

Comprehensive Analysis of TGF β & β – Catenin Components in Various Human Cancer Tissues

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Abstract

Studies over the last years revealed significant insights into the β -Catenin & TGF β signal transduction pathways and that such pathways are abnormal activated in abundant cancer types. According to the straight forward effect of these pathways in various tumor types, both pathways are currently considered targets for innovative cancer therapies. This view study emphasizes 13 proteins that are implicated in these two pathways. As there has been widespread research into the proteins that involved in these pathways, we have utilized data

existing in the Human Protein Atlas database in this paper to examine the expression of 53 crucial proteins that are recognized to be involved in the activation of these pathways in a distinct group of 45 cancer types. Our findings revealed notably that the proteins (SKIL, SHC, ERK1/2, RAS, PI3K (PIK3CA), SMAD8, ACVR2A/1B SNON, AKT, and SMAD3, from TGF β and (RNF43, SNAIL1 and DVI) for β catenin show high expression in most cancer tissues. Our results strongly suggest that these proteins might have the ability to act as potential objects for remedies and provide perception into the molecular basis of cancer.

Keywords: TGF β , β -Catenin; PI3K, Cancer, SMAD, Tumorigenesis

1. Introduction

Cancer is considered the second cause of mortality globally; it has been found that many genes mutations are involved in cancer pathogenesis. The fact that it is a disease at the tissues level makes it all more difficult and complicated. Further information has been gained, useful for primary diagnosis and also for treatment (Hassanpour, Dehghani, & Practice, 2017).

Cell transduction is a course in the elaboration and development of tumor. Alterations in different cell signaling pathways stimulate tumor cell proliferation, development, and survival. The two pathways TGF β & β - catenin are model that are integrated in growth, proliferation, persistence, motility, metabolism, and the regulation of immune response. Stimulation of these pathways is an important causes of cancer cell endurance to antitumor remedies. This causes these pathways an essential purpose for discriminating the improvement and progression of this illness. Therefore, they may play a part as a potential anti-cancer drug (Ortega et al., 2020).

TGF- β is a secreted polypeptide which has the ability to induce fibroblast and the production of collagen. After this discovery, TGF- β was also found to inhibit cell proliferation. It has also been found that it has a role in apoptosis, so being an inhibitor of cell proliferation and playing a role in apoptosis shows that it has a very big importance in controlling the cell cycle and the cell death (Kubiczkova, Sedlarikova, Hajek, & Sevcikova, 2012).

In mammals, three types of TGF- β (TGF- β 1, 2 and 3), encoded by various genes, that work during the same receptor signaling systems (Kubiczkova et al., 2012). They act as tumor suppressors that inhibit cell proliferation by inhibiting C-Myc, Certain cyclin-dependent kinase inhibitors (CDKIs) expression (Kubiczkova et al., 2012).

The two pathways Smad and non-Smad transduced TGF- β signaling which mediated by TGF- β ligands, type1 and type2 receptors and Smad or non-Smad proteins, including Akt, extracellular signal-regulated kinase (ERK) 1/2 and p38 mitogen-activated protein kinase (Liu, Chen, & Zeng, 2018). Disruption of the TGF- β pathway has been involved in many human diseases, including both solid and hematopoietic tumors. TGF- β acts as a tumor suppressor; but in tumor cells, TGF- β loses its anti-proliferative response and becomes an oncogenic factor, and this lead to losing its main function as an Inhibitor (Kubiczkova et al., 2012). Sensitivity to these effects of TGF- β is lost during tumor progression, so TGF- β signaling will have a pro-oncogenic function in later stages (Kubiczkova et al., 2012).

Mutation and/or functional inactivation of TGF- β receptors or downstream alterations in the SMAD-signaling pathway because malignant cells become resistant to effects of TGF- β . So during late stages of tumor progression, TGF- β will act as a tumor promoter and is over-expressed in many cancers (Kubiczkova et al., 2012). the stimulation of matrix deposition induce it to function as a tumor promoter .perturbation of immune function and induction of epithelial-mesenchymal transition (Liu et al., 2018). For Beta Catenin pathway it is a 3-domain consisting, it is a highly regulated member of signal transduction pathway, an adhesion component and a pivotal component of the Wnt signaling pathway. It has also an important task in physiological homeostasis. Its elevated expression leads to different diseases, including cancer. It can act together as a transcriptional co-regulator and an adaptor protein for intracellular adhesion. In mid-1990s, groups found independently that the signaling function of β catenin in the nucleus is facilitated by T-cell factor or lymphoid enhancer-binding factor (Prakash & Swaminathan, 2015).

β catenin consists of 130 amino acid amino-terminal domain where the Central domain is the most conserved. , it also acts as a link between α -catenin and cadherins, to sustain the cytoskeleton structure, cell–cell interaction, and cell signaling (Kim et al., 2019). It plays a role in cancer by accumulates in the nucleus and stimulates the transcription of several oncogenes such as c-Myc and CyclinD-1, which leads to the contribution to carcinogenesis and tumor progression of many cancers, including colon cancer, hepatocellular carcinoma, pancreatic cancer, lung cancer and ovarian cancer (Shang, Hua, & Hu, 2017).

In human cancer phosphorylation sites in the N-terminal domain of β -catenin are mutational flashpoints, showing that getaway from the demolition of the complex-mediated β -catenin protein is the way how tumorigenesis happens (El-Sahli, Xie, Wang, & Liu, 2019) Figure 1(a, b) (SinoBiological, 2021).

