Analysis of PI3K pathway components in human cancers

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Abstract. Recent advances in genomics, proteomics, cell biology and biochemistry of tumors have revealed new pathways that are aberrantly activated in numerous cancer types. However, the enormous amount of data available in this field may mislead scientists in focused research. As cancer cell growth and progression is often dependent upon the phosphoinositide 3-kinase (PI3K)/AKT pathway, there has been extensive research into the proteins implicated in the PI3K pathway. Using data available in the Human Protein Atlas database, the current study investigated the expression of 25 key proteins that are known to be involved with PI3K pathway activation in a distinct group of 20 cancer types. These proteins are AKTIP, ARP1, BAD, GSK3A, GSK3B, MERTK-1, PIK3CA, PRR5, PSTPIP2, PTEN, FOX1, RHEB, RPS6KB1, TSC1, TP53, BCL2, CCND1, WFIKKN2, CREBBP, caspase-9, PTK2, EGFR, FAS, CDKN1A and XIAP. The analysis revealed pronounced expression of specific proteins in distinct cancer tissues, which may have the potential to serve as targets for treatments and provide insights into the molecular basis of cancer.

Introduction

Phosphoinositide 3-kinases (PI3Ks) are an evolutionarily conserved family of lipid kinases that promote various cellular functions, including cell growth, metabolism and survival (1,2). The lipid second messengers that are generated in this reaction interact with specialized lipid-binding domains that are present in a wide variety of signaling molecules. PI3Ks may be classified into one of three classes, each of which possesses different structures and characteristics (3). The PI3K pathway may be activated by upstream receptor tyrosine kinases, leading to the generation of phosphatidylinositol-3,4,5-trisphosphate (PIP_3) via the phosphorylation of phosphatidylinositol-4,5-bisphosphate. The phosphatase and tensin homolog (PTEN) may dephosphorylate PIP_3, which terminates PI3K signaling. The accumulation of PIP_3 activates a signaling cascade, commencing with the phosphorylation (activation) of the protein serine-threonine kinase AKT (also known as protein kinase B) at threonine 308 by phosphoinositide-dependent kinase 1. Activation of AKT serves a crucial role in essential cellular functions, including cell proliferation and survival, via the phosphorylation of a variety of substrates (Fig. 1) (4).

Although the PI3K/AKT pathway has been extensively investigated in detail in distinct *in vitro* and *in vivo* systems (5), its role in molecular targeted therapy for cancer required further study. Molecular targeted therapies (e.g. inhibitors of target molecules with critical roles in tumor growth and progression) have been investigated in various cancer models, particularly hematological malignancies, such as leukemia, lymphoma and myeloma, due to the ease in obtaining samples for examination (6). The PI3K/AKT pathway has been reported to be activated in numerous types of malignancy (7), and inhibitors associated with this pathway have been shown to induce apoptosis in targeted tumor cells (8).

Aberrant activation of the PI3K pathway may promote carcinogenesis and tumor angiogenesis (9,10). For example, a previous study reported that ~30% of breast cancer cases demonstrated activating missense mutations of phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit α (PIK3CA), the gene encoding the catalytic p110α subunit of class I PI3K (2); this mutated gene provides cells with a growth advantage and promotes tumorigenesis (11). In addition, dysregulated PI3K pathway signaling has been implicated in conferring resistance to conventional therapies, including biologics, hormonal therapy, tyrosine kinase inhibitors, radiation and cytotoxic drugs in breast cancer, glioblastoma and non-small cell lung cancer (12).

