INTRODUCTION

A gene is defined as a tumor-suppressor gene (TSG) if its mutation predisposes the animal to cancer. A TSG encodes for a protein that blocks tumor development, negatively regulating cell proliferation and/or contributing to the maintenance of genome stability. Tumor suppressors fall into two classes: caretakers and gatekeepers. Caretakers suppress cancer by repairing damaged DNA (e.g., BRCA1/2, MSH2, etc.), whereas gatekeepers suppress cancer by halting the cell cycle long enough to repair damaged DNA (e.g., p53, pRb, etc.) (1,2).

TIP30, also known as HTATIP2 or CC3, is a tumor-suppressor gene initially identified in 1997. The CC3 gene was first identified from a differential display analysis of messenger RNAs (mRNA) from highly metastatic human variant small-cell lung carcinoma (v-SCLC) versus less metastatic classic small-cell lung carcinoma (c-SCLC) cell lines (3). Following the CC3 discovery, human TIP30 (tat-interacting protein of 30 kDa) was first identified in 1998, in a separate research study aimed at identifying proteins that can bind to human immunodeficiency virus-1 (HIV-1) transcription protein Tat, which is encoded by HIV-1 genome, functioning primarily to increase the level of transcription during viral replication (4,5). The amino acid sequence of human TIP30 protein was 98% identical to that of human CC3, which is evolutionarily highly conserved ubiquitously expressed as a 27-kDa protein in many human normal tissues, including the heart, brain, lung, kidney, skeletal muscle, and pancreas. Subsequently, it was realized that CC3 and TIP30 were in fact one and the same protein (6). However, the precise cellular function of TIP30/CC3 remains unclear. Sequence analysis showed that TIP30/CC3 is a member of short-chain dehydrogenases/reductase (SDR) family, a large protein family of NAD(P)(H)-dependent enzymes with over 2,000 annotated enzymes with minimally 60 genes found in the human genome (7–9).

TIP30/CC3 was first identified and characterized as a “candidate” tumor-suppressor gene in 1997. Recently, the TIP30 tumor-suppressor status has been fully established since several studies have described that TIP30 protein expression is frequently downregulated in diverse types of human tumors, and the downregulation is often associated with tumor progression. TIP30 is involved in the control of cell apoptosis, growth, metastasis, angiogenesis, DNA repair, and tumor cell metabolism. Moreover, TIP30−/− mice spontaneously develop hepatocellular carcinoma and other tumors at a higher incidence than that of wild-type mice. In this review, we provide an overview of current knowledge concerning the role of TIP30 in tumor development and progression. To our knowledge, this is the first review about the role of novel tumor-suppressor gene TIP30 in tumor development and progression.

Key words: TIP30; Cancer; Tumor-suppressor gene (TSG)
develop HCC and other tumors at a higher incidence than wild-type mice (10). TIP30 is considered as a tumor suppressor via its proapoptotic activity as well as antiproliferative and angiogenesis-inhibiting abilities (3,11–16). Furthermore, TIP30 missense mutation in exon 3 was found in approximately 24% of various types of cancers by comparing the TIP30 cDNA sequences in the National Center for Biotechnology Information databases (10). TIP30−/− mice have a higher incidence of HCC and other tumors than wild-type mice (10).

In this article, we will review the current knowledge of TIP30 gene and protein in the regulation of tumorigenesis and their specific deregulations in human tumors. We will focus on the involvement of TIP30 functions in tumor suppressors.

**TIP30: STRUCTURAL FEATURES AND FUNCTIONS**

TIP30 gene is located on human chromosome 11p15.1. It is an evolutionarily conserved gene encoding TIP30 protein with the molecular masses of 27 kDa and a polypeptide of 242 amino acids. Human TIP30 is a cofactor that specifically enhances HIV-1 tat-activated transcription (5). TIP30 is ubiquitously expressed in normal human tissues, including the heart, brain, lung, kidney, skeletal muscle, and pancreas, in which its biological cellular function is unknown. Sequence analysis showed that TIP30 is a member of the SDR family, which always contains a characteristic motif at the catalytic site (6,12,17). The amino terminus of TIP30 is the nucleotide cofactor-binding domain, characterizing Gly-Xaa-Xaa-Gly- Xaa-Xaa-Gly motif (Xaa means any amino acid), while the residues of the carboxyl terminus binds to the SDR substrate (6).

Many studies have been conducted to invest the biochemical functions of TIP30 in humans. Elucidation of the enzymatic activities of TIP30 can provide insights into its biological functions, as well as its tumorigenic properties. It has been reported that TIP30 has Ser/Thr protein kinase activity, which can undergo autophosphorylation and to phosphorylate the heptapeptide repeats of the C-terminal domain of the largest RNA polymerase II subunit in a taut dependent manner (5). Mutations of two glycine residues in the putative nucleotide-binding motif (GXXGXXG) in the amino terminus of TIP30 abolished its protein kinase activity, as well as its proapoptotic functions. In addition, TIP30 was reported to act as a negative regulator of nuclear transport, binding directly to importins to inhibit the nuclear import of proteins (18). Overexpression of TIP30 resulted in a slower rate of nuclear transport and higher sensitivity to death signal. Follow-up studies showed that TIP30 overexpression represses estrogen receptor α-mediated c-myc transcription, whereas CC3 deficiency enhances it. c-myc is an oncogene encoding a nuclear transcription factor. Deregulated expression of c-myc is observed in many cancers and is associated with poor prognosis (19–21). TIP30-mediated c-myc transcription might be one of the possible mechanisms associated with the tumorigenesis property of TIP30 (22). Recent study of the crystal structure of TIP30 showed that it has a short-chain dehydrogenases/reductase (SDR) fold and binding specificity for NADPH family, suggesting that NADPH-binding activity is important for its biological functions (12).

**TIP30 STATUS IN HUMAN CANCERS**

Most studies have demonstrated that TIP30 expression is decreased or lost in various human cancers, consistent with the role for TIP30 as a tumor-suppressor gene. In this section, we will discuss the current findings of the expression of TIP30 in various human cancer types.

