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TGF-beta-dependent and -independent roles of STRAP in cancer

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1. ABSTRACT

The serine-threonine kinase receptor-associated protein (STRAP) was initially identified as a putative inhibitor of the canonical TGF-beta signaling pathway. Because the Smad-dependent TGF-beta pathway negatively regulates cellular growth, early functional studies suggested that STRAP behaves as an oncogene. Indeed, a correlation between STRAP overexpression and various cancers has been identified. With the emergence of new studies on the biological function of STRAP, it is becoming clear that STRAP regulates several distinct cellular processes and modulates multiple signaling pathways. While STRAP itself does not possess enzymatic activity, it appears that STRAP influences biological processes through associations with cellular proteins. In this review, we will describe the TGF-beta-dependent and -independent functions of STRAP and provide a context for the significance of STRAP activity in the development of cancer.

2. INTRODUCTION

The development of cancer is a multi-step process by which cells acquire a malignant phenotype through the accumulation of somatic mutations. While cancer progression is dependent on the disruption of many normal cellular processes, deregulation of cellular growth signals is often an early step in tumorigenesis. Previous studies on STRAP suggest that it promotes cellular proliferation and oncogenesis by blocking the anti-proliferative effects of TGF-beta (1, 2). Overexpression of STRAP has been reported in lung, colon, and breast carcinomas (1, 2), which further supports a role for STRAP as an oncogene. However, inhibition of TGF-beta signaling can not account for the full oncogenic potential of STRAP as many tumors become resistant to TGF-beta signaling through mutation of downstream effectors.

Taking the present literature into account, very little is known about STRAP. It has been determined that

