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Review Article

Role of PTEN and LKB1 in cellular metabolism: Implications in cancer cell biology

Iqra Shaukat, Talha Saleem
Department of Medical Laboratory Technology, Superior University, Lahore, Pakistan

Abstract
Cellular metabolism is crucial for sustaining life, as it generates adenosine triphosphate (ATP) and provides essential building blocks for macromolecules. Recent research has expanded our understanding of metabolism, revealing its significant roles in cellular signaling networks related to immune responses, development, and aging. Metabolic profile of cancer cells is distinct due to reprogramming, particularly the Warburg effect, where they exhibit metabolic preference for glycolysis regardless of aerobic conditions. This metabolic shift supports their uncontrolled proliferation and survival. This review explains the roles of two key tumor suppressor proteins, PTEN and LKB1, in regulating cellular metabolism and their implications for cancer biology. It aims to elucidate how these proteins influence metabolic pathways such as glycolysis and oxidative phosphorylation and to highlight their potential as therapeutic targets in cancer treatment. Dysregulation of LKB1 and PTEN due to mutations leads to enhanced glycolytic activity and metabolic reprogramming in cancer cells, contributing to tumorigenesis. LKB1 acts as a critical activator of AMP-activated protein kinase (AMPK), promoting energy homeostasis and regulating cellular metabolism under stress conditions. Conversely, PTEN functions as a negative regulator of the PI3K/AKT/mTOR signaling pathway, preventing uncontrolled cell growth. Understanding the mechanisms by which LKB1 and PTEN regulate cellular metabolism is essential for developing targeted anticancer therapies that exploit the unique metabolic vulnerabilities of cancer cells. By focusing on these pathways, researchers can identify new strategies to improve treatment efficacy while minimizing harm to normal tissues.

Corresponding Author: Talha Saleem
Email: talha.saleem@superior.edu.pk

INTRODUCTION

Cellular metabolism is essential for life. The degradation of biomolecules leads to the production of metabolic energy in the form of ATP, which is crucial for nearly all cellular functions. In addition, metabolic processes and the resulting metabolites serve as the building blocks for cells to produce biomolecules, including proteins, carbohydrates, fats, and nucleic acids [1, 2]. Recent research has significantly expanded our understanding of metabolism, revealing its critical roles beyond the traditional energy production activity. This emerging perspective highlights the interplay between metabolic pathways and various cellular signaling networks, including immune responses, development, and aging which plays a crucial role in defining the cell behavior and pathophysiology in different diseases [3]. In normal cells, Glycolysis and oxidative phosphorylation are crucial metabolic pathways contribute not only to energy production but also play significant roles in cellular health, proliferation, differentiation, and intercellular communication (Figure 1) [4, 5]. Normal cells in our body undergo replication in a systematic manner known as mitosis. When these cells become densely packed during growth, they stop proliferation through a mechanism called contact inhibition. In cases where a cell experiences a defect or mutation, it is eliminated by the cellular machinery through a process known as apoptosis or programmed cell death. This dead, mutated cell is then replaced by a new, healthy cell [6, 7]. Mutations in the DNA not only lead cells to resistance against apoptosis but also accelerate their replication rate. As a result, the newly formed cells retain the same mutations leading to the development of a lump of abnormal cells. These abnormal, invasive and mutated cells are cancerous: exhibit several distinct characteristics that differentiate them from normal cells. Uncontrolled proliferation, resistance to apoptosis, genetic abnormalities, immune evasion and nutrient consumption are the features of cancer cells contribute to formation of tumors [8-10]. The metabolic profile of cancer cells is distinct from healthy cells, driven by adaptive reprogramming of energy and nutrient utilization. This process enables cancer cells to adapt their metabolism

to meet the heightened demands associated with uncontrolled growth and proliferation [11, 12].

Cancer cells show modified patterns of cellular respiration, a process known as Wartburg effect. Under normal conditions, cells generate ATP through oxidative phosphorylation in the mitochondria. In contrast, cancer cells preferably adopt aerobic glycolysis process for energy production even when oxygen is sufficiently available as shown in Figure 1. This shift results in an increase in lactate level and alters the cellular environment contributing to unchecked cell proliferation [12-14]. The Warburg effect describes the tendency of cancer cells to favor glycolysis for ATP generation, even when oxygen is plentiful. This process, known as aerobic glycolysis, leads to higher lactate production and modifies the cellular environment, promoting rapid cell division and tumor development [15, 16].Focusing on the Warburg effect, a promising approach for cancer therapy can be achieved. This metabolic shift enables cancer cells to swiftly generate energy and vital metabolites, facilitating their growth and survival, especially in low-oxygen conditions [17-19].