Wet laboratory research has revealed enormous data in the field of cancer research, and expression levels of certain proteins can be found at the Human Protein Atlas (www.proteinatlas.org). However, these proteins are not classified according to a specific disease or disorder. The aim of the present study was to utilize data deposited in the Human Protein Atlas to investigate the protein expression level of 25 proteins that are known to be implicated in the PI3K pathway in various cancer tissues. The proteins investigated were as follows: AKTIP, ARP1, BAD, GSK3A, GSK3B, MERTK-1, PIK3CA, PRR5, PSTPIP2, PTEN, FOX1, RHEB, RPS6KB1, TSC1, TP53, BCL2, CCND1, WFIKKN2, CREBBP, capase-9, PTK2, EGFR, FAS, CDKN1A and XIAP. The analysis reveals a pronounced expression of specific proteins in distinct cancer tissues, which may be potential targets for cancer treatment and provide insights into the molecular basis of cancer.

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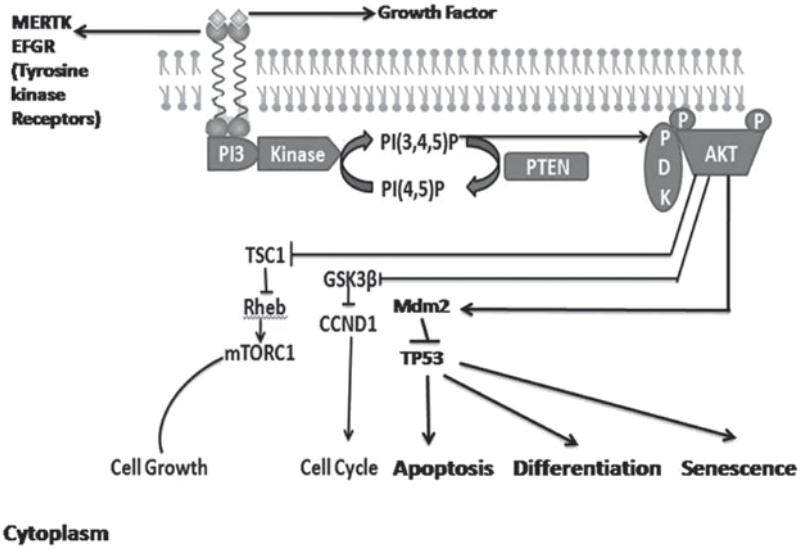

Figure 1. PI3K/AKT signaling pathway. Binding of the ligand to membrane receptor tyrosine kinases activates PI3K, which phosphorylates PIP_2 to produce PIP_3. PIP_3 recruits PDK1 to the plasma membrane. PDK1 phosphorylates and activates AKT, which regulates various cellular processes. The lipid phosphate activity of cytoplasmic PTEN dephosphorylates PIP_3, thereby decreasing PIP_3 levels and increasing levels of PIP_2, resulting in a concomitant decrease in AKT activity. PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; PIP_2 [PI(4,5)P], phosphatidylinositol 4,5-bisphosphate; PIP_3 [PI(3,4,5)P], phosphatidylinositol (3,4,5)-trisphosphate; PDK1, phosphoinositide-dependent kinase 1; PTEN, phosphatase and tensin homolog.

Materials and methods

Data were collected from the Human Protein Atlas database (www.proteinatlas.org) via manual searches of the desired gene names. The expression levels of 25 specific proteins that are known to be involved in the PI3K pathway were investigated in 20 different cancer tissues types: Carcinoid, glioma, liver cancer, lymphoma, melanoma, ovarian cancer, pancreatic cancer, skin cancer, testis, urothelial, lung cancer, breast cancer, cervical cancer, colorectal cancer, head and neck, renal, thyroid, prostate, endometrial and stomach cancer.

The expression of the 25 proteins in the different cancer tissues were reported as high, medium or low (excluding no expression, which was considered as a separate category) relative to normal tissues as shown in the database. Thereafter, the percentage of high, medium and low expression in each tissue type was calculated by dividing the number of patients exhibiting high expression, for example, over the total number of patients in the sample for each tissue type. The number of patients per sample ranged from 8-18. Furthermore, high and medium percentages were combined as the biological impact of high and medium expression was believed to be similar. Graphs were created using Microsoft Excel 12.0 (Microsoft Corporation, Redmond, WA, USA) to represent the percentage of each level of protein expression as it was expressed in these patients.