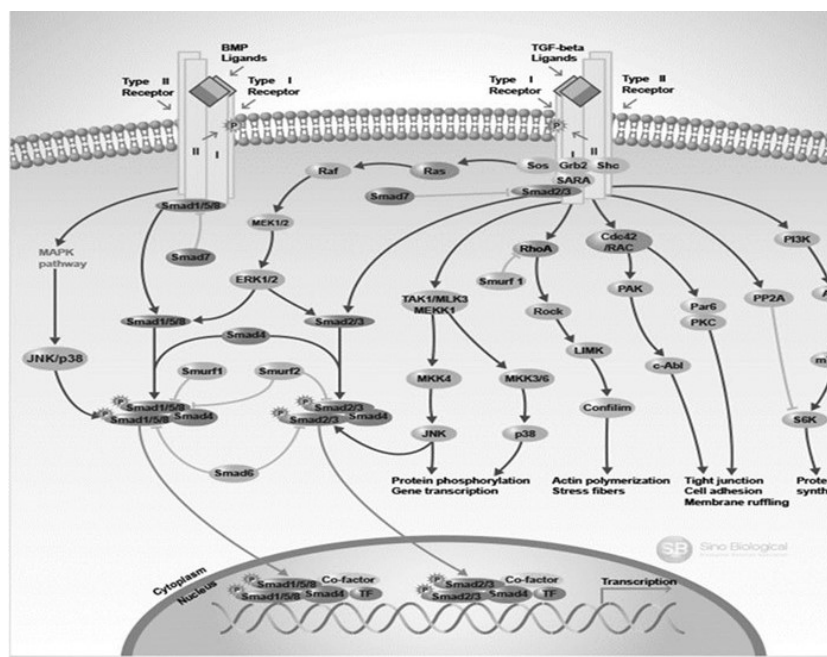


Figure 1.a .TGF beta signaling pathways

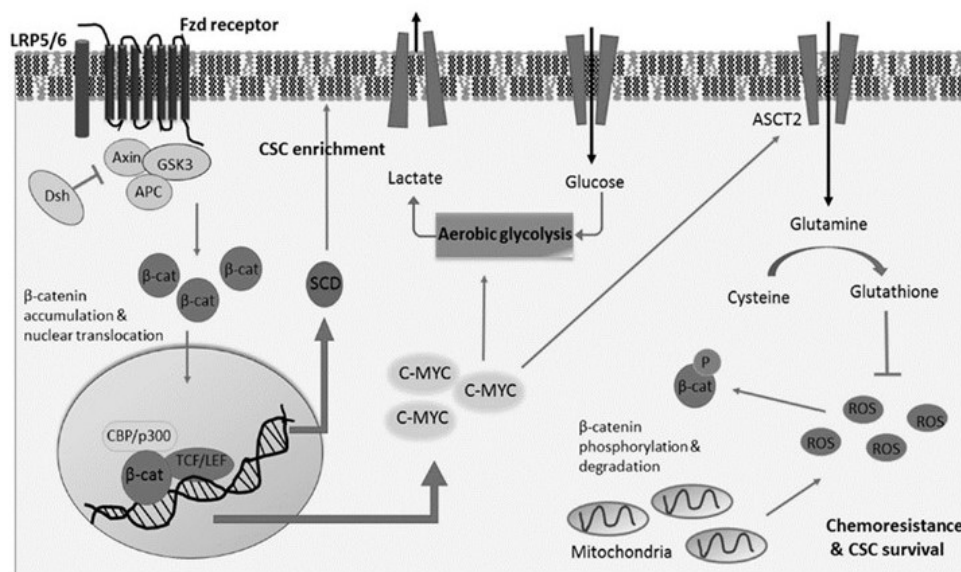


Figure 1.b. the role of the canonical Wnt/β-catenin pathway in tumor metabolism

2. Materials and Methods

Information was obtained from the database (www.proteinatlas.org) by searching for the chosen gene names. The level of expression for the 53 specified proteins that were identified for implication in the β-Catenin & TGF beta pathways were investigated in 45 different cancer tissues types include, Cerebral cortex, Cerebellum, Nasopharynx, Bronchus, Stomach, Duodenum, Small intestine, Colon, Rectum, Gallbladder, Kidney, Seminal vesicle, Fallopian tube, Cervix, uterine, Appendix, Lung, Liver, Urinary bladder, Heart muscle, Bone marrow, Soft tissue, Hippocampus, Caudate, Thyroid gland, Parathyroid gland, Adrenal gland, Oral mucosa, Salivary gland, Esophagus, Pancreas, testis, Epididymis, Prostate cancer, Vagina, Ovary Endometrium, Placenta, Breast, Smooth muscle, Skeletal muscle, Adipose tissue, Skin, Spleen, Lymph node, and Tonsil.

The level of expression for the 53 specific proteins in the various tumor tissues were stated as high, medium or low (excluding no expression) according to normal tissues illustrated in the protein atlas data base. Afterward, the high, medium and low percentage of expression in each cancer tissue was represented for patients exhibiting high expression. Pie charts were generated using Microsoft Excel 2010 to signify the percentage of each level of protein expression.

3. Results

In current study, the levels of expression for 53 specific proteins in 45 different cancer tissues were studied using the data base (www.proteinatlas.org). (Atlas, 2021) (36 genes for TGF beta & 17 genes for β-Catenin) were studied. The following proteins were examined: SMAD4, SNON, SMAD1, SMAD8, SMURF2, USP4, RAC1, WLS, TAB1, TAZ, ACVR2A/1B,

SMAD2, SMAD3, RPS6KB1, AKT1, GSK-3, RNF43, DV11, SNAI1, TGFBR1/2, ALK5, SKIL, SMAD7, GRB2, P38, MAPK, PPP2CA, PIK3CA, MTOR, RHOA, ROCK2, SMURF1, NEDD4, JNK, CYLD, NLK, LGR5/6, LRP5/6, TAB2, BCL9, SHC, RAS, LEP1, TCF3, ACVR2A/1B, SKI, TF, PP2A, P70 56K, PI3K, SOS, ERK 1/2 and FOXO.

The physiological activity and full name of these proteins, as well as their part in cancer initiation and control, is briefed in (S. Table I, II). The results concealed that 13 of the 53 proteins tested exhibited high expression levels in different cancer tissues 10 from TGF beta and 3 from β -Catenin pathway. The proteins from TGF beta include, (SKIL, SHC, ERK1/2, RAS, PI3K (PIK3CA), SMAD8, ACVR2A/1B, AKT, SMAD3, and SNON). For β catenin: 3 proteins are (RNF43, SNAIL1 and DV11).

The rest 40 proteins showed medium, low or no expression in cancer tissues (data presented in supplementary figures). The level of expression for each protein examined was classified as high, medium or low. So, from the data that were analyzed we found That SNON protein showed high expression in 26 cancer tissues, (Figure 2). For AKT protein it showed high expression in 28 cancer tissues, (Figure 3). SKIL protein was highly expressed in 26 tissues, (Figure 4). For SHC protein, it was found in 25 cancer tissues. (Figure 5). PI3K was founded in 18 tissues. (Figure 6). ACVR2A/1B was founded in 18 cancer tissues. (Figure 7). ERK1/2 was founded in 23 tissues. (Figure 8), RAS was founded in 20 tissues. (Figure 9), Protein SMAD3 exhibited ~100% high expression in 26 cancer tissues, Figure 10). SMAD8 was founded in 20 tissues. (Figure 11).