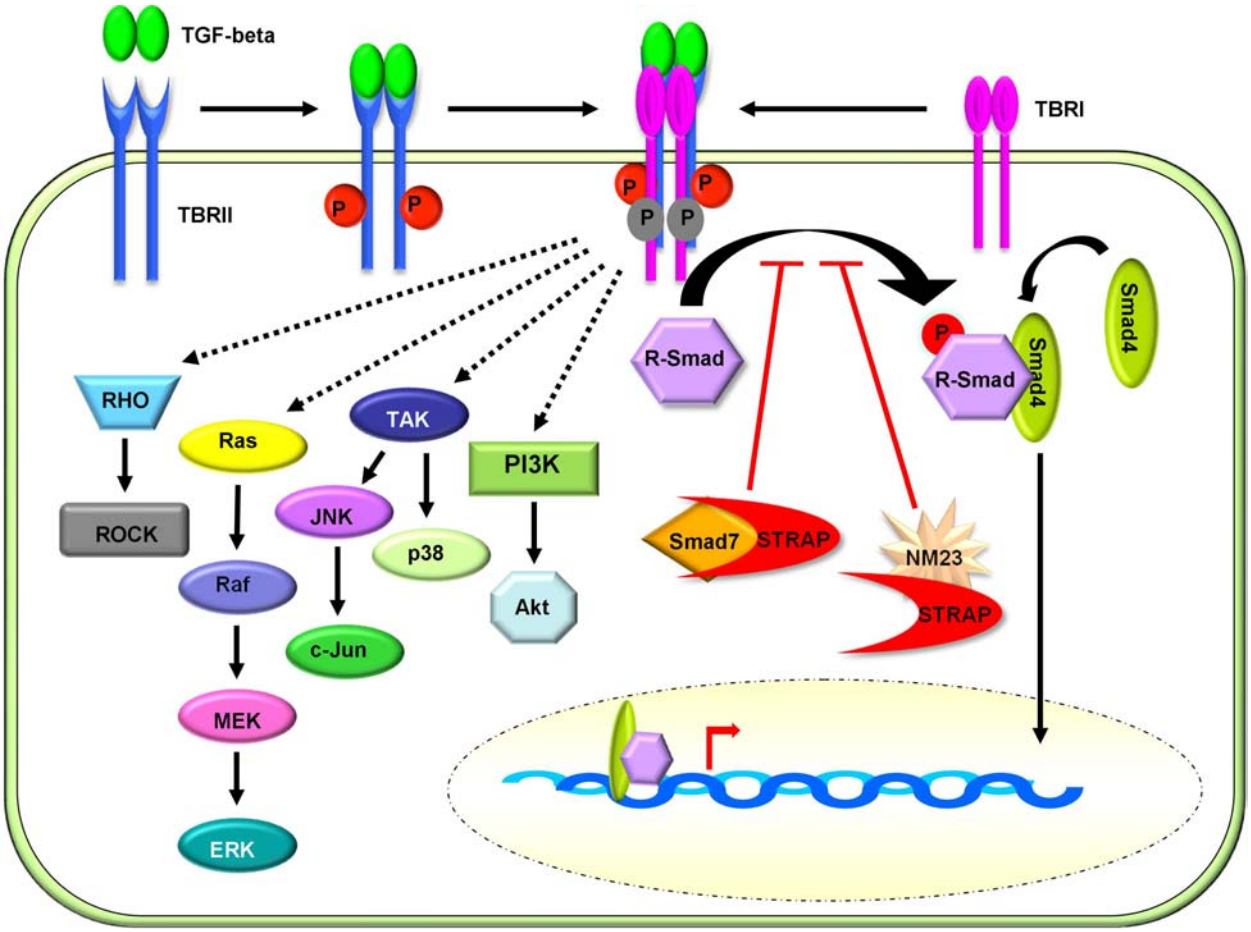

Figure 1. The TGF-beta signaling pathways. TGF-beta signaling can be propagated through Smad-dependent and Smad-independent pathways. In the Smad-dependent pathway, the activated TGF-beta receptor complex phosphorylates the R-Smads, Smad-2 and Smad-3. The phosphorylated R-Smads associate with the common Smad-4 and translocate to the nucleus where they function as transcriptional activators and repressors of gene expression. The inhibitory Smad, Smad-7, inhibits activation of the R-Smads by associating with TBRI. The WD40 domain protein, STRAP, also functions as an inhibitor of Smad-dependent signaling by associating with Smad-7 and TBRI. In addition to Smad activation, The TGF beta receptor complex can induce signaling through the Ras, RhoA, TAK1, and PI3K pathways. TGF-beta mediated activation of these non-Smad pathways has been associated with cellular transformation, proliferation, EMT, and migration.

STRAP is a conserved 38 kDa protein that localizes to both the cytoplasm and nucleus of cells (1). Mutation of the Drosophila STRAP homologue, pterodactyl, has been implicated in tubulogenesis and branching morphogenesis defects (3). Furthermore, STRAP knockout in mice is embryonic lethal due to defects in neural tube closure, somitogenesis, and organogenesis (4). The ubiquitious expression of STRAP and requirement for normal development suggests that STRAP is important for normal cellular and physiological processes. Although STRAP itself lacks catalytic activity, analysis of its primary structure indicates that STRAP is comprised of seven WD40 domains. A common feature of the WD40 domain is its capacity for establishing protein-protein interactions and scaffolds for the formation of protein complexes (5). In recent years, studies on STRAP have led to the identification of new binding partners and functional roles. While some of these interactions can modulate TGF-beta signaling, others suggest a broader role for STRAP in cellular homeostasis and oncogenesis.

3. TGF-BETA SIGNALING

3.1. The Smad-dependent and Smad-independent TGF-beta pathways

The transforming growth factor beta (TGF-beta) super family of proteins regulates diverse biological functions such as growth, differentiation, EMT, invasion, and apoptosis. TGF-beta signaling can be broadly subdivided into the Smad-dependent and the Smad-independent pathways (6, 7). While the signaling cascade and regulatory proteins that influence Smad signaling have been extensively characterized, little is known regarding signal transduction through the Smad-independent pathway. Signaling through both pathways is initiated by an oligomeric complex comprised of the TGF-beta receptor (TBR) I and II homodimers (Figure 1). Following receptor

oligomerization and activation, TBRI propagates Smad-dependent signaling by phosphorylating the receptor associated Smads (R-Smads) -2 and -3 (8-10). Both Smads-2 and -3 contain a mad-homology 1 (MH1) domain for DNA binding and an MH2 domain that mediates interactions with TGF-beta receptors, other Smads, and transcriptional cofactors (6, 11). The activated Smad-2/Smad-3 complex then binds to the common Smad-4 (8, 10) and translocates to the nucleus where it associates with other transcriptional regulators to activate or suppress transcription from TGF-beta target genes such as $p21^{Cip1}$, $p15^{Ink4b}$, $p16^{Ink4a}$ and PAI-1 (7). Although Smad-4 contains both the MH1 and MH2 domains, Smad-4 expression may not be required for TGF-beta mediated transcription in all cell types (12). Furthermore, the specific gene expression profile induced by TGF-beta has been reported to vary according to cell type. Despite the contextual differences in TGF-beta Smad signaling, the Smad-dependent pathway is recognized as a potent suppressor of tumor formation as Smad activation is correlated with inhibition of cell cycle progression and induction of apoptosis.