**Lung Cancer**

A high-density tissue microarray using a large-scale study of clinical samples from lung cancers and adjacent nontumor tissues has revealed that the expression of TIP30 was undetectable or significantly decreased in lung cancer tissues, and the downregulation of TIP30 was significantly associated with poor differentiation, poor prognosis, and high metastatic progression of lung cancer (16). The significant reduction or absence of TIP30 protein expression in lung cancers implicated its role in the development of lung cancer. In mice models, TIP30 deletion resulted in spontaneous development of lung adenomas and adenocarcinomas (23). In human lung adenocarcinoma cells, knockdown of TIP30 led to prolonged EGFR (epidermal growth factor receptors) activity, delayed EGFR degradation, increased EGFR nuclear localization. ERGR is a transmembrane protein that transduces important growth factor signaling from the extracellular milieu to the cell, and the aberrant activity of EGFR plays a critical role in the progression of cancer, involving in various cellular responses including proliferation and apoptosis (24). Dysregulation of EGFR has been implicated in the pathogenesis of non-small-cell lung cancer (NSLC) (25). Thus, TIP30-mediated EGFR upregulation might be one of the mechanisms that lead to the development of lung adenomas and adenocarcinomas.

**Gastric Cancer**

In 106 cases of gastric tumors, TIP30 expression is lost or significantly decreased in primary gastric cancer compared with that in normal gastric mucous, and loss of TIP30 expression correlates with the poor clinical outcome of gastric cancer patients (15). In vitro experiment proved that restoration of TIP30 expression significantly inhibited gastric cancer cell growth. Moreover, in animal models, restoration of TIP30 expression greatly inhibited gastric cancer cell tumorigenicity and metastasis. The enforced expression of TIP30 downregulated the
expression of cyclin D1, Bcl-2, Bcl-xl, but upregulated the expression of p27, Bax, p53, caspases 3 and 9, which may be the underlying molecular mechanism of TIP30-mediated cell cycle progression (15).

**Breast Cancer**

In a study including 87 patients with surgically removed breast carcinoma, the expression of TIP30 was inversely associated with axillary lymph node metastasis and vascular invasion, supporting that the expression of TIP30 had a suppressive function on tumor metastasis (13). TIP30 expression is significantly associated with positive HER-2/neu status in breast cancer; HER-2/neu is a proto-oncogene and an established adverse prognostic factor in breast cancer (26). Thus, it was predicted that the relation between expression of TIP30 gene and the HER-2/neu oncogene-mediated signal pathway might be the possible molecular mechanism that lead to the suppressive function of TIP30 on breast carcinoma (27). In mouse mammary glands, deletion of TIP30 gene leads to ductal hyperplasia early in life and extensive mammary hyperplasia with age. In mammary epithelial cells (MEC), TIP30 deletion promotes proliferation of MECs and ductal hyperplasia, leading to rapid immortalization of MECs, suggesting the absence of TIP30 in the mammary gland may predispose MECs to neoplastic transformation (28). In the MMTV-Neu mouse model of breast cancer, TIP30 deletion dramatically accelerated the onset of mammary tumors with ER+/PR−, which account for about 15% to 25% of breast cancers and display more aggressive malignant characteristics than ER+/PR+ cancers (29,30).

**Hepatocellular Carcinoma**

TIP30−/− mice spontaneously develop HCC and other tumors at a higher incidence than wild-type mice (27,10). In HCC cells negative for endogenous TIP30, TIP30 mutants promoted cell growth and invasion and inhibit cisplatin-induced apoptosis. In immunodefficient mice, one of the TIP30 mutants can greatly accelerate formation of HCC (31). Overexpression of TIP30 greatly inhibited the growth and lung metastasis of HCC cells in nude mice, while downregulation of TIP30 significantly promoted HCC growth and metastases (32). TIP30 gene promoter was hypermethylated with reduced mRNA expression in 6 of 10 HCC cell lines, as well as in 47% of the 59 paired HCC cases. In addition, epigenetic silencing of TIP30 gene expression by hypermethylation of the CpG island DNA in promoter region is associated with poor prognosis in patients with HCC (33).

**Other Cancers**

TIP30 expression was significantly decreased in gallbladder adenocarcinoma than in peritumoral tissue using immunochemistry analysis. Absence of TIP30 was significantly associated with poor differentiation, large tumor mass, lymph node metastasis, and invasion, serving as an independent predictor of a poor prognosis in gallbladder adenocarcinoma (34). TIP30 protein levels were lower in colorectal carcinomas compared to normal tissue from the control group (35). In addition, a higher frequency of hypermethylation (36%) of TIP30 was observed in colorectal carcinomas, while there was no aberrant methylation in paired adjacent nontumor tissue. Decreased TIP30 was associated with lymph node metastasis and served as an independent predictor for poor outcomes in pancreatic cancer patients (36). Moreover, decreased TIP30 expression was associated with loss of E-cadherin expression, a cell adhesion molecule required for the formation of stable adherens junctions whose expression has been reported in various cancers and is associated with tumor progression and metastasis (37). In pancreatic cancer, lower TIP30 levels were associated with a more poorly differentiated histology and downregulation of TIP30 enhanced EGFr-dependent invasion (38). TIP30 was proved to be the direct target gene of microRNA-10b (miR-10b), which can enhance pancreatic cancer cell (PCC) invasion mediated by epidermal growth factor (EGF), a promoter of PCC invasion and metastasis essential for pancreatic ductal adenocarcinoma initiation and progression (38–40).

Contrary to its status observed in many cancers, the serum concentration of TIP30 level was significantly increased in 23 patients with ovarian cancer than in the control group (41). Moreover, TIP30 expression was increased in metastatic prostate cancers. In addition, overexpression of TIP30 was also proved to promote the metastatic potential of prostate cancer cells, whereas knockdown of TIP30 inhibits the prostate cancer cell invasion (42). In prostate cancer cells, TIP30 enhanced androgen receptor (AR)-mediated transcription activity. Androgens and their receptor play a critical role in the regulation of the physiological function of prostate and are therefore implicated in the genesis and progression of prostate cancer (43,44). Alterations in the relative expression of AR coregulators have been found to associate with prostate cancer progression (45). It is possible that TIP30 might act as a coactivator in AR-mediated transcription by contributing to differences in AR ligand specificity or transcriptional activity. Those studies suggested that TIP30 might serve as an oncogene in certain tumors. There are also other TSGs that also have oncogenic properties, such as E2F1. E2F1, regulating cell death through activating p53 and p73α pathway, has also been reported to promote tumor cell migration and invasion, giving it oncogenic properties (46).