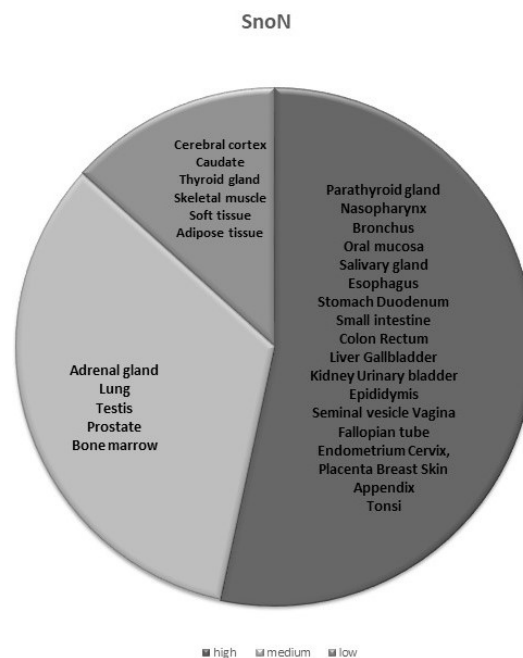


Figure 2. The levels of expression for protein (SnoN) in various tumor tissues

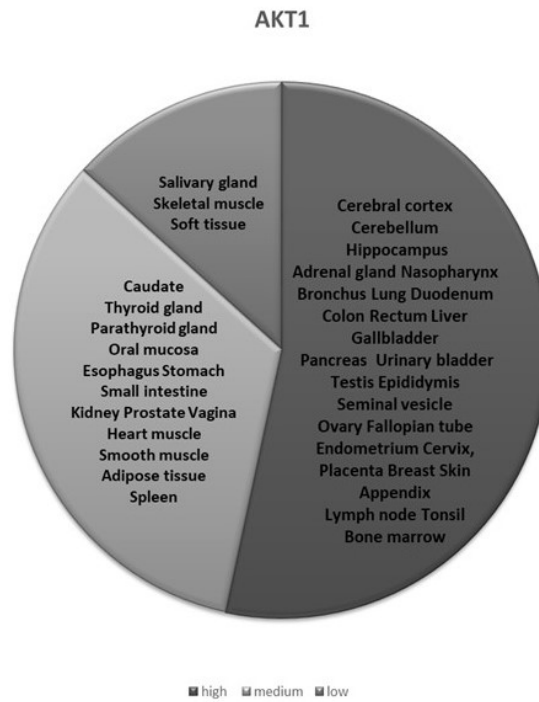


Figure 3. Expression levels of AKT1 protein in various tumor tissues

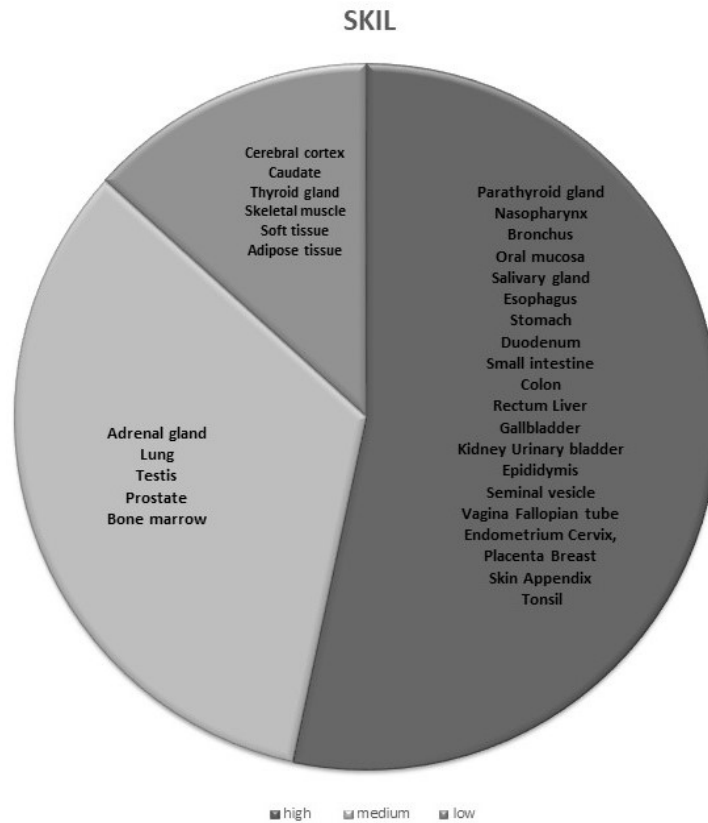


Figure 4. SKII protein Expression levels in different tumor tissues

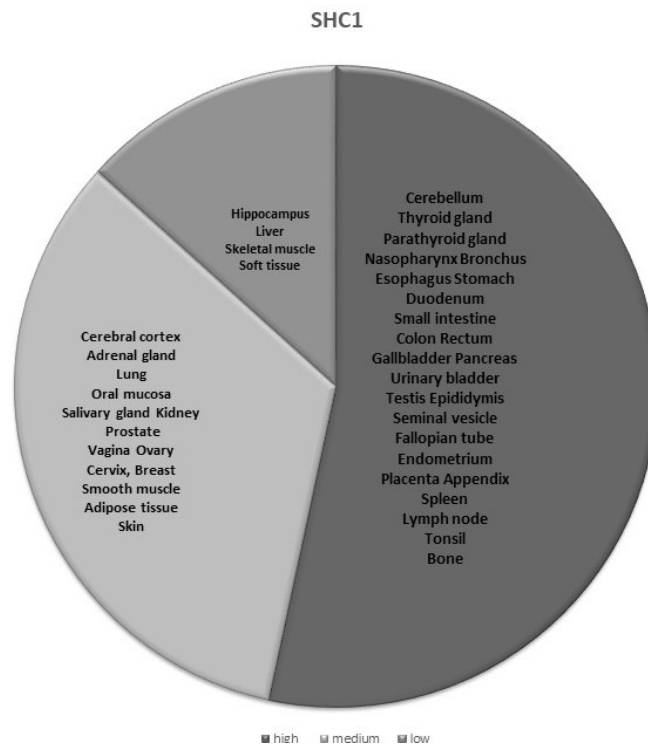


Figure 5. Expression levels of SHC1 protein in various tumor tissues