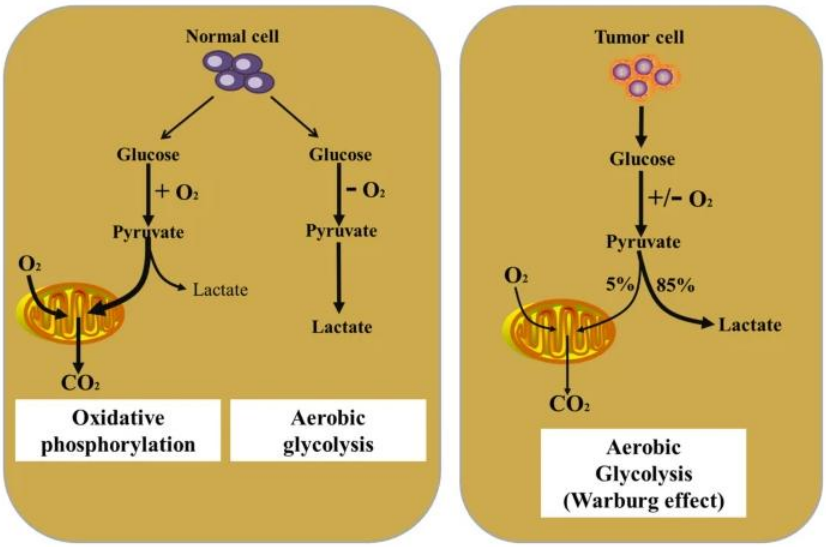

Figure1: Metabolic pathways in normal cells and tumor cells [20]

Oncogenic pathways and mutations in tumor suppressor genes play a key role in promoting metabolic shift and driving Warburg effect. For example, the activation of oncogenes such as MYC and RAS increases the expression of glycolytic enzymes. Additionally, mutations in tumor suppressor genes like TP53 and PTEN further stimulate glycolysis [21]. Experiments have projected that metabolic pathways improve the effectiveness of existing treatments as well as identifies new strategies against cancer. Thus, in short, the Warburg effect gives an example on how cancer cells adapt their metabolism to thrive on conditions that usually suppress normal cellular functions, yet it presents opportunities and challenges to cancer therapy. The most recent achievements in cancer research show that elucidation of metabolism in cancer cells is crucial in developing more potent and less harmful targeted anticancer therapies [20]. Exploitation of specific metabolic pathways of cancer cells, which diverge significantly from normal cells, by using LKB1 and PTEN can be a rationale of cancer therapeutic strategy.

LKB1 Function and Mechanism

LKB1 as a Serine/Threonine Kinase

LKB1, also referred to as STK11, is a tumor suppressor serine/threonine kinase, which is very important for maintaining cellular homeostasis by the phosphorylation and activation of many downstream targets, most notably AMPK, the central energy sensor in cells. Activation of AMPK by LKB1 thus balances cellular metabolism and growth by responding effectively to metabolic stress and preventing uncontrolled cell proliferation. LKB1 acts in several of the most pivotal pathways, notably glucose metabolism and autophagy and cell cycle control. For the regulation of cell growth and metabolism and of cell polarity through its kinase function, LKB1 is the crucial protein, whose dysfunction correlates with several cancer types. Its impairment causes oncogenic transformation and promotion of tumor, either through enhancement of mTORC1 signaling activity or through destabilization of genomes. Moreover, LKB1 is involved in processes other than tumor suppression; it regulates apoptosis and cell differentiation, which shows that it has multifaceted contributions to cellular physiology and cancer biology [22-25].

LKB1-mediated Activation of AMP-activated Protein Kinase (AMPK)

LKB1 is a crucial activator of AMPK, a key regulator of energy homeostasis. When cellular ATP levels are low, LKB1 activates AMPK by phosphorylating it on Thr172. AMPK activation leads to a series of metabolic adaptations aimed at restoring energy balance, such as promoting catabolic processes like glucose uptake and fatty acid oxidation while inhibiting anabolic processes like protein and lipid synthesis. In cancer cells, LKB1 loss can lead to impaired AMPK activation, thereby disrupting cellular energy sensing and promoting uncontrolled cell growth in a nutrient-deficient environment [24, 26].