**TIP30 TUMOR-SUPPRESSIVE FUNCTIONS**

Since its identification, TIP30 cellular functions have been revealed in large-scale studies. In recent years, the
frequent downregulations of TIP30 in various types of human cancers have provided new insight in the understanding of TIP30 functions. Both in vitro and in vivo studies have demonstrated several cellular functions of TIP30 that contribute to its tumor-suppressive functions. TIP30 exerts its tumor-suppressive role through influencing multiple cellular processes including apoptosis, proliferation, metastasis, angiogenesis, DNA damage repair, and metabolic adaptation. Here we will discuss what defines TIP30 as a TSG, as well as how TIP30 deregulations contribute to cancer development. As we mentioned above, there are two kinds of TSG: caretakers and gatekeepers. Caretakers suppress cancer by repairing damaged DNA (e.g., BRCA1/2, MSH2, etc.), whereas gatekeepers suppress cancer by halting the cell cycle long enough to repair damaged DNA. Some functions characterize TIP30 as gatekeepers, while others characterize TIP30 as caretakers (Figs. 1 and 2).

**TIP30 Regulates Apoptosis**

Apoptosis, or programmed cell death (PCD), plays a significant role in normal development, as well as in the pathogenesis of cancers. Mutated and deleted proapoptotic genes can give rise to carcinogenesis and tumor growth (47). Many studies in vitro have proved that TIP30 has proapoptotic activity. TIP30 played an important role in inducing cancer cells to apoptosis in various types of cancers, such as lung cancer, HCC, and gastric cancer (3,15,16,48–50). High levels of acutely overexpressed exogenous TIP30 stimulated apoptosis (3,48), while stable expression of exogenous CC3 sensitizes cells to apoptosis in response to various factors, including serum withdrawal, cytotoxic drugs, γ-irradiation, and microtubule poisons (48).

Despite the fact that TIP30 is defined as a proapoptotic factor, the molecular mechanism by which TIP30 gene mediates apoptosis and which component is involved in the TIP30 pathway remain largely unknown. TIP30 is proved to be involved in apoptosis partly by cooperating with the transcription factor p53, a tumor suppressor that plays an essential role in preserving genome stability and inhibiting cancer growth. p53 shares one common downregulator with TIP30: pig12 (51). TIP30 can directly and indirectly enhance the expression of p53 (49,50,52). In hepatoblastoma cells infected with TIP30, the level of p53 was increased with asynchronous apoptosis, suggesting that TIP30 participates in apoptotic pathway by cooperating with p53. TIP30 was reported to induce apoptosis by sensing of intracellular oxidative stress through regulating p53 mRNA stability in HCC (49). In HCC, TIP30-induced apoptosis was dependent on TIP30–p53–Bax cascade, requiring the translocation of Bax and the subsequent release of cytochrome c and Smac/DIABLO from the mitochondria (52). In gastric cancer cells, overexpression of TIP30 led to upregulation of p27, Bax, p53, caspases 3 and 9 expression, and the downregulation of cyclin D1, Bcl-2, Bcl-xL (15). Recently, TIP30 was found to directly bind to p53 protein and subsequently inactivate the p21-promoting ability of p53 (50). TIP30 protein had a characteristic of phosphorylase kinase activity, which can phosphorylate the N-terminal of p53 protein (13). TIP30 protein might phosphorylate p53 C- or N-terminus to enhance the p53-dependent apoptotic pathway. In addition to p53, several other factors are implicated in...
TIP30 is a novel tumor suppressor

The proapoptotic action of TIP30. The ectopic expression of TIP30 was found to elevate the expression of a subset of proapoptotic genes, such as Bad and Siva (13). Bad is associated with Bcl-2 and induces apoptosis (53) and Siva participates in the CD27-mediated apoptosis DNA repair response and proliferation within cells (54). In addition, TIP30 can bind directly to karyopherins of the importin family of nuclear transportins in a Ran-GTP-insensitive manner to inhibit nuclear import and increase sensitivity to a variety of death signals (18).

**TIP30 Regulates Proliferation**

Ectopic expression of TIP30 in HCC cells inhibited cell proliferation with an increased level of p53 expression and a decreased level of Bcl-2/Bcl-xL expression. Moreover, a combination of an adenovirus expressing TIP30 and the cytotoxic drug 5-fluorouracil treatment suppressed tumor growth and prolonged survival in nude mice with HCC tumors (55). This finding implicates a role of TIP30 in suppressing tumor cell proliferation.

**TIP30 Regulates Metastasis**

In addition to its role in promoting apoptosis and inhibiting proliferation, TIP30 can also inhibit tumorigenesis by inhibiting tumor cell metastasis. TIP30 was reported to suppress tumor metastasis in various cancer cells in vitro, including lung cancer, HCC, gastric cancer, breast cancer, and colorectal carcinoma (14–16,31–32,35). The suppressive effect of TIP30 on cancer metastasis was further demonstrated in nude mice. Inhibition of TIP30 expression significantly promoted lung metastasis and angiogenesis in nude mice.

There seems to be two different mechanisms by which TIP30 inhibit tumor cell metastasis. The first mechanism is an apoptosis-inducing effect, which was first shown in v-SCLC cells deprived of growth factors (3). The second is through its indirect angiogenesis-inhibiting effect (11). In HCC and lung cancer cells, TIP30 inhibited metastasis through inhibition of osteopontin (OPN) expression, a key molecule that enhances tumor metastasis through the induction of metalloproteinase (MMP) and vascular endothelial growth factor (VEGF) expression (16,32,56,57). In addition, overexpression of TIP30 can also repress ERα-mediated c-myc transcription, and loss of TIP30 increases c-myc expression in the mammary gland of mice, indicating that TIP30 may regulate tumorigenesis and tissue development of ERα-targeted organs (22,58,59). However, in breast cancer, neither ER expression nor p53 protein was associated with TIP30 expression, suggesting that TIP30 contributes to the metastasis at a different step from them. Further investigations are needed to elucidate the exact mechanism.