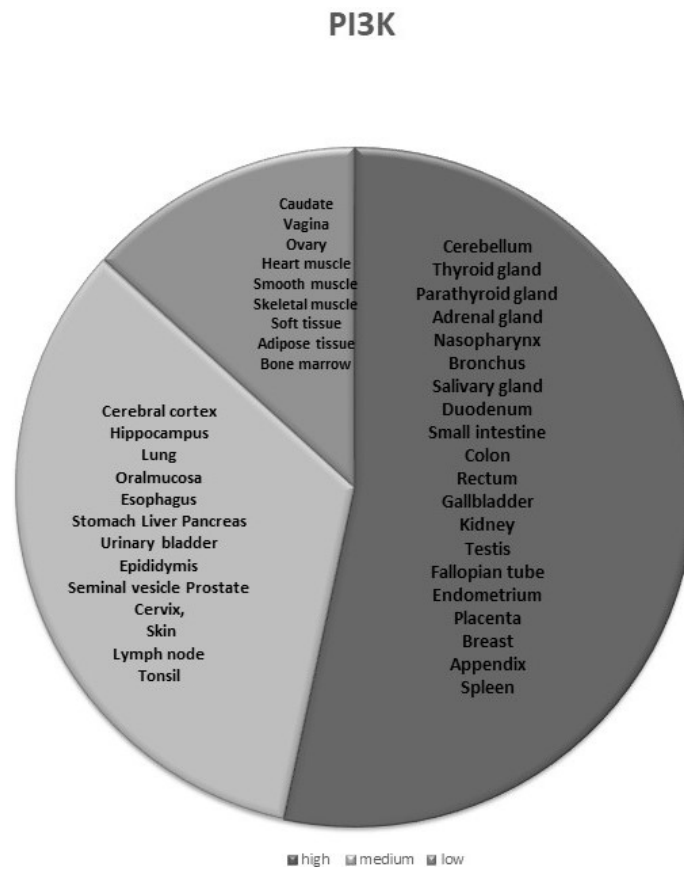


Figure 6. The expression levels of PI3K protein in various tumor tissues

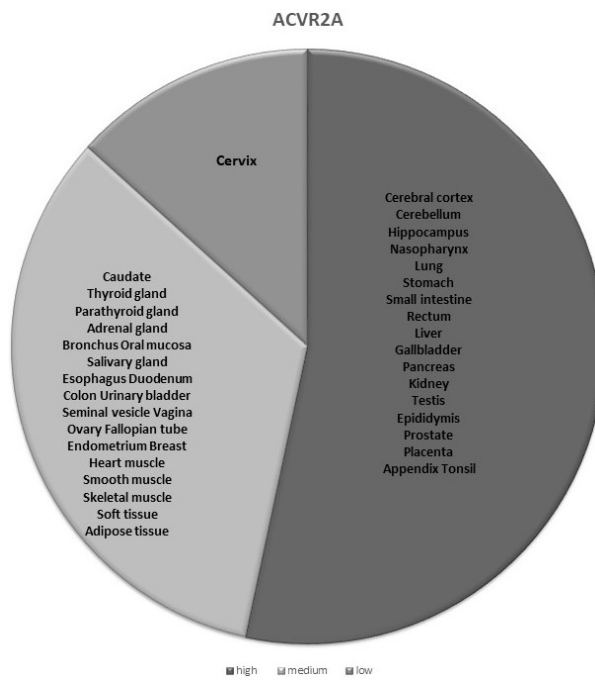


Figure 7. Expression levels of ACVR2A protein in different tumor tissues

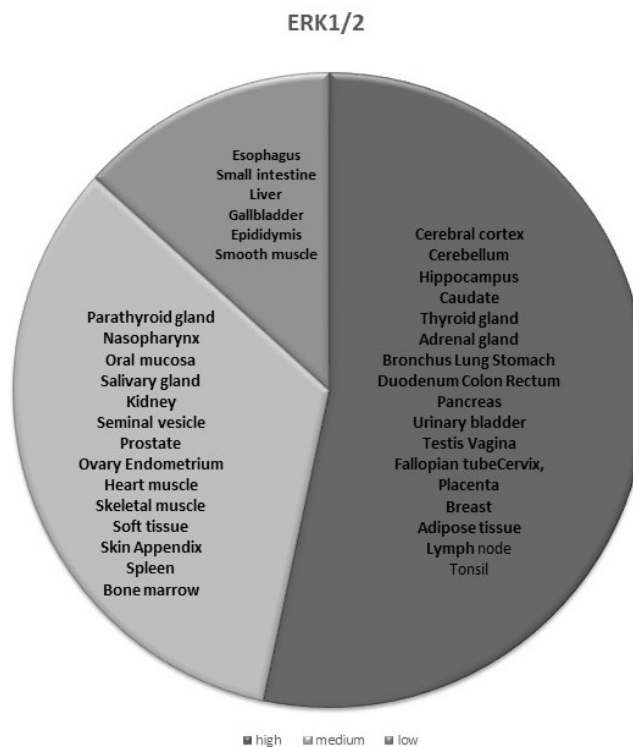


Figure 8. Expression levels of ERK1/2 protein in different tumor tissues

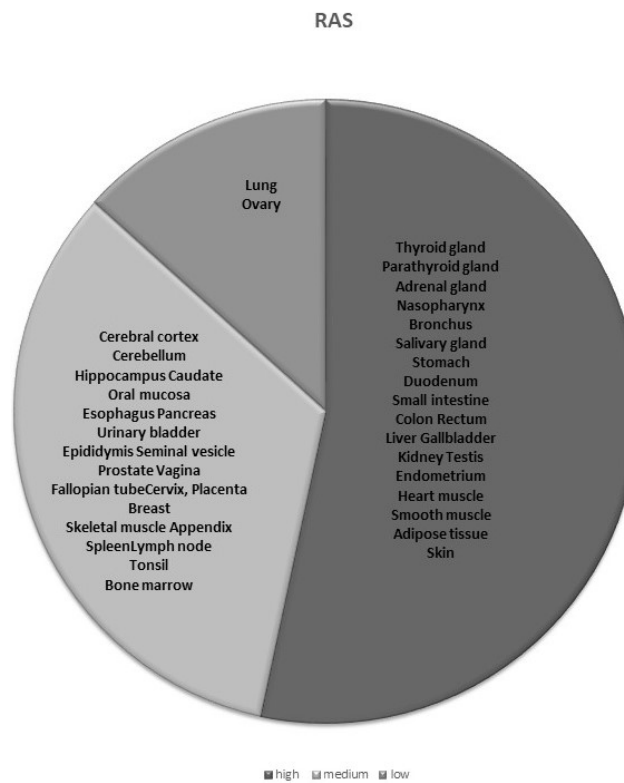


Figure 9. Expression levels of RAS protein in different tumor tissues