LKB1 and Cellular Energy Sensing

Regulation of Cellular Energy Homeostasis

LKB1 is involved in the regulation of cellular energy homeostasis, controlling key pathways of metabolism. When energy stores are low, like in low glucose or oxygen concentrations, LKB1 activates AMPK, and this latter can activate energy-yielding pathways like glycolysis and fatty acid oxidation while at the same time inhibiting energy-requiring processes such as protein synthesis and cell growth. In cancer cells, LKB1 often behaves as a sensor of metabolism for the response against changes in tumor microenvironment; these changes involve nutrient deprivation and hypoxia [27, 28].

Impact on Glycolysis, Oxidative Phosphorylation, and Autophagy:

LKB1 serves as critical regulator of cellular metabolism through its activation of AMP-activated protein kinase, especially under conditions of low ATP availability. Activation of AMPK by LKB1 under such depleted cellular energy conditions enhances glycolysis, an important pathway for the quick generation of energy in the presence of low oxygen concentrations, representing a Warburg effect. In the absence of LKB1 function, glycolysis becomes dysregulated, contributing to metabolic reprogramming in cancer cells, which are often dependent upon enhanced glycolytic activity for growth and survival. The activation of AMPK by LKB1 also modulates mitochondrial metabolism and oxidative phosphorylation (OXPHOS). Enhancement of mitochondrial biogenesis and function may contribute to an increase in ATP production through OXPHOS in normal cells, although impaired OXPHOS has been considered in cancer cells lacking LKB1. LKB1 is also known to regulate autophagy, a critical process for maintaining energy balance by degrading and recycling cellular components. Under nutrient-scarce conditions, LKB1 activates AMPK to promote autophagy, helping cells maintain energy levels despite metabolic stress Figure 2 [24, 29-32].

LKB1 in Tumor Suppression

LKB1 Loss-of-Function Mutations in Cancer

LKB1 is a tumor suppressor gene, and loss-of-function mutations in the gene are frequently found in various cancers, such as lung cancer, melanoma, and colorectal cancer. These mutations inactivate the kinase activity of LKB1, which inhibits its ability to regulate AMPK and other downstream targets. This impairment enhances glycolytic activity and alters cellular metabolism, which supports tumorigenesis by promoting the survival and growth of cancer cells. For example, in lung adenocarcinomas, LKB1 loss is detected in approximately 30% of the cases and even usually associates with oncogenic KRAS mutations, further complicating the tumor's metabolic landscape [33, 34]

LKB1's Role in Suppressing Cell Proliferation and Promoting Cell Death

LKB1 functions in promoting repression of the pathways involved with the initiation, survival, metabolism of tumor; suppression of apoptotic processes ensures uncontrolled proliferating cell through interruption of cancer's growth-controlling signals- its absence due to mutations loses that would serve to stop rapid growing cells due to unchained growth-signal processes-. Moreover, LKB1 plays a role in enhancing cell death mechanisms like autophagy and apoptosis upon cellular stress, further establishing its role as a tumor suppressor (Figure 2) [25, 35]. The dysregulation brought about by LKB1 mutations not only increases glycolysis but also alters metabolic processes in cancer cells toward more aggressive phenotypes [36, 37].