**TIP30 Regulates Angiogenesis**

Angiogenesis is required in advanced tumor growth and metastasis. In vitro experiment showed that TIP30 can diminish angiogenesis of tumor cells of both macro- and microvascular origin (11,16).

The inhibitory effects of TIP30 might be modulated through the regulation of angiogenic modulators at the transcription level. TIP30 can induce changes in RNA levels of several angiogenic-modulating factors, consistent with the overall reduction in angiogenesis (11). The expression of angiogenic stimulator angiopoietin 1 was markedly reduced, while the expression of some angiogenic inhibitors, including angiopoietin 2, BAI1, and SPARC, was elevated, indicating that TIP30 inhibit angiogenesis of tumor cells through the regulation of various angiogenic modulators.

**TIP30 Controls Gene Transcription**

It is clear that TIP30 is a transcriptional factor, which can promote HIV-1 tat-activated transcription through interaction with tat protein and RNA polymerase II. TIP30-mediated tumor-suppressive regulation can be explained by two possible mechanisms. One possible mechanism is that TIP30 directly affects the transcription of genes in the nucleus (13,22). Evidence supporting this mechanism is that overexpression of TIP30 directly inhibited transcription of c-myc and osteopontin (OPN) genes (22,32). Both c-myc and OPN are well-known...
TIP30 regulates tumor cell glucose metabolism

Cancer is a metabolic disease. Cancer growth depends on the ability of tumor cells to balance the metabolic equation, which is characterized by highly variable oxygen and glucose inputs on one side and survival and unbridled proliferation on the other side. HeLa cells with silenced TIP30 showed superior metabolic adaptation and long-term survival in low glucose in comparison to control HeLa cells, implicating that silencing of TIP30 strongly improves survival of tumor cells in response to glucose limitation (65). Absence of TIP30 expression promotes mitochondrial oxidative phosphorylation (OXPHOS) in tumor cells in low glucose but does not affect the glycolytic pathway. Silencing of CC3 in tumor cells highly dependent on glycolysis gives them metabolic flexibility to utilize both OXPHOS and glycolysis for their metabolic needs. Given that TIP30 has a negative effect on myc expression and that myc plays a significant role in regulating genes involved in both glycolysis and OXPHOS (66–68), it was concluded that myc gene might contribute to the high mitochondrial respiration in TIP30 silenced cells. The metabolic flexibility acquired by cells after silencing of TIP30 may be one of the mechanisms for the development of human tumors that frequently have low or absent expression of TIP30.

TIP30 regulates DNA damage responses

The human genome integrity is constantly disrupted by various genotoxic agents from the exogenous environment [chemicals, ultraviolet (UV), etc.] and endogenous environment (replication, oxidative stress, etc.). Thus, the ability to repair damaged DNA is critical for living organisms. TIP30 has been demonstrated to be involved in DNA damage responses. Excess TIP30 impaired DNA damage repair after both UV exposure and oxidative stress, negatively influencing cell survival (69). Excess TIP30 inhibited the expression levels of DDB2/XPE and p21CIP1, and prevented the induction of c-FOS after UV exposure (69). These genes are all proven to be involved in the DNA damage repair through various mechanisms in numerous publications. DDB2, also known as Xeroderma pigmentosum group E, is required in the nucleotide excision repair (NER) of DNA damage (70). p21CIP was proven to be involved in the UV-induced DNA damage response (71,72). C-FOS is an early response gene induced by UV (23) and was necessary for the efficient repair of the UV-induced DNA damage (73–75). The changes in those genes are potential culprits in the effects of CC3 on cellular responses to UV.

REGULATION OF TIP30 EXPRESSION

As mentioned above, TIP30 was frequently deregulated in a variety of human malignancies. However, the mechanism leading to its deregulation in human cancer remains unclear. Deregulation of gene expression can be caused by two mechanisms: genetic alterations, namely gene mutation or loss of heterozygosity (LOH), and epigenetic events, such as CpG island promoter hypermethylation.

Regulation of TIP30 expression by genetic alterations

One possible mechanism is that TIP30 itself is mutated and subsequently results in its aberrant expression. Evidence to support this notion is that mutations were frequently present in TIP30 exon 2 in many cancer cells, while no mutations existed in normal cells. For example, somatic missense mutations of TIP30 gene were present in human HCC tissue specimens, leading to either instability or the abnormal cellular distribution of TIP30 protein. Mutations in the region of a nucleotide-binding motif (GXXGXXG) between residues 25 and 31 of TIP30 proteins resulted in a lack of apoptotic properties (18). TIP30 mutations not only lead to losing the tumor-suppression function but also to gaining new functions including acceleration of tumorigenesis by altering the expression of N-cadherin gene (31). In addition, it is well known that TIP30 gene was located in human chromosome 11p15, at which loss of heterozygosity (LOH) is frequently present in many tumor types, including the breast cancer, esophageal adenocarcinoma, gastric adenocarcinoma, and sporadic adenocortical cancer (76–78). LOH at 11p15 was reported to be present in 61.5% of gastric cancers and 53.3% of esophageal adenocarcinoma, implicating that LOH might be the mechanism for the deregulation of TIP30 in various malignancies.
Regulation of TIP30 Expression by Epigenetic Change

Epigenetic change refers to a stable change in gene expression that can be inherited through subsequent cell divisions, without a change in DNA sequence. Epigenetic changes could be divided into two categories: DNA methylation (79) and histone modifications (80). DNA methylation occurs mainly in CpG islands and results in transcriptional repression (81). In addition to silencing due to gene mutations, epigenetic changes are associated with transcriptional inactivation of many genes and play an important role during carcinogenesis and tumor development. Aberrant promoter hypermethylation is a common mechanism for loss of function of several tumor-suppressor genes, DNA repair genes, and other genes in human cancers. Hypermethylation of TIP30 was found in 47% of the HCC patients, whereas it was not detected in normal liver tissues, and epigenetic silencing of TIP30 gene by CpG island DNA hypermethylation is proven to be associated with poor prognosis of HCC (33). In addition, in human colorectal carcinoma, a higher promoter methylation was involved in the decreased expression of TIP30 (35). Thus, the methylation of specific promoters may lead to the transcriptional silencing of TIP30 in these cancers and subsequently leads to cancer progression. However, the methylation status in other cancers remains unknown. Further studies are needed to elucidate the possible relationship between the expression of TIP30 and promoter hypermethylation in other malignancies.