In contrast to the Smad pathway, the Smad-independent pathways are believed to be important for the pro-oncogenic functions of TGF-beta. Ligand binding to TGF receptors activates MAP kinase signaling through Ras and TGF-beta activated kinase 1 (TAK1) phosphorylation as well as the RhoA and phosphoinositide 3-kinase (PI3K) pathways. While the precise mechanism by which the activated TGF-beta receptors promote signaling through non-Smad pathways has not been determined, numerous independent studies suggest that activation of these pathways can impart malignant characteristics to normal and neoplastic cells (Figure 1). TGF-beta mediated activation of Ras has been shown to promote proliferation of cancer cells (13), and epithelial to mesechymal transition (EMT) in mammary epithelial cells (14) while activation of RhoA promotes EMT of chick heart endothelial cells (15) and migration of macrophages (16). Activation of the PI3K/Akt pathway by TGF-beta has been shown to promote cell survival, EMT, and migration depending on the cell type (17-19). TGF-beta-induced activation of the p38 and c-Jun N-terminal kinase (JNK) pathways has also been shown to elicit biological responses favorable to cancer progression. For example, JNK activation by TGF-beta is necessary for upregulation of the urokinase-type plasminogen activator receptor (uPAR), suggesting that JNK activity is important for extracellular matrix degradation and cancer cell invasion (20) (Figure 1). Furthermore, TGF-beta-induced EMT and migration of mammary epithelial cells has been reported to be dependent on p38 activation (21). Importantly, the non-Smad TGF beta pathways have also been reported to function in a concerted manner to induce specific biological responses. TAK1 and Ras can cooperate to transform epithelial cells (22) whereas activation of RhoA appears to be necessary for Ras-mediated transformation and migration (23, 24). These studies represent a small fraction of the literature pertaining to the pro-oncogenic effects of the non-Smad signaling pathways. Although the specific cellular response to TGF-beta depends on the cell type and precise genetic makeup, these reports underscore the importance of developing therapeutic compounds that can specifically block signaling through the non-Smad pathways. Several TGF-beta inhibitors are presently at various stages of pre-clinical and clinical testing for their efficacy as chemotherapeutic agents (25).

3.2. STRAP inhibits Smad-dependent TGF-beta signaling

Several proteins have been shown to negatively regulate the Smad-dependent pathway by interfering with Smad-2/3 activation. The inhibitory Smads (I-Smads) -6 and -7 block R-Smad activation through association with TBRI (26, 27) while TRIP-1 binding to TBRII has been reported to inhibit downstream transcriptional responses (28, 29). Like the I-Smads, STRAP has also been shown to inhibit Smad-dependent transcriptional activity through association with TBRI (7). Because this association was initially observed in a yeast two hybrid screen for proteins that bind to TBRI, STRAP was strongly implicated in the regulation of TGF-beta signaling. Importantly, the identification of STRAP in this study is not only the first account of STRAP in the scientific literature but also led to the first functional characterization of this protein. It was later shown that STRAP interaction with Smad-7 was required for maximum inhibition of Smad-dependent transcriptional activity (8). Additionally, STRAP has been reported to simultaneously associate with both Smad-7 and TBRI, suggesting that the STRAP/Smad-7 complex may inhibit Smad-dependent signaling by sterically blocking R-Smad binding to TBRI (30) (Figure 1).

Since many tumors develop resistance to TGF-beta due to functional inactivation of Smad proteins, it is likely that STRAP overexpression would also confer resistance to the anti-tumor effects of TGF-beta. It has already been shown that wild type mouse embryonic fibroblasts (MEFs) exhibit a greater capacity for proliferation in the presence of TGF-beta compared to STRAP null fibroblasts (1). Furthermore, STRAP expression has been correlated with decreased TGF-beta mediated transcriptional activity in epithelial cell lines (1). The prevailing model for TGF-beta mediated carcinogenesis dictates that inactivation of the Smad tumor suppressor pathway would promote tumor formation because signal transduction events could only be propagated through the oncogenic Smad-independent pathways. Overexpression of Smad-7 has been shown to decrease Smad-dependent signaling as well as influence activation of c-Jun and Akt in response to TGF-beta (31). Moreover, overexpression of STRAP has been shown to activate the mitogen-activated ERK kinase (MEK)/extracellular signal regulated kinase (ERK) pathway and to downregulate $p21^{Cip1}$ in the absence of exogenous TGF-beta (1). Although it has not yet been determined whether STRAP directly affects signaling through the TGF-beta Smad-independent pathways, it is possible that STRAP may affect these oncogenic pathways through cooperation with Smad-7.