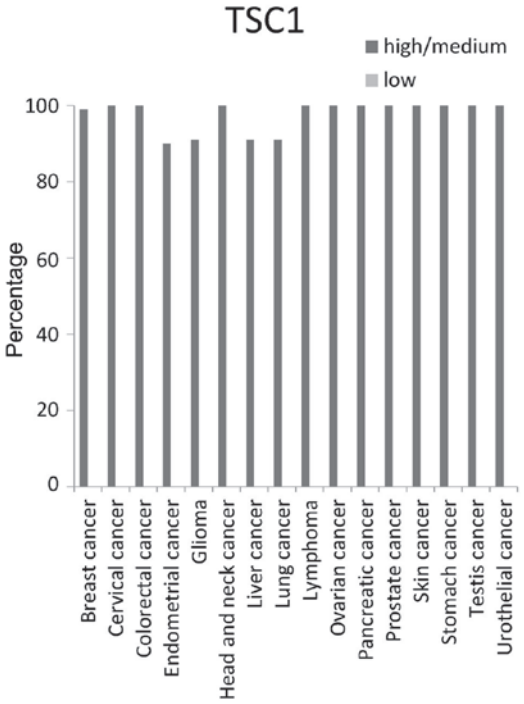

Figure 2. Expression levels of tuberous sclerosis 1 (TSC1) protein in different cancer tissues based on Human Protein Atlas.

Results and Discussion

In this study, the expression levels of 25 proteins in tissues from 20 cancer types were analyzed utilizing the Human Protein Atlas (www.proteinatlas.org). The following proteins examined: AKTIP, ARP1, BAD, GSK3A, GSK3B, MERTK-1, PIK3CA, PRR5, PSTPIP2, FOX1, RHEB, TSC1, TP53, BCL2, CCND1, WFIKKN2, CREBBP, RPS6KB1, caspase-9, EGFR, PIK2, FAS, CDKN1A, XIAP and PTEN. The physiological activity and full name of these proteins, as well as their role in cancer initiation and control, is summarized in Table I (13-43).

The results revealed that 9 of the 25 proteins tested exhibited high expression levels in various cancer tissues. These proteins were PIK3CA, RPS6KB1, MERTK, RHEB, EGFR, TSC1, CCND1, TP53 and PTEN. The other 16 proteins exhibited low or no expression in tumor tissues (data not shown).

The expression level for each protein tested was categorized as either high/medium or low. The protein TSC1

Table I. Summary of the physiological function and associated signaling pathways of the 25 proteins studied.