MicroRNAs (miRs) are endogenous 18–25 nucleotide noncoding RNAs that target specific mRNA for translational repression or degradation (82). miRs can regulate various cellular functions, including cell survival, proliferation, migration, invasion, and metastasis, and expression levels of miRs are often deregulated in cancer (83,84). In pancreatic cancer, miR-10b promoted pancreatic cancer cell proliferation and invasion by suppressing the expression of TIP30 (38). The study provides a novel sight involving a miR–TSG–tumor-suppressor axis to understand the mechanism of TIP30’s tumor-suppressive function.

IMPLICATIONS IN CANCER MANAGEMENT

Given that deregulated expression of TIP30 was identified in a number of human cancers, it provides an attractive approach for anticancer therapies. First of all, TIP30 can be used as biomarkers for cancer diagnosis. By monitoring the TIP30 status in an individual tumor, such as alterations in gene and protein levels, we can predict the risk of cancer development and progression, as well as the prognosis of the cancer. Since TIP30 was downregulated in many kinds of cancers, reintroduction of the TIP30 gene or stabilization of the TIP30 protein level may be an attractive strategy for cancer management. Moreover, given that TIP30 inhibits tumorigenesis by promoting tumor apoptosis, inhibiting tumor metastasis and angiogenesis, restoration of its tumor-suppressing function may inhibit tumor growth, serving as a potential target for cancer therapy.

CONCLUSIONS AND FUTURE DIRECTIONS

In conclusion, TIP30, mutated or depleted in a variety of human malignances, is a well-characterized tumor suppressor. TIP30 exerts its tumor-suppressor function through induction of apoptosis, inhibition of proliferation, metastasis and angiogenesis, regulation of gene transcription, and participation in the glucose metabolism and DNA damage repair process. TIP30 can regulate the expression of various tumor-related genes and proteins, such as p53, c-myc, OPN, and EGFR, all of which are involved in the tumorigenesis and might be the underlying mechanism for the tumor-suppressive functions of TIP30. The studies on the molecular mechanism that lead to the deregulations of TIP30 were relatively limited. Both gene mutations and epigenetic modifications of TIP30 were all proven to be involved in the regulation of TIP30.

Previous studies have focused on cellular and molecular mechanisms on how TIP30 exert its tumor-suppressive role. However, how and why TIP30 is lost in tumors remains unclear. Relatively little is known about the mechanism that leads to downregulation of TIP30 in human cancers. Quite recently, several mechanisms, such as promoter hypermethylation as well as miRNAs (microRNAs) including miR-10b, have been showed to regulate TIP30’s tumor-suppressor functions (33,35,38). The exact molecular mechanism that initiates TIP30 downregulation remains unclear. Genetic and epigenetic susceptibility as well as environmental factors might play a role in this process. A better understanding of the upstream regulator for TIP30 could provide important insights for scientists and physicians to design better strategies to restore the TIP30 tumor-suppressor function as an efficient means to treat cancer patients.

ACKNOWLEDGMENTS: This work was supported by a grant from the National Natural Science Foundation of China (NSFC) (Grant Number: 81401847). No benefits in any form have been or will be received from any commercial party related directly and indirectly to the subject of this article. The authors declare no conflicts of interest.

REFERENCES

1. Kinzler, K. W.; Vogelstein B. Cancer-susceptibility genes. Gatekeepers and caretakers. Nature 386(6627):761, 763; 1997.
2. Hanahan, D.; Weinberg, R. A. Hallmarks of cancer: The next generation. Cell 144(5):646–674; 2011.
3. Shivelman, E. A link between metastasis and resistance to apoptosis of variant small cell lung carcinoma. Oncogene 14(18):2167–2173; 1997.
4. Jones, K. A.; Peterlin, B. M. Control of RNA initiation and elongation at the HIV-1 promoter. Annu. Rev. Biochem. 63:717–743; 1994.
5. Xiao, H.; Tao, Y.; Greenblatt, J.; Roeder, R. G. A cofactor, TIP30, specifically enhances HIV-1 Tat-activated transcription. Proc. Natl. Acad. Sci. USA 95(5):2146–2151; 1998.

6. Baker, M. E. TIP30, a cofactor for HIV-1 Tat-activated transcription, is homologous to short-chain dehydrogenases/reductases. Curr. Biol. 9(13):R471; 1999.

7. Jornvall, H.; Persson, B.; Krook, M.; Atian, S.; Gonzalez-Duarte, R.; Jeffery, J.; Ghosh, D. Short-chain dehydrogenases/reductases (SDR). Biochemistry 34(18):6003–6013; 1995.

8. Kallberg, Y.; Oppermann, U.; Jornvall, H.; Persson, B. Short-chain dehydrogenase/reductase (SDR) relationships: A large family with eight clusters common to human, animal, and plant genomes. Protein Sci. 11(3):636–641; 2002.

9. Kavanagh, K. L.; Jornvall, H.; Persson, B.; Oppermann, U. Medium- and short-chain dehydrogenase/reductase gene and protein families: The SDR superfamily: Functional and structural diversity within a family of metabolic and regulatory enzymes. Cell. Mol. Life Sci. 65(24):3895–3906; 2008.

10. Ito, M.; Jiang, C.; Krumm, K.; Zhang, X.; Pecha, J.; Zhao, J.; Guo, Y.; Roeder, R. G.; Xiao, H. TIP30 deficiency increases susceptibility to tumorigenesis. Cancer Res. 63(24):8763–8767; 2003.

11. NicAmlaiboith, R.; Shitivelman, E. Metastasis suppressor CC3 inhibits angiogenic properties of tumor cells in vitro. Oncogene 20(2):270–275; 2001.

12. El Omari, K.; Bird, L. E.; Nichols, C. E.; Ren, J.; Stammers, D. K. Crystal structure of CC3 (TIP30): Implications for its role as a tumor suppressor. J. Biol. Chem. 280(18):18229–18236; 2005.

13. Xiao, H.; Palvan, V.; Yang, Y.; Roeder, R. G. TIP30 has an intrinsic kinase activity required for up-regulation of a subset of apoptotic genes. EMBO J. 19(5):956–963; 2000.