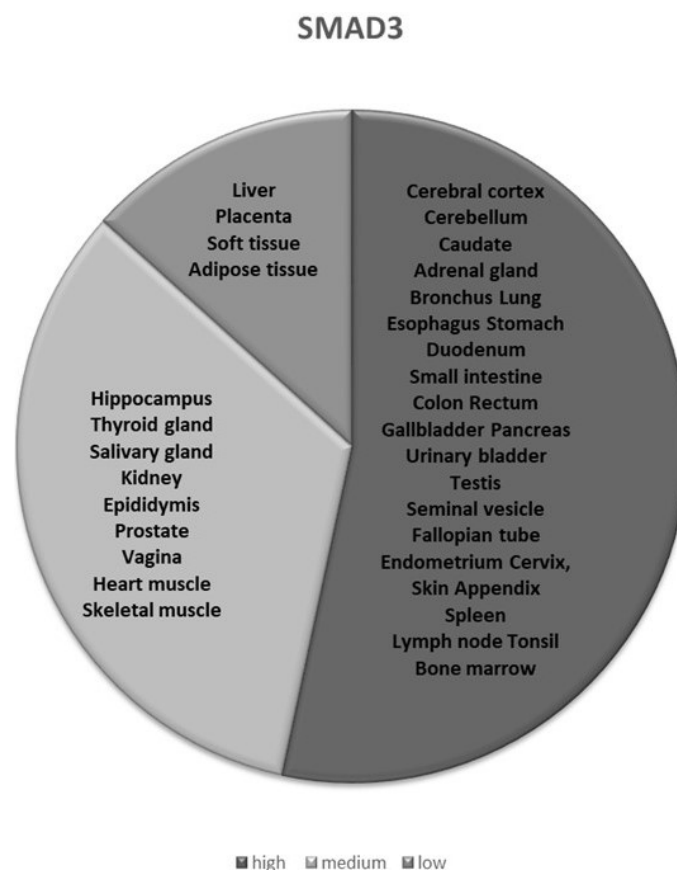


Figure 10. Expression levels of SMAD3 protein in different tumor tissues

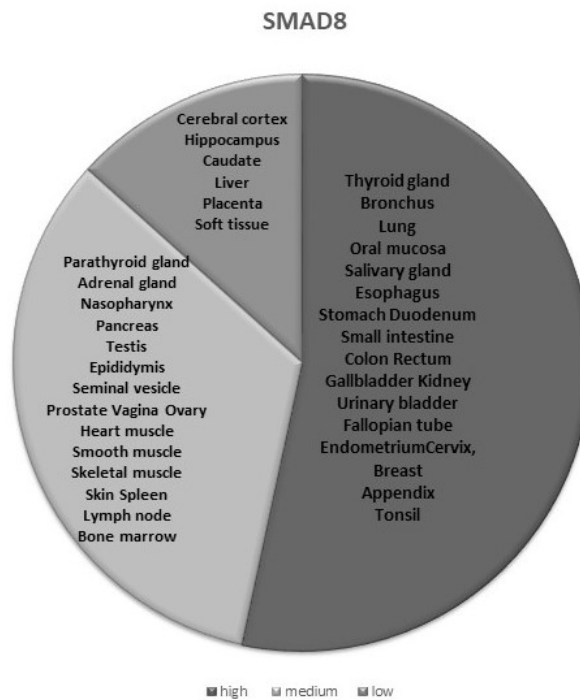


Figure 11. Expression levels of SMAD8 protein in different tumor tissues

For β catenin pathway, 3 proteins have ~ 100% expression in most of the cancer tissues that were examined DV11 that was found in 32 tissues. (Figure 12), (RNF43 was founded in 39 Tissues, (Figure 13). SNAIL1 was founded in 39 tissues, (Figure 14).