Protein	Description/full name	Main function	References
TSC1	Tuberous sclerosis 1	Tumor suppressor; stimulates specific GTPases	(13)
EGFR	Epidermal growth factor receptor	Activates PI3K, which activates Akt (promotes cell survival and proliferation)	(14)
MERTK	MER proto oncogene tyrosine kinase	Tyrosine kinase receptor with oncogenic properties that is often overexpressed or activated in various types of malignancy; member of the MER/AXL/TYRO3 receptor kinase family; regulates melanoma cell migration and survival	(15,16)
RHEB	Ras homolog enriched in brain	Regulates growth and cell cycle progression via the insulin/TOR/S6K signaling pathway	(17)
RPS6KB1	Ribosomal protein S6 β1	mTOR downstream protein; promotes protein synthesis, cell growth, and cell proliferation	(18)
CCND1	Cyclin D1	Functions as a regulatory subunit of cyclin-dependent kinase (CDK)4 or CDK6, whose activity is required for cell cycle G1/S transition	(19)
TP53	Tumor protein p53	Tumor suppressor; induces cell cycle arrest, apoptosis, senescence, DNA repair or changes in metabolism	(20)
PTEN	Phosphatase and tensin homolog	Tumor suppressor; mostly mutated in a large number of cancers	(21,22)
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit α	Belongs to the PI3K family; has roles in various signaling pathways; involved in proliferation, oncogenic transformation, cell survival and migration, and intracellular protein trafficking	(23,24)
GSK3A	Glycogen synthase kinase 3α	Control of several regulatory proteins including glycogen synthase and transcription factors	(25)
BAD	BCL2-associated agonist of cell death	Regulator of programmed cell death; proapoptotic activity of this protein is regulated through its phosphorylation; AKT and mitogen-activated protein kinase are involved in the regulation of this protein	(26,27)
AKTIP	AKT interacting protein	Mediates insulin-induced translocation of glucose transporter-4 to the cell surface	(28)
GSK3B	Glycogen synthase kinase 3β	Involved in energy metabolism, neuronal cell development and body pattern formation	(29)
ARP1	Actin-related protein 1	Transcriptional regulator involved in basal and hormone-regulated activity of prolactin; regulates the cell-specific trafficking of a receptor protein involved in apoptosis	(30,31)
PRR5	Proline rich 5 (renal)	Regulates platelet-derived growth factor receptor	(32)
FOX1	Fox-1 homolog. Also known as: ataxin 2-binding protein 1 (A2BP1); or hexaribonucleotide-binding protein 1 (HRNBP1)	Possesses RNA binding motif; associated with spinocerebellar ataxia due to its binding to ataxin-2; regulator of tissue-specific alternative splicing in mammals	(33)
BCL2	B-cell lymphoma 2	Oncogene; blocks apoptosis	(34,35)
WFIKKN2	WAP, follistatin/kazal, immunoglobulin, kunitz and netrin domain containing 2	Protease-inhibitor that contains distinct protease inhibitor domains	(36)
CREBBP	CREB binding protein	Regulates embryonic development, growth control, and homeostasis by coupling chromatin remodeling to transcription factor recognition	(37)
Caspase-9	Apoptosis-related cysteine peptidase	Plays a central role in the execution-phase of cell apoptosis	(38)
PTK2	Protein tyrosine kinase 2. Also known as: focal adhesion kinase (FAK)	Focal adhesion-associated protein involved in cellular adhesion and spreading processes; when it is blocked, cancer cells become less metastatic due to decreased mobility	(38,39)
FAS	Cell surface death receptor. Also known as: apoptosis antigen 1 (APO-1 or APT)	Plays a central role in the physiological regulation of programmed cell death	(40)
CDKN1A	Cyclin-dependent kinase inhibitor 1A. Also known as: P21; CIP1; SDI1; WAF1; CAP20; CDKN1; MDA-6; or p21CIP1	Inhibits the activity of cyclin-CDK2 or -CDK4 complexes, and thus functions as a regulator of cell cycle progression at G1 phase	(41)
PSTPIP2	Proline-serine-threonine phosphatase-interacting protein 2	Substrate for a number of important signaling proteins	(42)
XIAP	X-linked inhibitor of apoptosis. Also known as: IAP3 and BIRC	Inhibits apoptosis	(43)

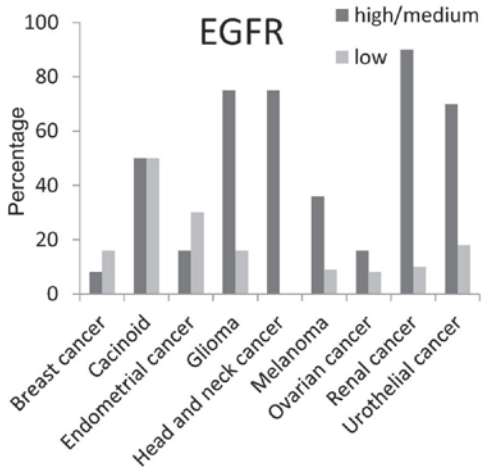

Figure 3. Expression percentages of epidermal growth factor receptor (EGFR) protein in 10 different cancer tissues based on Human Protein Atlas.