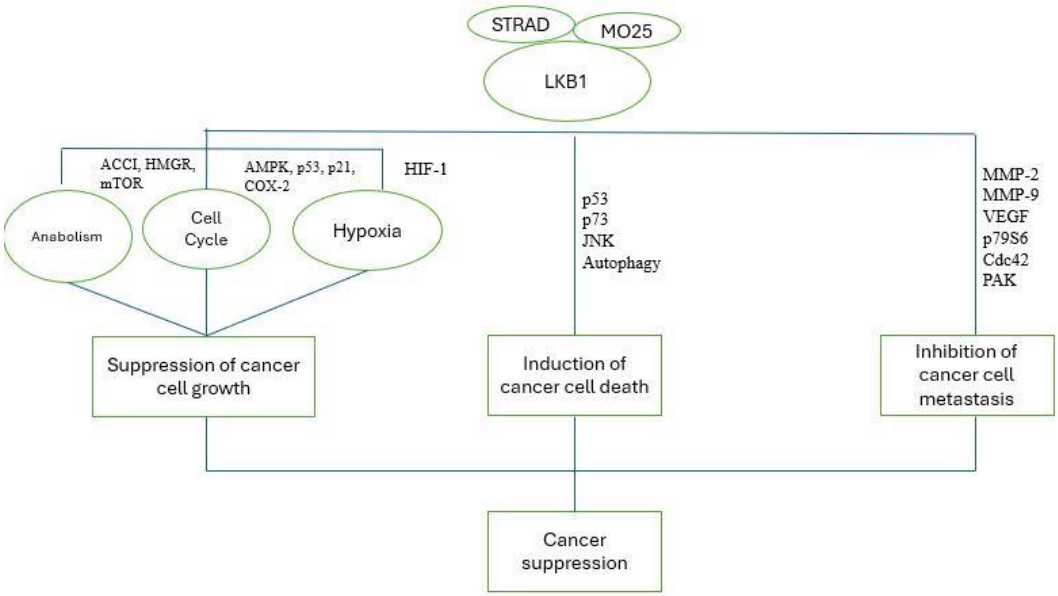

Figure 2: Mechanism of LKB1 derived cancer suppression [38]

LKB1 and Tumor Metabolism

LKB1 as a Metabolic Sensor in Cancer Cells

LKB1 acts as an important metabolic sensor in cancer, helping the cell adjust to changes in nutrient and oxygen supply. Activation of the pathway during hypoxia or nutrient starvation triggers AMPK and other metabolic responses needed for survival. This adjustment includes increasing glucose uptake, enhancing glycolysis, and promoting autophagic degradation to fuel cellular energy. When LKB1 is lost or mutated, the cancer cells bypass these regulatory mechanisms, and therefore, growth becomes uncontrolled with metabolic dysregulation. The loss of LKB1 has been associated with increased glycolytic activity and a shift toward a more aggressive metabolic phenotype that contributes to tumor progression and survival in adverse microenvironments [24, 25].

Interaction with Metabolic Pathways (mTOR, AMPK)

This factor significantly influences the metabolic process in the tumor as LKB1 impacts the pathway regulated by the mechanistic target of rapamycin under its AMP-activated protein kinase effects. AMPK becomes activated by LKB1 at times of low energy, inhibiting mTOR from further anabolic processes that may include the synthesis of proteins and lipids and instead activate more catabolic processes, including autophagy, thus readjusting to energy stress conditions in cells. This results in an elevated mTOR activity that is permissive to proliferation and survival of tumor cells within nutrient-deficient environments in the case of cancer. The results have demonstrated that LKB1/AMPK signaling negatively regulates mTOR activity, thereby playing a significant role in the repression of growth by causing energy stress in non-small cell lung cancer cells

LKB1 in Specific Cancer Types

Lung Cancer and Other Cancers Associated with LKB1 Mutations

LKB1 mutations are especially common in lung cancer, particularly in NSCLC, where they are commonly related with poor prognosis. Around 30% of NSCLC tumors display LKB1 mutations, which results in the loss of its tumor-suppressive function. This leads to deregulated metabolism and survival of the cancer cells. LKB1 has been identified mutated in other cancers besides lung, including breast and endometrial cancer and even pancreatic cancer. In these cancer types, defects in LKB1 function and expression alter a set of metabolisms that supports tumorigenesis, positioning LKB1 as a potentially interesting target in the development of therapeutic strategies able to reactivate its function [39, 40].

PTEN Function and Mechanism

PTEN as a Lipid and Protein Phosphatase

PTEN, or Phosphatase and Tensin Homolog, is an important tumor suppressor gene that encodes a dual-specificity phosphatase that acts mainly as a lipid and protein phosphatase. Its most important activity is dephosphorylation of PIP3 to PIP2, which antagonizes the PI3K/AKT/mTOR signaling pathway that regulates cell survival, growth, and metabolism. In addition, PTEN regulates other pathways involved in cell cycle progression, apoptosis, and cellular migration. The proper role of PTEN is a critical function for maintaining cellular homeostasis and preventing uncontrolled cell growth, therefore often associated with cancer development [41].

Role in Regulating the PI3K/AKT Signalling Pathway

PTEN negatively controls the PI3K/AKT signalling pathway by dephosphorylation of phosphatidylinositol-3,4,5-trisphosphate, a product of the PI3K reaction that mediates cell growth, survival, metabolism, and angiogenesis. The inactivation of AKT (Protein Kinase B) via inhibition of the pathway prevents further activation of targets, such as mTOR, involved in promoting cell growth and survival. Conversely, in the case of PTEN inactivation or loss, PIP3 starts to accumulate and causes hyperactivation of AKT, thereby creating aberrant signalling that promotes tumorigenesis and reprogrammed metabolic processes. Mutations in PTEN are one of the most common mutations in cancer cells and have led to unchecked activation of the PI3K/AKT pathway, thus facilitating cellular metabolic reprogramming, favouring glycolysis, and other anabolic processes [42, 43].