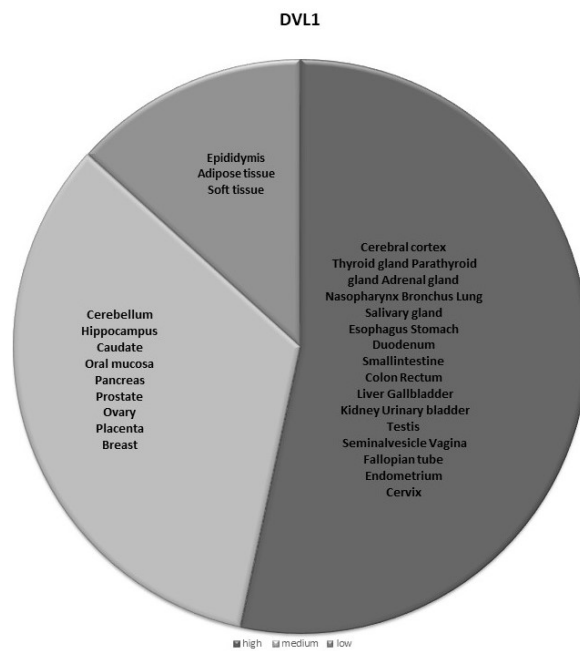


Figure 12. Expression levels of DVL1 protein in different tumor tissues

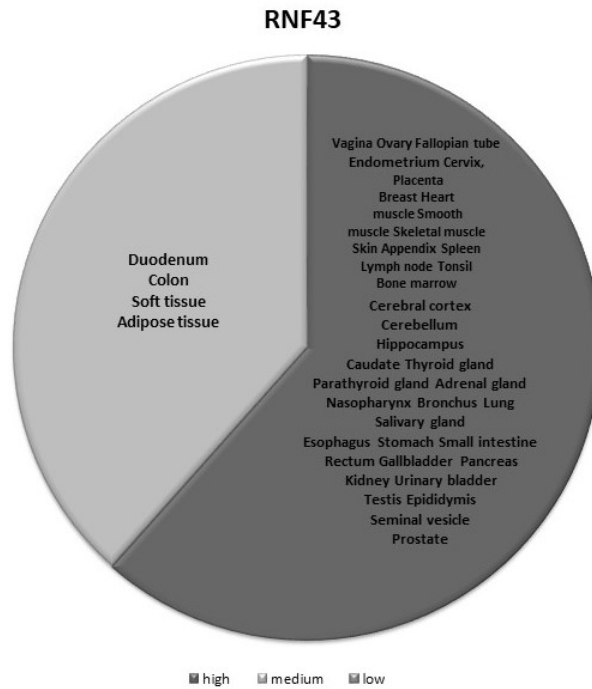


Figure 13. Expression levels of RNF43 protein in different tumor tissues

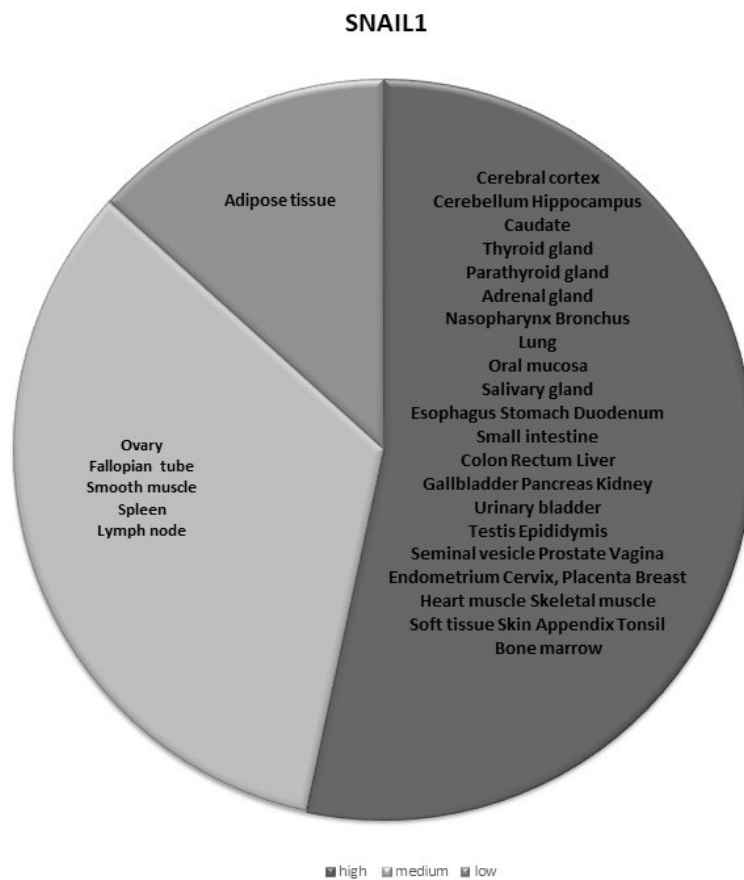


Figure 14. Expression levels of Snail1 protein in different tumor tissues

Our study was conducted utilizing these two pathways, and detailed information is provided in an Additional file.(supplementary figs).

The data that were collected show that the proteins (ACVR2A/1B, ERK1/2, SMAD2, SMAD3, RPS6KB1, AKT1, MKK, SOS1, GSK-3, RNF43, Dvl1 and Snail1) are highly expressed in cerebral cortex cancer tissues. Fig.S1. For cerebellum cancer tissues 12 proteins are highly expressed which includes (ACVR2A/1B ERK1/2, SMAD2, SMAD3, RPS6KB1, AKT1 MKK, SOS1, GSK-3, RNF43, Dvl1 and SMAIL1 as shown in Fig.S2

For Nasopharynx, we found that (ACVR2A/1B, SKI, SNON, RPS6KB1, PIK3CA, AKT1, SKI1, SHC1, RAS, RNF43, Dvl1, TAB2, SNAI1 and, LGR5) show high expression. Fig.S3. In bronchus cancer tissues the proteins which show high expression are: SMAD3, SNON, SMAD8, RPS6KB1, PIK3CA, AKT1, USP4, SKI1, ERK1/2, SHC1, RAS, RNF43, LGR5/6, and DVI1, TAB2 and snail1. FigS4.

For Stomach cancer tissues 18 protein were highly expressed (ACVR2A/1B, SMAD3, SNON, SMAD1, SMAD8, RPS6KB1, MTOR, SMURF1, ERK1/2, USP4, SKI1, SHC1, SARA, RAS, RNF43 DVI1, TAB2, and SNAI1. Figure S5. For Duodenum cancer tissues (SMAD3, SMAD4, SNON, SMAD8, PIK3CA, AKT1, MTOR SKI1, ERK1/2, SHC1, SARA, RAS, DVI1, TAZ, and SNAI1. Figure S6.

Small intestine proteins that highly expressed (ACVR2A/1B, SMAD3, SMAD4, SNON, SMAD8, SHC1- PIK3CA, MTOR, SKI1, SARA, RAS, RNF43, DVI1, TAB2, TAZ, and SNAI1. FigS7. Colon cancer tissues (SMAD3, SMAD4, SNON, SMAD8, PIK3CA, AKT1, JNK SKI1, ERK1/2, SHC1, SARA, RAS, DVI1, SNAI1. Fig. S8.

Rectum cancer tissues proteins (ACVR2A/1B SMAD3, SMAD4, SNON, SMAD8, PIK3CA, AKT1, JNK, SKI1, ERK1/2 SHC1, SARA, RAS, RNF43, DVI1, TAB2, and SNAI1, Fig.S9.

Gallbladder cancer tissues (ACVR2A/1B, SMAD3, SNON, SMAD8, PIK3CA, AKT1 MTOR, SHC1 SMURF1, SKI1, RAS ,RNF43 ,Dvl1, TAZ, and SNAI1.Fig.S10. Kidney tissues (ACVR2A/1B, SNON, SMAD8, PIK3CA, USP4, SKI1, RAS, WLS, LRP5/6, RNF43, DVI1, SNAI1. Fig.S11.

Seminal vesicle 10 proteins are highly expressed including SMAD3, SNON, AKT1, SKI1, SHC1, MTOR, RNF43, DVI1, and snail1. Fig.S12. Fallopian tube (SMAD3, SNON, SMAD8, PIK3CA, AKT1, MTOR, ERK1/2, SHC1, SMURF1 SKI1, RNF43, LGR5/6, and DVI1. Fig. S13.

Cervix, Uterine (SMAD3, SNON, SMAD8, AKT1, ERK1/2, SMURF1, JNK, KIL, RNF43, DVI1 and SNAI1. Fig. S14. Appendix (ACVR2A/1B, SMAD3, SMAD4, SNON, SMAD8, GRB2, PIK3CA, SHC1 AKT1, MTOR SKI1, RNF43, DVI1 and SNAI1. Fig. S15.

Lung (ACVR2A/1B, SMAD3, SMAD8, AKT1, SMURF1 ERK1/2, SARA, RNF43, Dvl1, TAB2 and SNAI1. Fig. S16. For Liver (ACVR2A/1B, SNON, RPS6KB1, AKT1, MTOR, SKI1, RAS, DVI1 and SNAI1. Fig. S17.