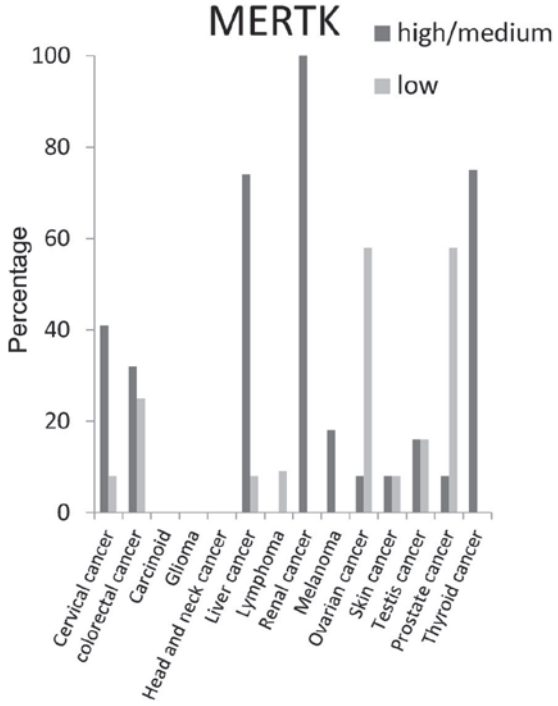

Figure 4. Expression percentages of MER proto oncogene tyrosine kinase (MERTK) protein in different cancer tissues based on Human Protein Atlas.

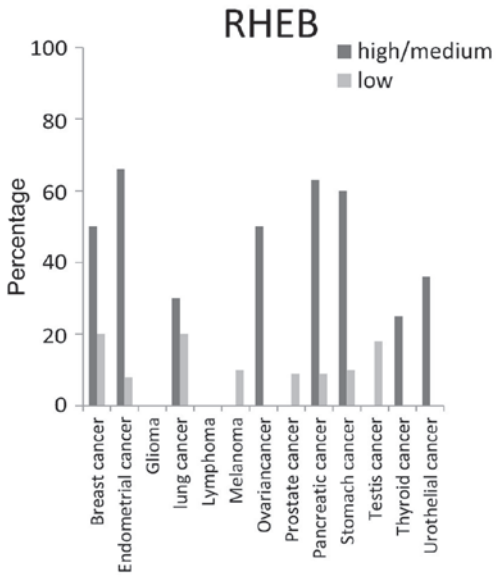

Figure 5. Expression percentages of Ras homolog enriched in brain (RHEB) protein in different cancer tissues based on Human Protein Atlas.

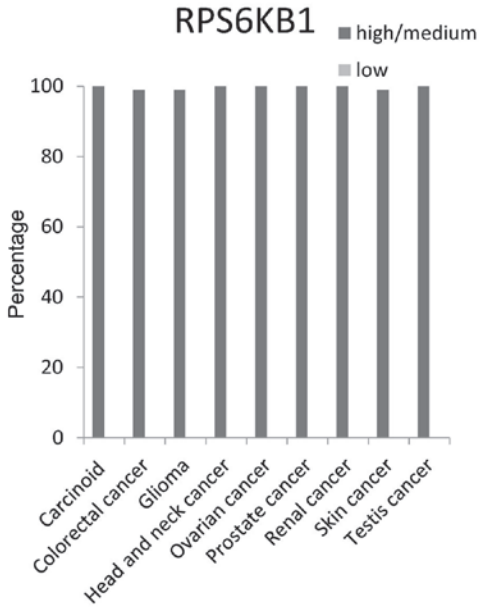

Figure 6. Expression percentages of ribosomal protein S6 β1 (RPS6KB1) protein in different cancer tissues based on Human Protein Atlas.

exhibited high/medium expression in all types of cancer tissue tested. TSC1 exhibited ~100% high/medium expression in breast, cervical, colorectal, head and neck, lymphoma, ovarian, pancreatic, prostate, skin, stomach, testis and urothelial cancer tissues. It expression was ~90% high/medium in endometrial, glioma, liver and lung cancers (Fig. 2).