PTEN and Cellular Growth Regulation

PTEN as a Negative Regulator of Cellular Growth and Survival

The main function of PTEN is its role as a negative regulator in cellular growth and survival through PI3K/AKT pathway inhibition. In normal cells, the presence of PTEN maintains balance between survival and apoptosis by counteracting the effects of overactive AKT to promote cell survival and inhibit pro-apoptotic signals. Unchecked cell growth and survival is a result when PTEN's function is lost. Loss of regulation is one hallmark of cancer. PTEN mutations or deletions are significant factors in the contribution to tumorigenesis and resistance to cell death signals [44, 45].

Involvement in Controlling Cell Cycle Progression

PTEN controls the cell cycle by regulating crucial checkpoints, especially by its function as an antagonist of the PI3K/AKT/mTOR pathway. Due to this inhibition of the pathway, PTEN prevents cells from proceeding in the cell cycle under less-than-ideal circumstances, such as DNA damage or insufficient energy resources. Consequently, cancer and genomic instability arise due to uncontrolled cycling. In addition to these roles, PTEN interacts with CDKs and other regulators to regulate G1-S phase transition and enforcement of the G1 checkpoint; it allows healthy cells to be further proliferated while keeping aberrant cells under arrest as shown in Figure 3 [46, 47].

PTEN and Metabolic Control

Regulation of Glucose Metabolism and Glycolysis through the PI3K/AKT/mTOR Pathway

PTEN plays an essential role in cellular metabolism, mainly glucose metabolism through its effect on the PI3K/AKT/mTOR pathway. When normally functioning, PTEN can suppress the pathway and prevents excessive activation of AKT to promote anabolic processes, including glycolysis and lipid biosynthesis. Loss of PTEN in cancer cells leads to hyperactivation of AKT, which results in enhanced glucose consumption and glycolysis—the defining characteristic of the Warburg effect, enabling cancer cells to prioritize glycolysis even under aerobic conditions. This metabolic adaptation to aerobic glycolysis supplies cancer cells with quick ATP production and biosynthetic intermediates necessary for rapid growth. Activation of mTOR downstream of AKT also promotes protein synthesis and metabolic reprogramming in cancer. This pathway, therefore, remains an essential point of regulation for PTEN in maintaining normal cellular metabolism and its loss contributes to altered states that support tumorigenesis [48, 49].

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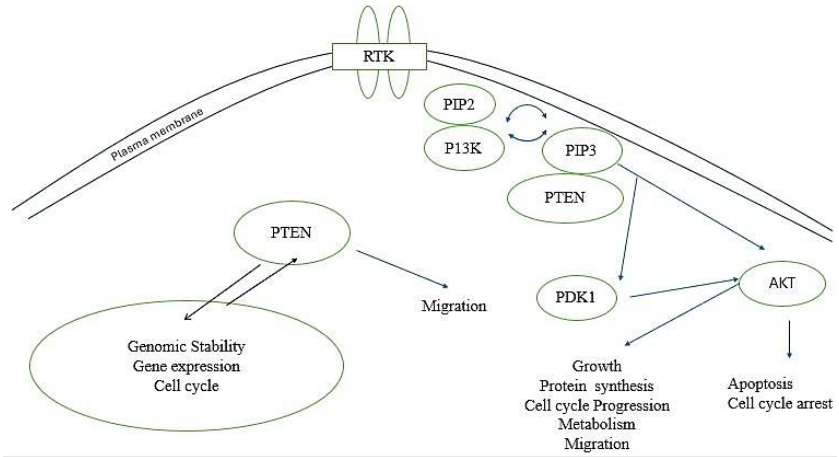

Figure 3: Functions of PTEN in cellular metabolism [50]

PTEN and Oxidative Stress Regulation

PTEN regulates oxidative stress significantly. It regulates the PI3K/AKT pathway, hence ensuring a balance between the rate of production of ROS and the level of antioxidant defences. Normally, PTEN supports cellular redox balance. In PTEN-deficient cells, increased oxidative stress leads to genomic instability and DNA damage through inflammation, hence fuelling the advancement of cancer. The regulation of ROS by PTEN is associated with its tumor-suppressive functions, because the absence of PTEN causes excessive oxidative stress that activates oncogenic pathways [51, 52].