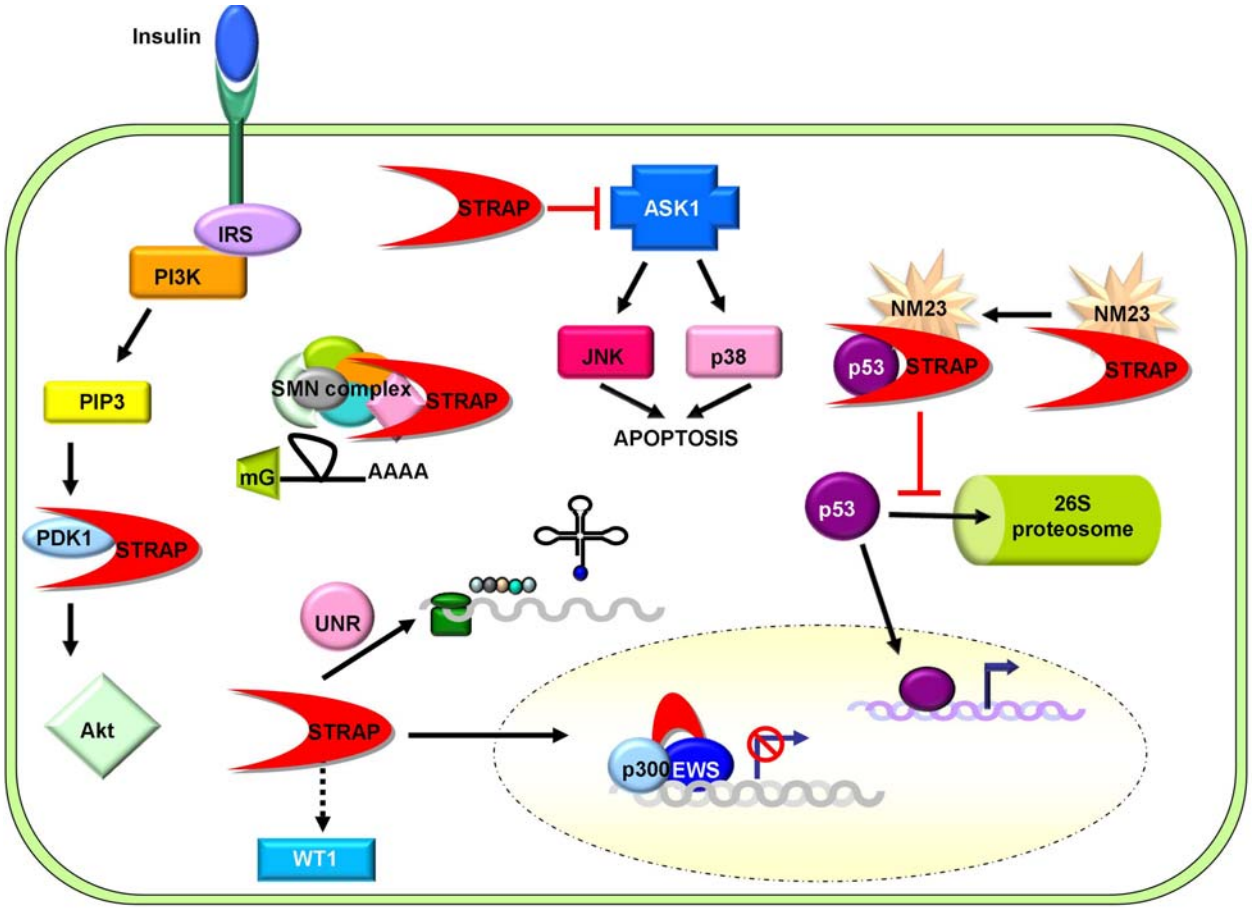

Figure 2. STRAP interactions influence cellular processes and signaling pathways independent of TGF-beta. The association of STRAP with cytoplasmic and nuclear proteins regulates a wide array of cellular activities such as signal transduction, gene expression, mRNA splicing, and protein synthesis. STRAP binding to PDK1 and ASK1 has been shown to increase cell survival by promoting PDK1-mediated phosphorylation of Akt and inhibiting ASK1 activation of the p38 and JNK stress pathways. STRAP has also been shown to regulate gene expression by modulating the activity of transcription factors. Ternary complex formation between STRAP, NM23, and p53 block ubiquitin-mediated proteolysis of p53 and increases p53 transcriptional activity. STRAP binding to the Ewing sarcoma protein, EWS, has been shown to block EWS/p300 dependent transcription. STRAP also regulates expression of mesenchymal markers by indirectly modulating WT1 activity. At the post-transcriptional level, STRAP has been implicated in the assembly of snRNPs for mRNA splicing through its association with the SMN complex. Additionally, STRAP association with unr may promote cap-independent translation of specific cellular transcripts.

4. STRAP INFLUENCES TGF-BETA AND NON-TGF-BETA PATHWAYS THROUGH INTERACTION WITH OTHER PROTEINS

Apart from association with the core components of the Smad pathway, STRAP has also been shown to interact with various other cellular proteins (Figure 2). The functional consequences of these associations influence a wide array of cellular activities including signal transduction, transcription, translation, and protein stability. These interactions and their potential role in cancer development are discussed below.

4.1. STRAP promotes signaling through the PI3K pathway by associating with PDK-1

The phosphoinositide-dependent kinase-1 (PDK1) is a serine-threonine kinase that phosphorylates a wide array of signal transduction proteins including protein kinase C (PKC), S6 ribosomal kinase (S6K), p21-activated kinase 1 (PAK1), and Akt. Activation of PDK1 signaling has been implicated in cellular proliferation, survival, migration, and invasion of tumor cells as well as breast cancer resistance to tamoxifen (32-36). As such, PDK1 inhibitors are currently being evaluated for their efficacy as anti-cancer drugs (37, 38).

A previous study by Seong *et al.* demonstrates that STRAP can bind to PDK1 and promote phosphorylation of the PDK1 substrates S6K, Akt, and Bad (39). In the same study, this association was shown to increase Smad7 binding to a constitutively active TBRI mutant and decrease TGF-beta induced transcription. It was later shown that PDK1 associates with Smads 2, 3, 4, and 7 in the absence of TGF-beta and that STRAP