14. Zhao, J.; Ni, H.; Ma, Y.; Dong, L.; Dai, J.; Zhao, F.; Yan, X.; Lu, B.; Xu, H.; Guo, Y. TIP30/CC3 expression in breast carcinoma: Relation to metastasis, clinicopathologic parameters, and P53 expression. Hum. Pathol. 38(2):293–298; 2007.

15. Li, X.; Zhang, Y.; Cao, S.; Chen, X.; Lu, Y.; Jin, H.; Sun, S.; Chen, B.; Liu, J.; Ding, J.; Wu, K.; Fan, D. Reduction of TIP30 correlates with poor prognosis of gastric cancer patients and its restoration drastically inhibits tumor growth and metastasis. Int. J. Cancer 124(3):1931–1939; 2009.

16. Tong, X.; Li, K.; Luo, Z.; Lu, B.; Liu, X.; Wang, T.; Pang, M.; Liang, B.; Tan, M.; Wu, M.; Zhao, J.; Guo, Y. Decreased TIP30 expression promotes tumor metastasis in lung cancer. Am. J. Pathol. 174(5):1931–1939; 2009.

17. Baker, M. E.; Yan, L.; Pear, M. R. Three-dimensional model of human TIP30, a coactivator for HIV-1 Tat-activated transcription, and CC3, a protein associated with metastasis suppression. Cell. Mol. Life Sci. 57(5):851–858; 2000.

18. King, F. W.; Shitivelman, E. Inhibition of nuclear import by the proapoptotic protein CC3. Mol. Cell. Biol. 24(16):7091–7101; 2004.

19. Nass, S. J.; Dickson, R. B. Defining a role for c-Myc in breast tumorigenesis. Breast Cancer Res. Treat. 44(1):1–22; 1997.

20. Pelengaris, S.; Khan, M.; Evan, G. c-MYC: More than just a matter of life and death. Nature Rev. Cancer 2(10):764–776; 2002.

21. Liao, D. J.; Dickson, R. B. c-Myc in breast cancer. Endocr. Relat. Cancer. 7(3):143–164; 2000.

22. Jiang, C.; Ito, M.; Piening, V.; Bruck, K.; Roeder, R. G.; Xiao, H. TIP30 interacts with an estrogen receptor alpha-interacting coactivator CIA and regulates c-myc transcription. J. Biol. Chem. 279(26):27781–27789; 2004.

23. Li, A.; Zhang, C.; Gao, S.; Chen, F.; Yang, C.; Luo, R.; Xiao, H. TIP30 loss enhances cytoplasmic and nuclear EGFR signaling and promotes lung adenocarcinogenesis in mice. Oncogene 32(18):2273–2281; 2013.

24. Wells, A. EGF receptor. Int. J. Biochem. Cell Biol. 31(6):637–643; 1999.

25. Herbst, R. S.; Heymach, J. V.; Lippman, S. M. Lung cancer. N. Engl. J. Med. 359(13):1367–1380; 2008.

26. Tsutui, S.; Ohno, S.; Murakami, S.; Hachitanda, Y.; Oda, S. Prognostic value of c-erbB2 expression in breast cancer. J. Surg. Oncol. 79(4):216–223; 2002.

27. Zhang, D. H.; Wong, L. L.; Tai, L. K.; Koay, E. S.; Hewitt, R. E. Overexpression of CC3/TIP30 is associated with HER-2/neu status in breast cancer. J. Cancer Res. Clin. Oncol. 131(9):603–608; 2005.

28. Pecha, J.; Ankrrapp, D.; Jiang, C.; Tang, W.; Hoshino, I.; Bruck, K.; Wagner, K. U.; Xiao, H. Deletion of Tip30 leads to rapid immortalization of murine mammary epithelial cells and ductal hyperplasia in the mammary gland. Oncogene 26(53):7423–7431; 2007.

29. Zhang, C.; Mori, M.; Gao, S.; Li, A.; Hoshino, I.; Upperlee, M. D.; Haslam, S. Z.; Xiao, H. Tip30 deletion in MMTV-Neu mice leads to enhanced EGFR signaling and development of estrogen receptor-positive and progesterone receptor-negative mammary tumors. Cancer Res. 70(24):10224–10233; 2010.

30. Ponzone, R.; Montemurro, F.; Maggirotatto, F.; Robba, C.; Gregori, D.; Iacumuzzi, M. E.; Kubatcki, F.; Marendo, D.; Dominguez, A.; Biglia, N.; Sismondi, P. Clinical outcome of adjuvant endocrine treatment according to PR and HER-2 status in early breast cancer. Ann. Oncol. 17(11):1631–166; 2006.

31. Jiang, C.; Pecha, J.; Hoshino, I.; Ankrrapp, D.; Xiao, H. Tip30 mutant derived from hepatocellular carcinoma specimens promotes growth of HepG2 cells through up-regulation of N-cadherin. Cancer Res. 67(8):3574–3582; 2007.

32. Zhao, J.; Lu, B.; Xu, H.; Tong, X.; Wu, G.; Zhang, X.; Liang, A.; Cong, W.; Dai, J.; Wang, H.; Wu, M.; Guo, Y. Thirty-kilodalton Tat-interacting protein suppresses tumor metastasis by inhibition of osteopontin transcription in human hepatocellular carcinoma. Hepatology. 48(1):265–275; 2008.

33. Lu, B.; Ma, Y.; Wu, G.; Tong, X.; Guo, H.; Liang, A.; Cong, W.; Liu, C.; Wang, H.; Wu, M.; Zhao, J.; Guo, Y. Methylidyne of Tip30 promoter is associated with poor prognosis in human hepatocellular carcinoma. Clin. Cancer Res. 14(22):7405–7412; 2008.

34. Liu, D. C.; Yang, Z. L. Clinicopathologic significance of minichromosome maintenance protein 2 and Tat-interacting protein 30 expression in benign and malignant lesions of the gallbladder. Hum. Pathol. 42(11):1676–1683; 2011.

35. Chen, X.; Cao, X.; Dong, W.; Luo, S.; Suo, Z.; Jin, Y. Expression of Tip30 tumor suppressor gene is down-regulated in human colorectal carcinoma. Dig. Dis. Sci. 55(8):2219–2226; 2010.