PTEN Loss and Cancer Development

PTEN Loss in Various Cancers (e.g., Prostate, Glioblastoma)

PTEN loss is an early and critical event in the pathogenesis of most cancers, such as prostate cancer, where mutation or deletion causes hyperactivation of the PI3K/AKT pathway. The result is an enhanced initiation, progression, and therapeutic resistance of the tumor. PTEN mutations also characterize glioblastoma with enhanced cell survival, invasion, and resistance to apoptosis. Breast cancer, endometrial cancer, and ovarian cancer are also characterized by PTEN loss in a significant percentage of cases. In such cancers, PTEN mutation or deletion leads to metabolic changes that positively support cell survival and proliferation, which is consistent with the aggressive behaviour of these cancers [53, 54].

Impact of PTEN Mutations on Metabolic Alterations in Cancer Cells

PTEN mutations cause dramatic alterations in the metabolic profiles of cancer cells. The reduction of PTEN activity removes a negative regulator for AKT and results in an increase in glycolysis and lipid biosynthesis. Cancer cells with PTEN loss often demonstrate increased glucose uptake, enhanced glycolytic activity, and elevated lipogenesis contributing to rapid cell growth. PTEN loss may also enhance mitochondrial function and diminish oxidative stress that supports long-term survival in a hostile tumor microenvironment. These metabolic changes contribute significantly to the Warburg effect and other kinds of metabolic reprogramming in cancer cells [55, 56].

PTEN and Tumor Microenvironment

Role in Regulating Tumor Vascularization and Nutrient Supply

PTEN regulates tumor vascularization and nutrient supply, which are critical for the growth of a tumor. Through regulation of the PI3K/AKT pathway, PTEN controls angiogenesis-the formation of new blood vessels supplying oxygen and nutrients to the tumor. Loss of PTEN may result in inappropriate angiogenesis leading to a more aggressive and poorly vascularized tumor phenotype that may increase tumor growth and metastasis. This dysregulation of vascularization in PTEN-deficient tumors may contribute to the hypoxic conditions commonly found in the tumor microenvironment and metabolic adaptations by cancer cells [57, 58].

PTEN's Role in Controlling Hypoxia and Angiogenesis

PTEN also has an important role in the regulation of hypoxia response, which is a feature common to many solid tumors. Hypoxia activates hypoxia-inducible factor (HIF), leading to the induction of genes for angiogenesis, metabolic adaptation, and survival. PTEN influences HIF through its control over the PI3K/AKT pathway. Reduced PTEN increases HIF activity, thereby favouring tumor angiogenesis and metabolic remodelling that further drives tumor growth and survival under hypoxic stress [59].

Integration of LKB1 and PTEN Signalling

Intersection of AMPK and PI3K/AKT/mTOR Pathways

LKB1 and PTEN are two important tumor suppressors. They regulate cell metabolism through mutually distinct but interconnected signalling pathways. LKB1 primarily works by activating AMPK, which regulates cellular energy homeostasis. PTEN controls the PI3K/AKT/mTOR pathway, acting as an integrator that controls cell growth, survival, and metabolism. These pathways have a substantial overlap, especially in metabolic control. Activation of AMPK by LKB1 suppresses mTOR, an important component of the PI3K/AKT/mTOR pathway. This suppression results in decreased protein synthesis and cell growth, thus promoting autophagy and catabolic pathways in response to low energy. PTEN, on the other hand, suppresses the PI3K/AKT pathway through dephosphorylation of PIP3 to PIP2, thus reducing AKT activation and mTOR signalling [25, 60, 61].

Critical balance between cell growth and energy conservation is maintained, and cells would not proliferate under unfavourable metabolic conditions, where the crosstalk between AMPK and PI3K/AKT/mTOR has been proven essential. Loss or dysfunction of either LKB1 or PTEN in cancer cells leads to the dysregulation of metabolism through metabolic reprogramming for tumor growth [62, 63].

Synergistic or Antagonistic Effects on Metabolic Pathways

The two proteins have complex interactions in regulating metabolic pathways and are capable of exerting both synergistic and antagonistic effects. Under normal physiological conditions, the proteins together suppress cell growth and maintain metabolic balance. Activation of AMPK by LKB1 acts against the

anabolic processes regulated by PTEN's control over the PI3K/AKT signalling pathway. A balance between catabolic and anabolic processes is critical for normal cellular function. Loss or mutation of either LKB1 or PTEN may lead to antagonistic effects on the regulation of metabolism within the context of cancer. For example, it can over activate the mTOR pathway through the PI3K/AKT pathway but fail to regulate AMPK and energy homeostasis appropriately. This results in increased glycolysis (the Warburg effect), enhanced protein and lipid synthesis, and cellular proliferation, all of which support tumor growth. In this scenario, the loss of either LKB1 or PTEN can potentiate each other's effects, leading to more aggressive cancer phenotypes.