overexpression promotes complex formation with Smad proteins (40). Taken together, it appears that STRAP and PDK-1 binding augments the inherent functional capabilities of its binding partner. In the context of cancer progression, overexpression of PDK1 could inhibit TGF-beta mediated growth suppression by increasing STRAP and Smad7 binding to TBRI. Likewise, overexpression of STRAP may lead to persistent PDK1 activity. Given that many tumors exhibit increased activation of PI3K/PDK1 signaling, STRAP may represent a novel target for inhibition of this oncogenic signaling pathway.

4.2. The tumor suppressor NM23-H1 physically interacts with STRAP

The NM23-H1 tumor suppressor belongs to the DNA-binding nucleotide diphosphate (NDP) kinase family of proteins. NM23-H1 is regarded as a favorable prognostic indicator of poorly metastatic tumors due to its reduced expression in aggressive late stage tumors (41-43). In addition to its role as a metastasis inhibitor, NM23-H1 has also been reported to affect proliferation and differentiation of some cell lines (44, 45). Currently, the mechanism by which NM23-H1 affects these biological pathways is unknown, but efforts to identify NM23-H1 binding partners may explain the diverse functions of this protein.

With respect to the TGF-beta signaling, previous studies have shown that NM23H-1 can antagonize TGF-beta induced anchorage independent growth (42, 46). However, data describing the effects of NM23-H1 expression on TGF-beta mediated growth suppression are contradictory. Early studies suggest that NM23-H1 potentiates Smad-dependent signaling in HT29 colon cancer cells as antisense NM23 blocks TGF-beta induced growth arrest (47). Contrary to these findings, a recent study reports that NM23-H1 association with STRAP reduces transactivation of Smad-dependent reporter genes and attenuates TGF-beta mediated apoptosis and growth arrest (48). Subsequently, the NM23-H1/STRAP complex was shown to directly bind and stabilize p53 by dissociating Mdm2 (49) (Figure 2). Although transactivation of some TGF-beta responsive genes is dependent on p53 (50), the dual functions of STRAP/NM23-H1 appear to have conflicting effects on the canonical TGF-beta pathway. Like TGF-beta signaling, STRAP/NM23-H1 complex formation may yield different biological outcomes depending on the experimental context. Further investigation will be required to resolve these discrepancies.