36. Guo, S.; Jing, W.; Hu, X.; Zhou, X.; Liu, L.; Zhu, M.; Yin, F.; Chen, R.; Zhao, J.; Guo, Y. Decreased TIP30 expression predicts poor prognosis in pancreatic cancer patients. Int. J. Cancer 134(6):1369–1378; 2014.

37. Huber, M. A.; Kraut, N.; Beeg, H. Molecular requirements for epithelial-mesenchymal transition during tumor progression. Curr. Opin. Cell Biol. 17(5):548–558; 2005.

38. Ouyang, H.; Gore, J.; Deitz, S.; Koc, M. microRNA-10b enhances pancreatic cancer cell invasion by suppressing
TIP30 expression and promoting EGF and TGF-beta actions. Oncogene 33(38):4664–4674; 2014.

39. Kore, M. Role of growth factors in pancreatic cancer. Surg. Oncol. Clin. N. Am. 7(1):25–41; 1998.

40. Ardito, C. M.; Gruner, B. M.; Takeuchi, K. K.; Lubeseder-Martellato, C.; Teichmann, N.; Mazur, P. K.; Delgiorno, K. E.; Carpenter, E. S.; Halbrook, C. J.; Hall, J. C.; Pal, D.; Briel, T.; Hemen, A.; Trajkovic-Arsic, M.; Sipos, B.; Liu, G. Y.; Storz, P.; Murray, N. R.; Threadgill, D. W.; Sibilia, M.; Washington, M. K.; Wilson, C. L.; Schmid, R. M.; Raines, E. W.; Crawford, H. C.; Siveke, J. T. EGFR receptor is required for KRAS-induced pancreatic tumorigenesis. Cancer Cell 22(3):304–317; 2012.

41. Kumtepe, Y.; Halici, Z.; Sengul, O.; Kunak, C. S.; Bayir, Y.; Klici, N.; Cadirci, E.; Puler, A.; Bayraktutan, Z. High serum HTATIP2/TIP30 level in serous ovarian cancer as prognostic or diagnostic marker. Eur. J. Med. Res. 18:18; 2013.

42. Zhang, H.; Zhang, Y.; Duan, H. O.; Kirley, S. D.; Lin, S. X.; McDougal, W. S.; Xiao, H.; Wu, C. L. TIP30 is associated with progression and metastasis of prostate cancer. Int. J. Cancer 123(4):810–816; 2008.

43. Gelmann, E. P. Molecular biology of the androgen receptor. J. Clin. Oncol. 20(13):3001–3015; 2002.

44. Brooke, G. N.; Bevan, C. L. The role of androgen receptor mutations in prostate cancer progression. Curr. Genomics 10(1):18–25; 2009.

45. Heinlein, C. A.; Chang, C. Androgen receptor in prostate cancer. Endocr. Rev. 25(2):276–308; 2004.

46. Engelmann, D.; Putzer, B. M. The dark side of E2F1: In transit beyond apoptosis. Cancer Res. 72(3):571–575; 2012.

47. Saikumar, P.; Dong, Z.; Mikhailov, V.; Denton, M.; Weinberg, J. M.; Venkatachalam, M. A. Apoptosis: Definition, mechanisms, and relevance to disease. Am. J. Med. 107(5):489–506; 1999.

48. Whitman, S.; Wang, X.; Shalaby, R.; Shitivelman, E. Alternatively spliced products CC3 and TC3 have opposing effects on apoptosis. Mol. Cell. Biol. 20(2):583–593; 2000.

49. Zhao, J.; Chen, J.; Lu, B.; Dong, L.; Wang, H.; Bi, C.; Wu, G.; Guo, H.; Wu, M.; Guo, Y. TIP30 induces apoptosis under oxidative stress through stabilization of p53 messenger RNA in human hepatocellular carcinoma. Cancer Res. 68(11):4133–4141; 2008.

50. Lee, S. H.; Ju, S. K.; Lee, T. Y.; Huh, S. H.; Han, K. H. TIP30 directly binds p53 tumor suppressor protein in vitro. Mol. Cells 34(5):495–500; 2012.

51. Lee, S. H.; DeJong, J. Microsomal GST-I: Genomic organization, expression, and alternative splicing of the human gene. Biomed. Biophys. Acta 1446(3):389–396; 1999.

52. Shi, M.; Yan, S. G.; Xie, S. T.; Wang, H. N. Tip30-induced apoptosis requires translocation of Bax and involves mitochondrial release of cytochrome c and Smac/DIABLO in hepatocellular carcinoma cells. Biochem. Biophys. Acta. 1783(2):263–274; 2008.

53. Yang, E.; Zha, J.; Jocket, J.; Boise, L. H.; Thompson, C. B.; Korsmeyer, S. J. Bad, a heterodimeric partner for Bcl-XL and Bcl-2, displaces Bax and promotes cell death. Cell 80(2):285–291; 1995.

54. Prasad, K. V.; Ao, Z.; Yoon, Y.; Wu, M. X.; Rizk, M.; Jacquot, S.; Schlossman, S. F. CD27, a member of the tumor necrosis factor receptor family, induces apoptosis and binds to Siva, a proapoptotic protein. Proc. Natl. Acad. Sci. USA 94(12):6346–6351; 1997.

55. Zhao, J.; Zhang, X.; Shi, M.; Xu, H.; Jin, J.; Ni, H.; Yang, S.; Dai, J.; Wu, M.; Guo, Y. TIP30 inhibits growth of HCC cell lines and inhibits HCC xenografts in mice in combination with 5-FU. Hepatology 44(1):205–215; 2006.

56. Chakraborty, G.; Jain, S.; Kundu, G. C. Osteopontin promotes vascular endothelial growth factor-dependent breast tumor growth and angiogenesis via autocrine and paracrine mechanisms. Cancer Res. 68(1):152–161; 2008.

57. Philip, S.; Bulbule, A.; Kundu, G. C. Osteopontin stimulates tumor growth and activation of promatrix metalloproteinase-2 through nuclear factor-kappa B-mediated induction of membrane type 1 matrix metalloproteinase in murine melanoma cells. J. Biol. Chem. 276(48):44926–44935; 2001.