Effects on Tumorigenesis and Tumor Progression

How LKB1 and PTEN Interact to Control Tumor Cell Metabolism

Both LKB1 and PTEN control the metabolic status of the tumorigenic process. This involves the convergence of LKB1 and PTEN signalling into important cellular functions in metabolism such as glucose uptake, glycolysis, oxidative phosphorylation, and autophagy. Normally, LKB1 and PTEN collaborate in a way to regulate energy homeostasis while limiting the effects of uncontrolled proliferation. LKB1 activates AMPK to promote energy conservation and autophagy. Under low-energy conditions, it stimulates energy conservation through AMPK. PTEN inhibits the PI3K/AKT/mTOR pathway to limit exaggerated cell growth and survival signals. However, mutation or loss-of-function in LKB1 or PTEN blunts this pathway and leads to reprogramming of cancer cell metabolism. Cancer cells derived from LKB1-deficient or PTEN-deficient patients are characterized often by increased glycolysis - the so-called Warburg effect - increased de novo lipid synthesis, and defects in oxidative phosphorylation. Each of these perturbations confers a hallmarks of cancer metabolism. These effects are combined and result in enhanced tumor aggressiveness, invasiveness, and resistance against apoptosis. Moreover, LKB1 and PTEN interact in the regulation of the tumor microenvironment through control of angiogenesis, hypoxia, and nutrient supply. Loss of both tumor suppressors may worsen hypoxic conditions, enhance angiogenesis, and generate a nutrient-rich environment for tumor growth [64, 65].

Influence on Cancer Stem Cells

Role of LKB1 and PTEN in Regulating Cancer Stem Cell Metabolism

Cancer stem cells are a subpopulation of tumor cells that make the bulk of tumor growth, metastasis, and recurrence due to their dependence on altered metabolic pathways that support their unique properties, including therapy resistance and self-renewal. Thus, LKB1 and PTEN both play critical roles in the regulation of CSC metabolism. LKB1 activates AMPK, which has been shown to modulate several of the key metabolic processes in CSCs, including glycolysis and oxidative phosphorylation. Loss of LKB1 function in these cells may therefore result in increased glycolysis, which is critical for their high proliferative capacity. PTEN loss activates the PI3K/AKT/mTOR pathway in CSCs, thereby promoting anabolic metabolism that supports proliferation and resistance to apoptosis. The combined loss of LKB1 and PTEN in CSCs further escalates metabolic reprogramming, and thereby further repositions glucose metabolism, mitochondrial functions, and lipid biosynthesis; such changes further help CSCs survive in poor oxygen and nutrient concentrations, thereby furthering tumor initiation and growth [66-68].

Impact on Therapeutic Resistance

LKB1 and PTEN are the critical regulators of therapeutic resistance in cancer cells, especially in cancer stem cells (CSCs). The mutation of LKB1 or PTEN usually results in resistance to conventional therapies like chemotherapy and radiation, which is based on inducing cellular stress and apoptosis. Altered metabolism in LKB1- and PTEN-deficient cancer cells, especially in CSCs, helps them survive through therapeutic interventions. Furthermore, the metabolic flexibility of CSCs lacking LKB1 or PTEN allows them to shift between glycolysis and oxidative phosphorylation depending on their microenvironment, thus making them more adaptable to changing conditions. This adaptability is one of the reasons why CSCs are resistant to therapies targeting specific metabolic pathways. Targeting the loss of both LKB1 and PTEN may offer a therapeutic strategy to overcome this resistance by reprogramming the metabolic networks that sustain CSC survival and proliferation [22, 69].

Current Therapeutic Approaches Targeting LKB1 and PTEN

Drugs Targeting the PI3K/AKT/mTOR Pathway

The PI3K/AKT/mTOR pathway is frequently altered in cancer, particularly due to PTEN loss or mutation, leading to therapeutic strategies aimed at inhibiting this pathway in PTEN-deficient tumors. PI3K inhibitors such as Idelalisib and Buparlisib downregulate the downstream AKT activation. The AKT inhibitors, Capivasertib and Ipatasertib, are effective in cancers like breast and prostate cancer. mTOR inhibitors, including Everolimus and Temsirolimus, are used for various cancers where the pathway is activated. Despite their promise, these therapies have the challenges of resistance and incomplete pathway inhibition. Activation of AMPK or mimicry of LKB1 function are promising strategies against metabolic reprogramming in cancer cells. AMPK activators such

as Metformin have shown promise in inhibiting mTOR signalling, which reduces tumor growth. LKB1 mimicry and gene therapy are being studied to restore the tumor-suppressive effects of this protein [70, 71]. Table 1 summarizes therapeutic strategies targeting PTEN and LKB1 in cancer along with their mechanism of action and their utilization to specific cancer type.

