with gastrointestinal carcinogenesis. As a member of the TGF-β signaling family, SMAD4 is involved in many cell functions including differentiation, apoptosis, and cell cycle control [68, 69]. In human cancers, the *SMAD4* gene can be damaged by mutation or LOH or silenced by gene deletion (Table 2 – 9). Furthermore, abnormal subcellular distribution of SMAD4 may also result in loss of its function. A previous study demonstrated that, in unstimulated cells, the NLS in its MAD homology 1 (MH1) domain and the leucine-rich NES in its linker region are both constitutively active, with the result that SMAD4 is shuttled continuously between the nucleus and the cytoplasm [70]. Activation of the SMAD4 NES is dependent on exportin-1, while the export of SMAD2/3 from the nucleus is clearly independent of this factor [71]. Treatment of cells with the exportin-1 inhibitor leptomycin B (LMB) causes a rapid accumulation of SMAD4 in the nucleus, which confirms that SMAD4 is exported by this specific exportin [71]. In addition, certain retention factors, including microtubules [72] and nuclear import proteins such as the E26 transformation-specific (ETS)-related TFs (ELFs) [73, 74], have also been implicated in the regulation of the subcellular distribution of SMAD4. Previously, we found that, in advanced gastric carcinomas, 41% of samples that were negative for SMAD4 nuclear staining had moderate-to-high cytoplasmic SMAD4 staining. This pattern of SMAD4 accumulation correlated with cytoplasmic accumulation of SMAD2/3 [75]. Therefore, dysregulation of nuclecytoplasmic shuttling may be another mechanism leading to functional loss of nuclear SMAD4.

TF regulation

TFs are key drivers of cell proliferation, and maintain the balance of expression of pro-apoptotic and anti-apoptotic genes. These factors typically bind to specific enhancer elements and/or other proteins of the transcriptional machinery, and can also recruit co-activators or co-repressors and RNA polymerase II directly, leading to expression or repression of key regulatory genes involved in tumorigenesis. Here, we provide a basic overview of a few TSGs that are inactivated by aberrant TF regulation.

Inactivation of CDH1 by aberrant TF regulation

E-cadherin (CDH1) is a cell adhesion molecule that is essential in maintaining the integrity of cell-cell contacts in epithelial cell layers [76]. Loss of *CDH1* enhances the invasiveness of epithelial tumor cells [77]. Dysregulation of CDH1 occurs in many human cancers, as a result of *CDH1* gene mutation, LOH, or epigenetic promoter methylation (Table 2 – 9). Hypermethylation and chromatin remodeling of the *CDH1* gene have emerged as the main mechanisms responsible for the downregulation of *CDH1* in most carcinomas. It was recently reported that dysregulation of CDH1 expression also contributes to the progression of cancer. The Snail family TFs, including the zinc finger factors Snail and Slug, play a vital role in the transcriptional repression of *CDH1* and induce epithelial-mesenchymal transition (EMT) by altering gene transcription during the invasion process [77]. The two-handed zinc finger proteins ZEB1 and ZEB2 and the basic helix-loop-helix (bHLH) family proteins E12/E47 are also able to repress *CDH1* expression. TWIST1 is a transcriptional repressor of *CDH1*, and an inverse correlation between TWIST1 and CDH1 expression has been reported in invasive lobular breast carcinoma [77]. These findings implicated TWIST1 in tumor cell intravasation, the process through which tumor cells enter into the circulation to seed metastases. More recently, another study demonstrated that the tumor suppressor Kruppel-like factor 6 (KLF6) directly transactivates the *CDH1* promoter [78]. These combined findings highlight multiple mechanisms through which aberrant TF regulation can lead to inactivation of the *CDH1* gene.

Inactivation of PTEN by aberrant TF regulation

Phosphatase and tensin homolog on chromosome 10 (*PTEN*) is a potent TSG located at chromosome 10q23.31. In many human cancers, *PTEN* is inactivated by mutation or epigenetic mechanisms, and PTEN protein stability or function can be weakened by other mechanisms [79, 80]. Inactivation of *PTEN* by HD, LOH, point mutations, or aberrant methylation is summarized in Table 2 – 9. However, in many cancers, the *PTEN* gene is intact, but appears to be transcriptionally silent. PTEN is a rapidly degraded protein with a half-life of less than 4 hours, and it appears that many of the genetic alterations found in *PTEN* in cancer cells further accelerate this rapid degradation. Sukhatme *et al.* found that the early growth response 1 (*EGR1*) TF binds directly to a consensus motif in the *PTEN* promoter and activates gene transcription, and is necessary for the upregulation of *PTEN* mRNA in response to UV light and other stress stimuli [81, 82]. In addition, Stambolic *et al.* demonstrated that *PTEN* transcription can also be induced by p53, which binds to a site in the promoter close to the EGR1-binding site [83]. The *TP53* TSG is the most common functionally lost gene in human cancers. Moreover, several reports show that the APE1/Ref-1 pathway also regulates the expression of *PTEN* [84, 85]. Therefore, it is possible that dysregulation of these TFs can inactivate PTEN function.