Urinary bladder, (SMAD3, SNON, SMAD8, RPS6KB1, AKT1, MTOR, ERK1/2 SHC1, SMURF1 SKI, RNF43, DVI1, and SNAIL1. Fig. S18. Heart muscles (RPS6KB1, MTOR, RAS, TCF3, RNF43, DVI1, TAZ, and SNAIL1. Fig. S19.

Bone marrow, (SMAD3, SKI, AKT1, SHC1, TCF3, RAC1, RNF43, DVI1, TAB2, and SNAIL1. Fig. S20. Soft tissue (TAB2, SNAIL1, SMAD4). Fig. S21. Hippocampus proteins (ACVR2A/1B SOS1, SMAD2, AKT1, ERK1/2, GSK-3, RNF43 and SNAIL1. Fig. S22.

Caudate tissues (SMAD3, ERK1/2, GSK-3, RNF43, and snail1. Fig. S23. Thyroid gland (SMAD8, RPS6KB1, PIK3CA, ERK1/2 SHC1, RAS, NEDD4 RNF43, DVI1, and SNAIL1. Fig. S24.

Parathyroid gland (SNON, RPS6KB1, SHC1, PIK3CA, SKI, MKK, RAS, RNF43, DVI1 and SNAIL1. Fig. S25. Adrenal gland (SMAD3, PIK3CA, AKT1 ERK1/2 SARA, RAS, WLS, RNF43, DVI1 and SNAIL1. Fig. S26.

Oral mucosa (SNON, SMAD8, MKK, SKI, and SNAIL1. Fig. S27. Salivary gland (SNON, SMAD8, PIK3CA, SKI, RAS, RNF43, DVI1 and SNAIL1. Fig. S28. Esophagus (SMAD3, SNON, MKK SHC1 SMAD8, SKI, RAC1, RNF43, DVI1 and SNAIL1. Fig. S29.

Pancreas (ACVR2A/1B, ERK1/2, SMAD3, AKT1, SHC1, SARA, RNF43, TAB2, ANAIL1. Fig. S30.

Testis (ACVR2A/1B, SMAD2, SMAD3, SKI, SMAD5, PIK3CA, AKT1, SOS1, ROCK2, SHC1 SMURF2 ERK1/2, RAS, RNF43, DVI1, TAZ, SNAIL1 and WLS. Fig. S31.

Epididymis (ACVR2A/1B, SKI, SMAD2, SHC1, SNON, SMAD1, AKT1, SARA, LRP5/6, RNF43, TAB2, SNAIL1. Fig. S32. Prostate (ACVR2A/1B, MKK, SMAD2, RNF43 and SNAIL1. Fig. S33.

Vagina (SNON, SKI, NEDD4, ERK1/2, JNK, RAC1, RNF43, DVI1 and SNAIL1. Fig. S34.

Ovary (SOS1, AKT1, RNF43. Fig. S35. Endometrium (SKI, SHC1, SMAD3, SNON, SMAD8, PIK3CA, AKT1, RAS, RNF43, DVI1, TAB2 and SNAIL1. Fig. S36.

Placenta (ACVR2A/1B, SKI, ERK1/2, SMAD2, SMAD4, SKI, SNON, TF, GRB2, RPS6KB1, SOS1, PIK3CA, AKT1, SMURF1 SHC1, SARA, WLS, RNF43, TAB2 and Snail1. Fig. S37.

Breast (SMAD2, SKI, SNON, SMAD8, RPS6KB1, ERK1/2, PIK3CA, AKT1, SMURF1, JNK, RAC1, WLS, RNF43 and SNAIL1. Fig. S38. Smooth muscles (RAS, RNF43, TAZ). Fig. S39. Skeletal muscle (RNF43, SNAIL1, DVI1). Fig. S40.

Adipose tissue (ERK1/2, RAS). Fig. S41. Skin (SMAD3, SNON, AKT1, NEDD4, SKI, RAS, RAC1, RNF43, DVI1, TAB2, TAZ, and SNAIL1. Fig. S42.

Spleen (SMAD3, SHC1 PIK3CA, RNF43, and DVI1). Fig. S43. Lymph node (SMAD3, GRB2, ERK1/2 SHC1, RPS6KB1, AKT1, TCF3, RNF43, DVI1 and LEF1). Fig. S44.

Tonsil (ACVR2A/1B, SKI, MKK, SMAD2, SMAD3, SNON, SMAD8, ERK1/2, SARA,

GRB2, AKT1, SHC1, RAC1, RNF43, DV11, SNAIL1, LEF1 and TCF3. Fig.S45.

4. Discussion

As there has been huge research into the proteins that are involved in TGF β & β -catenin pathways, we have utilized data presented in the database in this paper to examine the level of expression for the crucial 53 proteins that are identified to be involved in the activation of these pathways in a distinct group of 45 cancer types. Our findings revealed notably that the 10 proteins SNON, AKT, SKIL, SHC, PIK3CA, ACVR2A/1B, ERK1/2, RAS, SMAD8, and SMAD3 which are involved in TGF β and 3 proteins RNF43, SNAIL1 and DV1 which are involved in the β catenin pathway to exhibit high expression in most cancer tissue types.

Regarding the TGF β pathway, the first protein examined was SNON which exhibited high expression in 26 cancer tissues. (Figure 2). From previous literature this protein plays an important part as a modulator of biological responses and TGF β -induced signal transduction. Recently, SNON protein was found to have an important role in proliferating cells and post mitotic neurons in both TGF β -dependent /independent. SNON arbitrates the ability of TGF β to induce cell cycle arrest in a cell-type at cellular level. Accumulating data implies that SNON performs a double role as a corepressor or coactivator of TGF β -induced transcription. Therefore, SNON employs oncogenic or tumor-suppressive effects in epithelial tissues. So we can spotlight our understanding of SNON as a target for cancer treatment (Bonni & Bonni, 2012).

The second protein (serine/threonine protein kinase Akt) had a high expression level in 28 cancer tissues, (Figure 3). This is a major signal transducer of the phosphoinositide 3-kinase (PI 3-K) pathway in all cells and tissues and plays an important role in the maintenance of cellular processes including cell growth, proliferation, survival and metabolism. Various studies showed that the frequent aberrant activation of the PI 3-K/Akt pathway in human cancer has made it an attractive therapeutic target. Otherwise, it has provided a comprehensive understanding of the specific functions of Akt signaling in cancer cells as well as the surrounding tumor microenvironment and this has informed and enabled the development of therapeutic drugs to target both PI 3-K and Akt (Chin & Toker, 2009).