EGFR protein had high/medium expression level in >50% of carcinoid, head and neck, glioma, renal and urothelial cancer tissues (Fig. 3). For MERTK protein the high/medium expression rate was >50% in liver and thyroid cancer tissues, and 100% in renal cancer tissues. It was not detected in carcinoid, glioma, or head and neck cancer tissues (Fig. 4).

For RHEB protein, the highest expression level was present in >50% of breast, endometrial, ovarian, pancreatic and stomach cancer tissues, but was not detected in glioma and lymphoma cancer tissues (Fig. 5).

The RPS6KB1 protein expression level had ~100% high/medium in 9 cancer tissue tested: Carcinoid, colorectal, glioma, head and neck, ovarian, prostate, renal, skin and testis cancer tissues (Fig. 6).

CCND1 protein high/medium expression level was present in ~50% of head and neck cancer and melanoma tissues (Fig. 7). The high/medium expression percentage of TP53 protein was ≥50% in colorectal, head and neck, ovarian, pancreatic and urothelial tissues, but was not detected at all in carcinoid, prostate and thyroid cancer tissues (Fig. 8).

The expression level of PTEN protein (a tumor suppressor gene) was low in various cancer tissues as was expected.

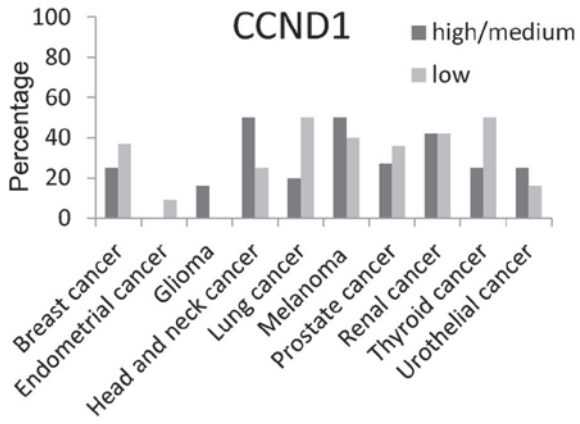

Figure 7. Expression percentages of Cyclin D1 (CCND1) protein in different cancer tissues based on Human Protein Atlas.

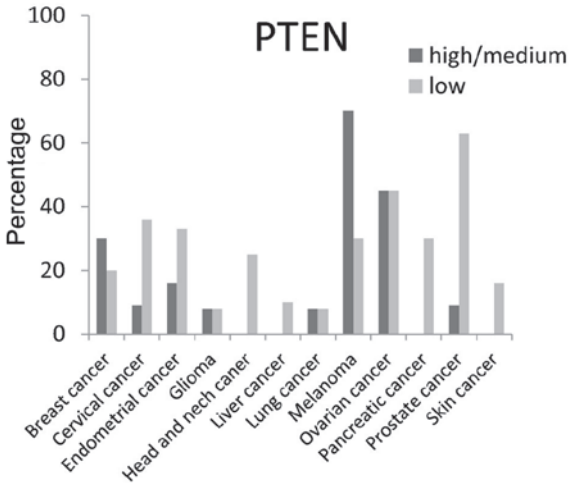

Figure 9. Expression percentages of phosphatase and tensin homolog (PTEN) protein (tumor suppressor gene) based on Human Protein Atlas.