4.3. STRAP modulates the function of Ewing Sarcoma protein

Ewing sarcoma (EWS) is a rare form of cancer originating in bone and soft tissues. The genesis of Ewing sarcoma has been attributed to chromosomal translocations that give rise to a chimeric transcript comprised of the EWSR1 gene and members of the E-twenty six (ETS) family of transcription factors (51). Currently little is known about the normal function of the wild type EWS protein. Previous studies on EWSR1 knockout mice suggest that EWS expression is required for B-cell maturation and segregation of chromosomes during meiosis (52). Structural analysis of protein domains within EWS indicates that it contains an RNA recognition motif as well as a transactivation domain that can strongly induce gene expression when fused to a gene containing a DNA binding domain (53-55).

Previous studies that focused on the identification EWS-ETS target genes suggest that the oncogenic fusion protein can function as a transcriptional activator and repressor. For example, EWS-ETS fusion proteins have been reported to repress transcription of TBRII (56) whereas the EWS-FLI protein cooperates with CBP/p300 to induce transcription of HNF4 dependent genes (57). Microarray analysis of validated EWS-FLI target genes in control and EWS silenced STA-ET-7.2 cells confirms that EWS-FLI1 can function as a direct activator and repressor of gene expression (58).

While ongoing studies aimed at identifying EWS-ETS target genes will be critical to understand the pathogenesis of Ewing sarcoma, it will also be necessary to identify proteins that can modulate EWS activity. It has been reported that STRAP can directly associate with EWS and attenuate EWS/p300 dependent activation of hepatocyte nuclear factor 4 (HNF4) reporter constructs (59) (Figure 2). HNF4 is a nuclear receptor that regulates tissue-specific differentiation and proliferation. Stable expression of HNF4 can restore a differentiated epithelial phenotype to hepatoma cells through induction of cytokeratins and E-cadherin (60). Furthermore, HNF4-alpha expression can decrease proliferation and alter cellular morphology of 293T cells (61). In the context of Ewing sarcoma, it is not yet clear whether EWS-FLI-mediated transactivation of HNF4 genes favors tumorigenesis. However, in light of the tumor suppressor functions of HNF, we predict that STRAP overexpression can confer oncogenic properties to cells that require HNF activity for maintenance of cellular differentiation and cell cycle progression.

4.4. STRAP association with ASK1 negatively regulates activation of MAPK stress pathways

The apoptosis signal-regulating kinase 1 (ASK1) is a MAPKK protein that functions as an upstream activator of the stress kinases, p38 and JNK. Under normal physiological conditions, ASK1 is maintained in an inactive state through its association with thioredoxin (Trx). Exposure to various chemicals and oxidative stress leads to its phosphorylation and dissociation from Trx. As its name suggests, ASK1 has been reported to function as a tumor suppressor due to its ability to induce apoptosis of both breast cancer and lung adenocarcinoma cell lines (62, 63).

It has recently been shown that STRAP associates with ASK1 and decreases hydrogen peroxide dependent ASK1 activation as well as ASK1 mediated apoptosis of HEK293 cells (64) (Figure 2). In light of these findings, STRAP overexpression in cancer could theoretically allow cancer cells to escape apoptosis. However, the precise biological significance of STRAP-mediated ASK1 inhibition may be more complicated. A

study by Iriyama *et al.* suggests that ASK1 mediated apoptosis is dependent on ASK2 expression but independently promotes production of pro-inflammatory cytokines (65). Taking this study into account, the effect of STRAP on tumorigenesis may be limited to the early stages of tumor initiation; thereafter, inhibition of ASK1 could block the inflammatory processes that promote tumor progression.

5. STRAP IS INVOLVED IN MAINTAINING MESENCHYMAL MORPHOLOGY OF FIBROBLASTS

The epithelial to mesenchymal transition (EMT) refers to a process by which normal and neoplastic cells downregulate expression of junctional epithelial markers and upregulate expression of mesenchymal genes. EMT is often gauged by a morphological switch that suggests an increased capacity for cellular migration. Recently, it has been shown that STRAP knockout in mouse embryonic fibroblasts causes cells to adopt a metastable phenotype due to induction of E-cadherin. Importantly, enforced expression of STRAP in knockout MEFs abrogated E-cadherin expression and restored the mesenchymal morphology to the fibroblasts (66).