58. Cunha, G. R.; Wiesen, J. F.; Werb, Z.; Young, P.; Hom, Y. K.; Cooke, P. S.; Lubahn, D. B. Paracrine mechanisms of mouse mammary ductal growth. Adv. Exp. Med. Biol. 480:93–97; 2000.

59. Cardiff, R. D.; Anver, M. R.; Gusterson, B. A.; Hennighausen, L.; Jensen, R. A.; Merino, M. J.; Rehm, S.; Russo, J.; Tavassoli, F. A.; Wakefield, L. M.; Ward, J. M.; Green, J. E. The mammary pathology of genetically engineered mice: The consensus report and recommendations from the Ann Arbor meeting. Oncogene 19(8):968–988; 2000.

60. Weber, G. F. The metastasis gene osteopontin: A candidate target for cancer therapy. Biochem. Biophys. Acta 1552(2):61–85; 2001.

61. Rittling, S. R.; Chambers, A. F. Role of osteopontin in tumour progression. Br. J. Cancer 90(10):1877–1881; 2004.

62. Lin, S. Y.; Makino, K.; Xia, W.; Matin, A.; Wen, Y.; Kwong, K. Y.; Bourguignon, L.; Hung, M. C. Nuclear localization of EGF receptor and its potential new role as a transcription factor. Nat. Cell Biol. 3(9):802–808; 2001.

63. Wang, S. C.; Nakajima, Y.; Yu, Y. L.; Xia, W.; Chen, C. T.; Yang, C. C.; McIntush, E. W.; Li, L. Y.; Hawke, D. H.; Kobayashi, R.; Hung, M. C. Tyrosine phosphorylation controls PCNA function through protein stability. Nat. Cell Biol. 8(12):1359–1368; 2006.

64. Zhang, C.; Li, A.; Zhang, X.; Xiao, H. A novel TIP30 protein complex regulates EGF receptor signaling and endocytic degradation. J. Biol. Chem. 286(11):9373–9381; 2011.

65. Chen, V.; Shitivelman, E. CC3/TIP30 regulates metabolic adaptation of tumor cells to glucose limitation. Cell Cycle 9(24):4941–4953; 2010.

66. Dang, C. V. Rethinking the Warburg effect with Myc micro-managing glutamine metabolism. Cancer Res. 70(3):859–862; 2010.

67. Dang, C. V.; Le, A.; Gao, P. MYC-induced cancer cell energy metabolism and therapeutic opportunities. Clin. Cancer Res. 15(21):6479–6483; 2009.

68. Gordan, J. D.; Thompson, C. B.; Simon, M. C. HIF and c-Myc: Sibling rivals for control of cancer cell metabolism and proliferation. Cancer Cell. 12(2):108–113; 2007.

69. Fong, S.; King, F.; Shitivelman, E. CC3/TIP30 affects DNA damage repair. BMC Cell Biol. 11:23; 2010.

70. Shiyakov, P.; Nag, A.; Raychadhuri, P.; Cullin 4A associates with the UV-damaged DNA-binding protein DBB. J. Biol. Chem. 274(50):35309–35312; 1999.

71. Arima, Y.; Hirota, T.; Bromer, C.; Mousli, M.; Fujitava, T.; Niwa, S.; Ishikawa H, Sayay H. Down-regulation of nuclear protein ICBP90 by p53/p21Cip1/WAF1-dependent DNA-damage checkpoint signals contributes to cell cycle arrest at G1/S transition. Genes Cells 9(2):131–142; 2004.
72. Gillis, L. D.; Leidal, A. M.; Hill, R.; Lee, P. W. p21Cip1/WAF1 mediates cyclin B1 degradation in response to DNA damage. Cell Cycle 8(2):253–256; 2009.

73. Haas, S.; Kaina, B. c-Fos is involved in the cellular defense against the genotoxic effect of UV radiation. Carcinogenesis 16(5):985–991; 1995.

74. Christmann, M.; Tomicic, M. T.; Origer, J.; Aasland, D.; Kaina, B. c-Fos is required for excision repair of UV-light induced DNA lesions by triggering the re-synthesis of XPF. Nucleic Acids Res. 34(22):6530–6539; 2006.

75. Christmann, M.; Tomicic, M. T.; Aasland, D.; Kaina, B. A role for UV-light-induced c-Fos: Stimulation of nucleotide excision repair and protection against sustained JNK activation and apoptosis. Carcinogenesis 28(1):183–190; 2007.

76. Lichy, J. H.; Zavar, M.; Tsai, M. M.; O’Leary, T. J.; Taubengerber, J. K. Loss of heterozygosity on chromosome 11p15 during histological progression in microdissected ductal carcinoma of the breast. Am. J. Pathol. 153(1):271–278; 1998.

77. Moskaluk, C. A; Rumpel, C. A. Allelic deletion in 11p15 is a common occurrence in esophageal and gastric adenocarcinoma. Cancer 83(2):232–239; 1998.

78. Libe, R.; Bertherat, J. Molecular genetics of adrenocortical tumours, from familial to sporadic diseases. Eur. J. Endocrinol. 153(4):477–487; 2005.

79. Lee, Y. S.; Dutta, A. MicroRNAs in cancer. Annu. Rev. Pathol. 4:199–227; 2009.

80. Lee, Y.; Jeon, K.; Lee, J. T.; Kim, S.; Kim, V. N. MicroRNA maturation: Stepwise processing and subcellular localization. EMBO J. 21(17):4663–4670; 2002.

81. Goll, M. G.; Bestor, T. H. Eukaryotic cytosine methyltransferases. Annu. Rev. Biochem. 74:481–514; 2005.

82. Valencia-Sanchez, M. A.; Liu, J.; Hannon, G. J.; Parker, R. Control of translation and mRNA degradation by miRNAs and siRNAs. Genes Dev. 20(5):515–524; 2006.

83. Esquela-Kerscher, A.; Slack, F. J. Oncomirs—microRNAs with a role in cancer. Nat. Rev. Cancer 6(4):259–269; 2006.

84. Iorio, M. V.; Croce, C. M. MicroRNAs in cancer: Small molecules with a huge impact. J. Clin. Oncol. 27(34):5848–5856; 2009.