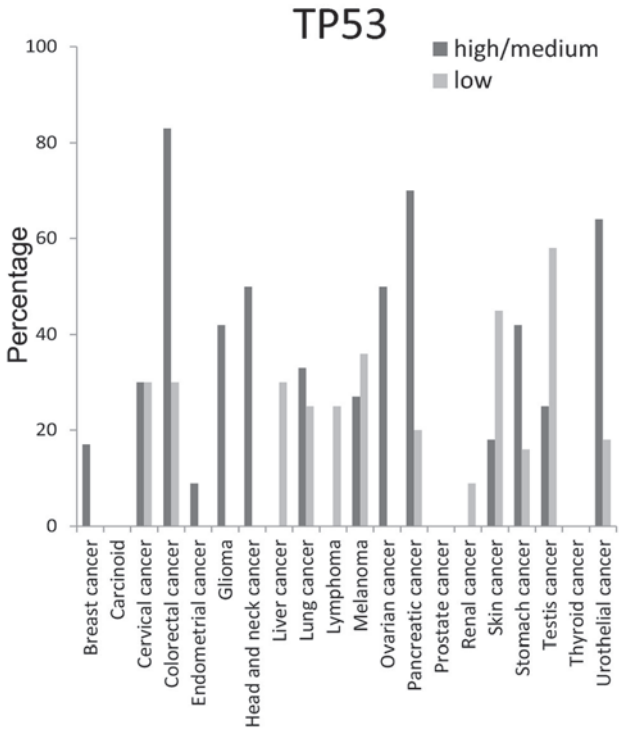

Figure 8. Expression percentages of tumor protein p53 (TP53) in different cancer tissues based on Human Protein Atlas.

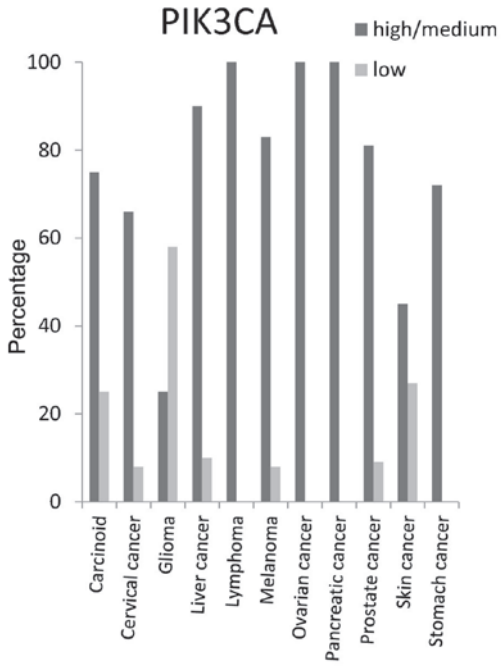

Figure 10. Expression percentage of phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit α (PIK3CA) protein based on Human Protein Atlas.

A high/medium PTEN expression level was present in <50% of breast, cervical, endometrial, glioma, head and neck, liver, pancreatic and skin cancer tissues; however, high/medium expression was present at a rate of ~75% in melanoma (Fig. 9).

PIK3CA protein expression level was high/medium in around 100% of lymphoma, ovarian and pancreatic cancer tissues, 90% of liver cancer tissues, 85% of melanoma and prostate cancer tissues, 70% of carcinoid and stomach cancer tissues and 65% of cervical cancer tissues (Fig. 10).

Taking this data together, the current analysis reveals a pronounced expression of specific proteins in distinct cancer tissues. These proteins may be potential candidates to serve as targets for cancer treatments and provide insights into the molecular basis of cancer. PI3Ks initiate signaling through a network of downstream effector pathways. Due to the direct implication of the pathway in numerous cancer types, this pathway has become the target for novel cancer therapies. This bird's-eye view study highlights 9 proteins that are involved in the PI3K pathway and which may be potential targets for cancer treatment. These proteins are highly expressed in several cancer tissues as indicated. Designing new drugs that modulate the activity of these proteins may decrease cancer growth, migration and metastasis.

Acknowledgements

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