As previously mentioned, disruption of STRAP expression causes branching morphogenesis defects in Drosophila as well as defects in neural tube closure in mice (3, 4). These observed defects may point to a failure in cellular migration as coordinated migration is required for both developmental processes. Retarded motility has been confirmed in STRAP knockout MEFs *in vitro* suggesting a positive correlation between STRAP expression and migration (unpublished data). These findings may suggest that STRAP expression could promote EMT and metastasis of neoplastic cells but further work will be needed to illuminate the role of STRAP in migration and cancer metastasis.

6. THE ROLE OF STRAP IN mRNA SPLICING AND CAP-INDEPENDENT TRANSLATION

Unr is a cytoplasmic RNA-binding protein that has been implicated in cap-independent translation of various proteins. Previous studies aimed at identifying cellular components that initiate internal translation of rhinoviral RNA led to the isolation of a 38 kDa WD40 repeat protein complexed with unr (67). This protein, termed unrip (Unr- interacting protein), is an alias for STRAP. Although *in vitro* translation assays could not establish a functional role for STRAP in the initiation of viral translation, it has been reported that unrip/STRAP can function in concert with other cellular proteins to increase c-myc internal ribosomal entry site (IRES) activity (68).

The survival of motor neurons (SMN) complex is composed of multiple individual proteins that cooperate to assemble small nuclear ribonucleoproteins (snRNPs) for pre-mRNA splicing. The functional significance of the SMN complex is underscored by the development of spinal muscular atrophy in patients carrying homozygous mutations in the SMN1 gene. STRAP has been identified as a necessary component of the SMN complex as immunodepletion of STRAP markedly reduces snRNP assembly (69) (Figure 2). Furthermore, nuclear accumulation of the SMN complex was observed following STRAP knockdown suggesting that incorporation of STRAP is necessary for cytosolic localization (70).

At the present time, there is insufficient data on the role of STRAP in cap-independent translation to definitively state that STRAP can promote oncogenesis through modulation of protein expression. Because translation of most cellular transcripts is dependent on a 5' cap, the effects of STRAP overexpression on protein translation would be limited to a small number of transcripts. However, given that c-myc is a recognized oncogene, STRAP may drive tumor formation by promoting c-myc overexpression. Apart from c-myc, STRAP has not been shown to regulate cap-independent translation of other proteins. This may indicate that STRAP can exhibit specificity with regards to transcript selection. Alternatively, the initial biochemical studies on Unr and STRAP activity may have lacked all of the necessary cellular components to detect an appreciable difference in translation initiation. With respect to STRAP's function in the SMN complex, it is less clear how STRAP could promote oncogenesis. A previous study indicated that STRAP, alongside other spliceosomal proteins, is a target of small ubiquitin-related modifier 4 (SUMO4) in serum starved 293 cells (71). Despite the absence of data describing a functional consequence of sumoylation, it would be difficult to generalize any associated phenotype with cancer because SUMO4 expression is restricted to kidney, pancreatic islets, and dendritic cells (71-73). Furthermore, dysfunction of the SMN complex has only been implicated in the development of specific neuropathies suggesting that the oncogenic activity of STRAP may be achieved through other mechanisms.

7. CLINICAL SIGNIFICANCE AND TARGETED INHIBITION OF STRAP

Preliminary studies suggest that STRAP overexpression may be relevant to the development of various cancers. Upregulation of STRAP has been reported in lung and colorectal tumor tissue samples analyzed by western blot and immunohistochemical staining (1). In a much larger clinical study of colorectal cancer specimens, STRAP overexpression was detected in 70.7% of specimens analyzed (74). Although there was no clinical evidence to suggest that STRAP was correlated with disease stage or survival in this study, it has been reported that STRAP amplification predicts disease outcome in response to chemotherapeutic regimens. Specifically, colorectal cancer patients whose tumors contained increased STRAP copy numbers exhibited decreased overall survival when adjuvant 5-FU therapy was administered whereas patients without STRAP amplification benefited from 5-Fluorouracil (5-FU) treatment (75). It is not yet clear why STRAP copy number affects chemotherapeutic response and survival but it is

important to note that amplification of other genes on chromosome 12p was not reported in this study. Gains in chromosome regions proximal to the STRAP locus has been reported in teratomas and basal-like breast cancer so it is possible that amplification of nearby genes may also account for the observed differences in these patients (76-79).