The third one was SKIL protein; the highest expression level was present in 26 cancer tissues, (Figure 4). Based on a literature search the human SKI-like (SKIL) gene encodes the SMAD transcriptional co-repressor SNON that antagonizes TGF- β signaling. Recent studies examined the molecular mechanisms involved in the self-regulation of SKIL gene expression by SNON (Tecalco-Cruz et al., 2012).

The fourth one was SHC protein 1 (which is a protein in humans that is encoded by the gene (SHC1)) which shows high expression in 25 cancer tissues. (Figure 5) It has an important role in drug resistance and apoptosis regulation in the cells of mammals. The adapter protein has an important role in the transmission of activated tyrosine phosphorylation signaling which has a vital role in the regulation of growth that includes metastasis and carcinogenesis and (Syed Mahfuzul et al., 2009).

The fifth one was PIK3CA protein which exhibited high expression in 20 cancer tissues, (Fig.6) Previous studies proved that this protein serves as an oncogene in tumor genesis and development of esophageal cancer at the levels of genetic mutation and epigenetics. Recent researches demonstrate that PIK3CA mutation has been found in a large variety of human tumors, Furthermore, the PIK3CA gene has been recognized as a candidate driver gene of lung squamous cell carcinoma and may contribute to the tumor cell growth and development of NSCLC (Wang, Wang, Li, Li, & Che, 2020).

The Sixth one was ACVR2A protein; showed high expression in 18 cancer tissues. (Figure 7). It is believed to be a tumor suppressor that inhibits the growth and differentiation of cells. Recent studies showed that its inactivation could lead to the development of colorectal cancer (Wodziński et al., 2019).

The seventh one was Extracellular signal-regulated kinases (ERKs) that exhibited high expression in 23 tissues. (Figure 8). Several studies showed that it has been related to multiple cancers, including breast cancer, hepatocellular cancer, lung cancer and colorectal cancer. ERK1/2 inhibitor can suppress growth of KRAS-mutant pancreatic tumors by targeting cancer cell. Their findings indicate that inhibition of ERK1/2 in cancer-associated pancreatic stellate cells suppresses cancer–stromal interaction and metastasis (Yan et al., 2019). So ERK, given its importance as a major driver and therapeutic target for multiple cancers.

The eighth protein was RAS that exhibited high expression in 20 cancer tissues. (Figure 9) RAS proteins are important in cancer research because of their role as 'on/off switch' signaling pathways that control cell division and failure to die like healthy cells do. Nowadays, researchers have been able to study precisely how RAS proteins interact with cell membrane surfaces.

The last two proteins were SMAD3 and SMAD8 proteins which showed high expression in 26, 20 cancer tissues in order; (Figure 10), (Figure 11). SMAD proteins which are considered as tumor suppressors are important because of their role within certain tumors as a result of the somatic mutations in these genes within certain cancers. For example, Smad2- and Smad4-encoding gene sequences mutations that are not present in the inhibitory Smad 6 or Smad7 nor Smad3 have been found in various carcinomas. As present TGF-beta receptors, nevertheless, previous studies showed decreasing in the expression of the Smad family members in human tumors and may account for TGF β – resistance. For Smad3 the literature proved that this protein has greater frequency of loss of their expression in human cancers. They also suggest that Smad3 could be a good target for epigenetic deactivation through gastric tumor genesis. TGF- β -mediated immunosuppression could be impaired by the absence of the expression of Smad3 and interject to inflammatory responses that influence carcinogenesis (Samanta & Datta, 2012).

Regarding the beta –catenin pathway, the 3 proteins that were detected (DVL1, RNF43, SNAIL1). Disheveled segment polarity protein 1 (DVL1) had high expression in 32 tissues; fig. (12) recent findings showed that it functions as a cytoplasmic phosphor protein that regulates cell proliferation. Missense mutations, nonsense mutations, and silent mutations are

observed in cancers such as fallopian tube cancer, intestinal cancer, and skin cancer (Genome, 2021).

For Ring Finger Protein 43 it showed high expression in in 39 tissues, Figure (13). So, this could be a New Target for Cancer Immunotherapy; recent studies identified the RNF43 gene, was up-regulated twice higher than tumor-to-normal intensity ratios in 10 of the 11 tumor tissues tested. They found that RNF43 was up-regulated genes in colorectal cancer tissues on cDNA microarray. Furthermore, they approved that raised expression of RNF43 is associated with better proliferation of the cancer cells with colony formation assay. Their findings suggest that RNF43 has the expression profile and functions hypothesized for the ideal TAA candidates (Uchida et al., 2004).

The third one was SNAIL1 which exhibited high expression in in 39 tissues. Figure (14).it is a transcription factor has been shown to be crucial for cellular movement during cancer progression and metastasis (Brzozowa et al., 2015).

In this paper, we presented a beta-catenin & TGF beta proteins that highly expressed in various cancer tissues. Since B-Catenin is overexpressed and constitutively activated in human cancer and contributes to cancer initiation, progression, metastasis, drug resistance, and immune evasion (Pai et al., 2017). Targeting β -catenin signaling has been proposed as a promising strategy to develop effective anticancer agents (Qin et al., 2018; Yu et al., 2020).

As an oncogenic transcription factor, β -catenin was conventionally considered as an undruggable target. However, recent discoveries of small molecules that directly bind to β -catenin suggest that β -catenin is a potentially drug gable target that is yet to be drugged (Cui, Zhou, Zhang, Qu, & Ke, 2018). In addition, transforming growth factor- β signaling pathway also known to play a multifunctional role in the regulation of embryonic development, immunity, carcinogenesis, inflammation, and fibrosis. In normal conditions, TGF- β signaling maintains tissue homeostasis by the regulation of cell proliferation.

It switches its function to speed up the progress and the development of diseases such as cancer and fibrosis in abnormal conditions (Yun, Kim, & Kim, 2019). TGF- β acts initially as a tumor suppressor through phosphorylation and activation of SMAD4/DPC4 gene (Ahmed, Schwartz, Dewan, & Xu, 2019).

Collecting these results together, the present study shows a noticeable expression of these proteins in discrete tumor tissues. These proteins play a part as a potential target for treating cancer and give perceptions into the molecular basis of cancer.

According to the straight effect of these pathways in various kinds of cancer, they have become the target for new cancer therapies. This study spotlights 13 proteins that are integrated in the β -Catenin & TGF beta pathways and which could be suitable targets for cancer remedies. The expression of these proteins is high in various tumor tissues pointed. Modeling novel drugs that decrease tumor growth, migration and metastasis via the modification of these proteins' activity.

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