Inactivation of KiSS1 by aberrant TF regulation

KiSS1 was first identified as a TSG in melanoma. Lee et al. found that the expression of KiSS1 was negatively related to the metastasis potential of melanoma cell lines and clinical samples [86]. Later, the loss or downregulation of KiSS1 was found in various metastatic cancers, including ovarian cancer, endometrial cancer, gastric cancer, bladder cancer, brain cancer, and prostate cancer, which further verify its metastatic suppressor role in cancer

progression [87]. The LOH, promoter methylation, or gene mutation might be responsible for downregulation of it in part of tumor cases [87]. Besides the above genetic and epigenetic regulation, dysregulation of TF was also demonstrated to contribute the downregulation of KiSS1. Previous study showed that transcription factors, including TCF21, CUX1, YY1, EAP1, and TTF1, could regulate the expression of KiSS1 at mRNA level [88, 89]. Recent research showed that loss of TCF21 in metastatic melanoma would result in the downregulation of KiSS1 and subsequently contribute to metastasis [88]. Furthermore, inactivation of CUX1 was also reported in acute myeloid leukemia [90]. Therefore, the above-mentioned data suggesting aberrant regulation of TFs would become an extra hit to inactivate KiSS1 gene. Hence, a better understanding of the multiple mechanisms that regulate TSG expression and their roles in cancer progression will enhance current treatment strategies.

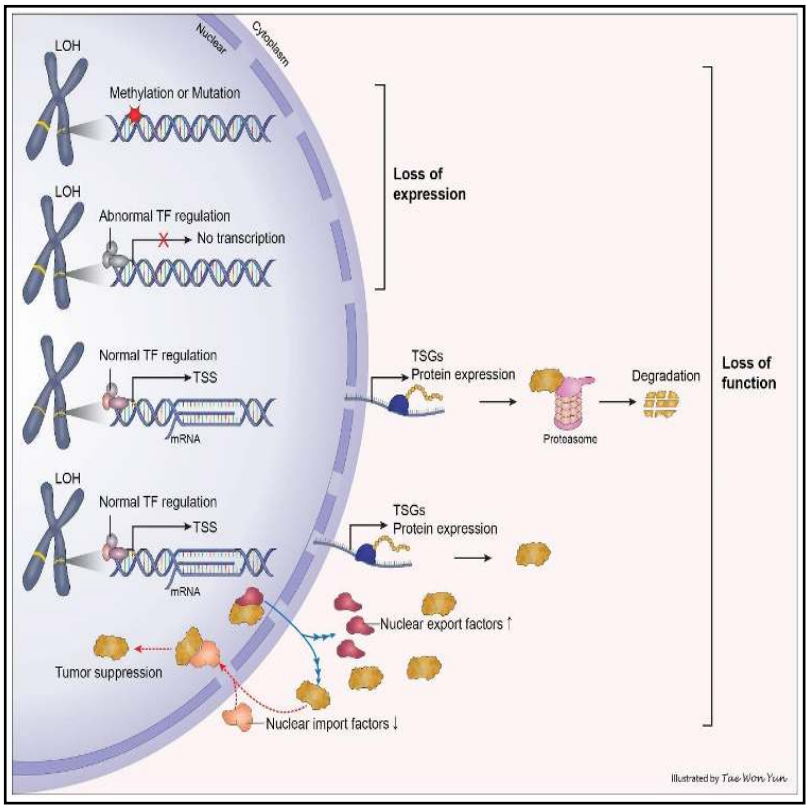

Fig. 1. A brief summary of "multiple hit" model for the loss of tumor suppressor gene function in human cancer.

Conclusion

Many reports demonstrate that the "two-hit" model, in which a genetic and an epigenetic event lead to loss of TSG expression, does not fully explain the inactivation of TSGs in human cancers. Therefore, we propose a revised "multiple-hit" model for the inactivation of TSGs, which includes a non-genetic/epigenetic event such as transcriptional regulation, proteasome degradation, or abnormal nucleocytoplasmic shuttling (Fig. 1). This revised "multiple-hit" model incorporates the inactivation of TSGs at the molecular level and could suggest novel targets for anti-cancer therapy.

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Disclosure Statement

The authors declare no competing interests.

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