Table 1: Therapeutic strategies targeting PTEN and LKB1 in cancer

Gene	Therapeutic Approach/method	Mechanism	Cancer Type	References
PTEN	Adenoviral PTEN gene therapy	Inhibition of P13K/Akt pathway, cell cycle inhibition at G2/M phase by dephosphorylation of MAPK and FAP	Colorectal cancer, NSCLC, Esophageal cancer, Endometrial cancer	(72-75)
PTEN	Combination with chemotherapy	PTEN therapy combined with doxorubicin was more effective in overcoming resistance mechanisms	Prostate cancer, SCLC	(76, 77)
PTEN	Anti-PD1 immunotherapy	PTEN mutation serve as biomarkers for immunotherapy resistance	Lung adenocarcinoma, NSCLC	(69, 78)
LKB1	Metabolic stress induction (Biguanides)	Disruption in mitochondrial function and reduction in available glucose	LKB1-mutated NSCLC	(79)
LKB1	Glutaminase inhibition (Telagenastat)	Inhibition in gluatamate production by reducing TCA cycle intermedicates	LKB1-mutated NSCLC	(80)
LKB1	MEK inhibitors and radiotherapy	mTOR/p70S6K pathway inhibition leading to induction of senescence	KRAS/LKB1 mutated NSCLC	(81)
LKB1	KEAP1/NRF2 pathway targeting	GLS1 inhibition via restoration of redox homeostasis	Radiotherapy resistant NSCLC	(40)

Challenges in Targeting LKB1 and PTEN

Tumor Heterogeneity and the Complexity of Metabolic Rewiring

Tumor heterogeneity is one of the main challenges in targeting LKB1 and PTEN in cancer: the cancer cells within a tumor are genetically, metabolically, and therapeutically heterogeneous. This makes the development of an effective treatment very challenging, particularly when PTEN or LKB1 mutations occur in only a subpopulation of cells. While some cancer cells may rely on the PI3K/AKT/mTOR pathway for survival, others may activate alternative pathways or metabolic processes. Furthermore, in response to therapy, tumors may undergo metabolic rewiring, and glycolysis, fatty acid metabolism, or autophagy can increase with a dynamic shift based on the treatment. Resistance mechanisms are often seen to arise as carcinoma cells activate compensatory pathways such as MAPK or Wnt signalling, metabolic shifts, or simply acquired mutations affecting targeted therapies. These resistance mechanisms can thus be overcome by innovative strategies targeting not only the primary metabolic pathways but also compensatory mechanisms of cancer cells, which allows them to avoid treatment [81].

CONCLUSION

The complex functions of the tumor suppressor proteins PTEN and LKB1 in governing cellular metabolism also underscore their crucial role in the biology of cancer. Both these proteins function as critical regulators of metabolic pathways, which are most often dysregulated in cancer cells, thus causing enhanced survival and proliferation. Primary action of LKB1 is activation of AMPK, which promotes catabolic processes and maintenance of energy homeostasis, especially in conditions of metabolic stress. In most of cancers loss of LKB1 function leads to uncontrolled cellular growth and aggressive tumor phenotypes due to altered metabolic programming. On contrary, PTEN is negative regulator of the PI3K/AKT/mTOR pathway and suppress signals for cell growth and survival. Loss or mutations in PTEN cause hyperactivation of AKT, which induces glycolysis and other anabolic processes that characterize the Warburg effect. The metabolic shift allows for tumorigenesis and supports resistance against apoptosis, further complicating the cancer landscape.

The interplay between these two tumor suppressors points to a very important aspect of cancer metabolism: the adaptation of cancer cells to their

microenvironment through metabolic reprogramming. The understanding of how LKB1 and PTEN regulate these key metabolic pathways will provide novel therapeutic strategies targeting these vulnerabilities. Such approaches could make current treatments more effective with less impact on normal tissues.

By targeting the metabolic pathways regulated by LKB1 and PTEN presents a promising avenue for the development of effective cancer therapies. Continued research into these mechanisms will provide deeper insights into cancer biology and pave the way for innovative treatments that exploit unique metabolic characteristics of cancer cells.

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