Further work will be needed to clarify the role of STRAP in carcinogenesis, but clinical data reported thus far indicates that there is a strong association between STRAP overexpression and cancer. *In vitro* studies on the biological functions of STRAP suggest that it can modulate various oncogenic signaling pathways while *in vivo* animal studies indicate that STRAP expression promotes tumor formation (1). Taken together, it is likely that STRAP influences the pathways and processes that drive cancer progression, and should not simply be regarded as a biomarker. As such, STRAP may be relevant target for the development of anti-cancer therapeutics. At the present time, there are no reports of any STRAP inhibitors in clinical use or development. Based upon our unpublished observations, STRAP is highly stable and does not appear to be subject to regulation by growth factors. Although we can't definitively state that STRAP expression can not be transcriptionally regulated, the absence of STRAP "inducibility" may indicate that gene amplification is the primary mechamism by which STRAP is overexpressed in cancer. Therefore, regulation of gene expression may not be a viable approach to drug design. However, like many other druggable targets, disrupting STRAP protein-protein interactions may be a useful avenue for the rational design of STRAP inhibitors. As a crystal structure for STRAP is not available yet, computational modeling programs may facilitate the identification of potential small molecule inhibitors of STRAP. Screening libraries of bioactive compounds may also lead to the identification of STRAP inhibitors. It has recently been shown that Pateamine A, a product of marine sponges, can bind to STRAP and the eukaryotic translation initiation factor eIF4A (80,81). Although the effects of Pateamine A association with STRAP have not been characterized, Pateamine A and its analogs have already been shown to block eukaryotic translation (81) and proliferation of cancer cells (82). Alternatively, intracellular single chain antibody fragments (scFvs) directed against STRAP may be a means of inhibiting STRAP association with other cellular proteins if effective tumor targeting and cellular uptake can be achieved.

8. CONCLUSION

Although STRAP is largely known as an inhibitor of classical TGF-beta signaling, it is now becoming apparent that STRAP's biological functions are not limited to TGF-beta signaling. Compared to other cellular proteins and signaling pathways, our understanding of the complex interactions and pathways that are influenced by STRAP is still in its infancy. While recent publications illuminate new biological functions for STRAP, it has not yet been determined whether any of the STRAP protein interactions directly impact other STRAP-mediated signaling events or whether they function independently of one another. Despite the significant void of data pertaining to STRAP, the literature published by this lab and others suggests that STRAP possesses oncogenic characteristics. Moreover, the pre-clinical data that is presently available corroborates these findings. Herein, we have provided an overview of the literature on STRAP with a focus on its potential role in cancer. Future studies on this protein will be required to obtain a comprehensive understanding of the mechanisms whereby STRAP promotes oncogenesis.

9. ACKNOWLEDGEMENTS

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A**bbreviations**: STRAP, serine-threonine kinase receptor-associated protein; TGF-beta, transforming growth factor-beta; TBR, transforming growth factor-beta receptor; BMP, bone morphogenic protein; MH, mad homology; PAI-1, plasminogen activator inhibitor- 1; MAP kinase, mitogen activated protein kinase; TAK1, TGF-beta activated kinase; PI3K, phosphoinositide 3-kinase; EMT, epithelial to mesenchymal transition; JNK, c-Jun N-terminal kinase; MEF, mouse embryonic fibroblast; MEK, mitogen-activated ERK kinase; ERK, extracellular signal-regulated kinase; PDK1, phosphoinositide-dependent kinase-1; PKC, protein kinase C; S6K, S6 ribosomal kinase; PAK1, p-21 activated kinase 1; NDP, nucleotide diphosphate; EWS, Ewing Sarcoma; ETS, E-twenty six; HNF4, hepatocyte nuclear factor 4; ASK1, apoptosis signal-regulating kinase 1; Trx, thioredoxin; Unrip, Unr-interacting protein; IRES, internal ribosome entry site; SMN, survival of motor neurons; snRNP, small nuclear ribonucleoprotein; SUMO4, small ubiquitin-related modifier 4; 5-FU, 5-Fluorouracil.

Key Words: STRAP, TGF-beta, Smad signaling, Cancer, Review

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