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The Potential Role Of STK11 as a Biomarker for Intestinal Cancer

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Abstract

Colorectal and small intestinal cancers together still pose a serious threat to world health. The necessity for trustworthy biomarkers is highlighted by the fact that early diagnosis is critical to better patient outcomes. In this regard, the serine/threonine kinase 11 (STK11) has come to light as a possible option. The STK11 gene codes for the serine/threonine kinase liver kinase B1 (LKB1), which is essential for preserving cellular polarity, adhesion, and metabolism. LKB1 inactivation is a frequent occurrence in many tumors, especially those that affect the gastrointestinal tract. The biological roles of STK11/LKB1 and its numerous contributions to the onset and spread of gastrointestinal cancer are reviewed in this study. This review addresses the role that STK11/LKB1 plays in the AMP-activated protein kinase (AMPK) pathway, which is a master regulator of cellular energy balance. Also, review how LKB1 regulates important signaling pathways, such as Wnt/β-catenin, PI3K/AKT/mTOR network, and how LKB1 depletion causes these pathways to become dysregulated, which in turn promotes cancer. It investigates the relationship between some gastrointestinal malignancies, such as Peutz-Jeghers syndrome, gastric cancer, and colorectal cancer, and LKB1 mutations. Lastly, we discuss the possible therapeutic implication of LKB1 signaling targeting in the management of gastrointestinal cancer.

Keywords: AMPK pathway, gastrointestinal cancer, LKB1, STK11, tumor suppressor

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Introduction:

First identified as the causative mutation causing Peutz-Jeghers Syndrome (PJS), an autosomal dominant condition characterized by multiple hamartomatous polyps in the gastrointestinal tract and an increased risk of cancer, were the innovative heterozygous mutations in the serine/threonine kinase 11 (STK11) gene(1, 2). STK11 is a gene that encodes a protein named liver kinase B1 (LKB1) belongs to the serine/threonine kinase family(3). This protein functions in the regulation of cell polarity and is also a tumor suppressor. It, also, play critical functions in cellular metabolism, cell polarity, apoptosis control, and the DNA damage response (4, 5). It has been found that 3.04 percent of cancer patients had STK11 changes in a number of malignancies, including gastrointestinal (GI) cancers (1, 6). Worldwide, colorectal cancer (CRC) and gastric cancer (GC) are the two most common types of cancer related to the GI that result in morbidity and mortality(7). And since LKB1 is a major tumor suppressor in a variety of malignancies, including those of the GI tract, an understanding of the underlying molecular processes of GI carcinogenesis is essential for the development of successful management options. The purpose of this review is to give an overview of STK11 biological activities and how they relate to GI malignancies. We report pre-clinical and clinical evidence assessing the role of STK11 mutations in GI carcinogenesis function and cellular mechanisms. subsequently, we go over the information that is currently known on STK11's therapeutic effect on patients with GI cancers.

STK11 Biological Functions: An Overview

On chromosome 19's short arm, the STK11 gene is situated at the telomeric locus (19p13.3)(8-11). The LKB1 protein is made up of a chain of 443 amino acids, which are encoded by nine exons(12, 13). When energy is in short supply, STK11/LKB1 acts as an essential main upstream kinase that activates Adenosine Monophosphate-Activated Protein Kinase (AMPK)(14, 15). AMPK is a key metabolic regulator in the cell, controlling the metabolism of fats and carbohydrates in response to changes in energy and nutrition. It also manages other cellular processes including polarity and autophagy and functions as a tumor suppressor(16, 17). Therefore, in the event of a nutrition insufficiency or hypoxia, AMP accumulates in conjunction with ATP depletion, resulting in the direct activation of AMPK via STK11/LKB1(18). When combined with other regulators, AMPK activation facilitates the transition from anabolic to catabolic metabolism, which increases cell survival under energy-stressed conditions(19). This procedure activates mechanisms in the body, which stimulates 12 more AMPK subfamily kinases and results in ATP regeneration(20). AMPK has a complex role in a number of metabolic pathways that contribute to increased levels of cellular ATP, mostly by promoting the production of ATP and reducing its use. AMPK plays a significant role in promoting lipid breakdown by elevating β-oxidation and fatty acid intake, which results in the production of NADPH and ATP(21-24). The LKB1/AMPK interaction additionally influences glucose metabolism by promoting glycolysis and increasing glucose absorption(25, 26).

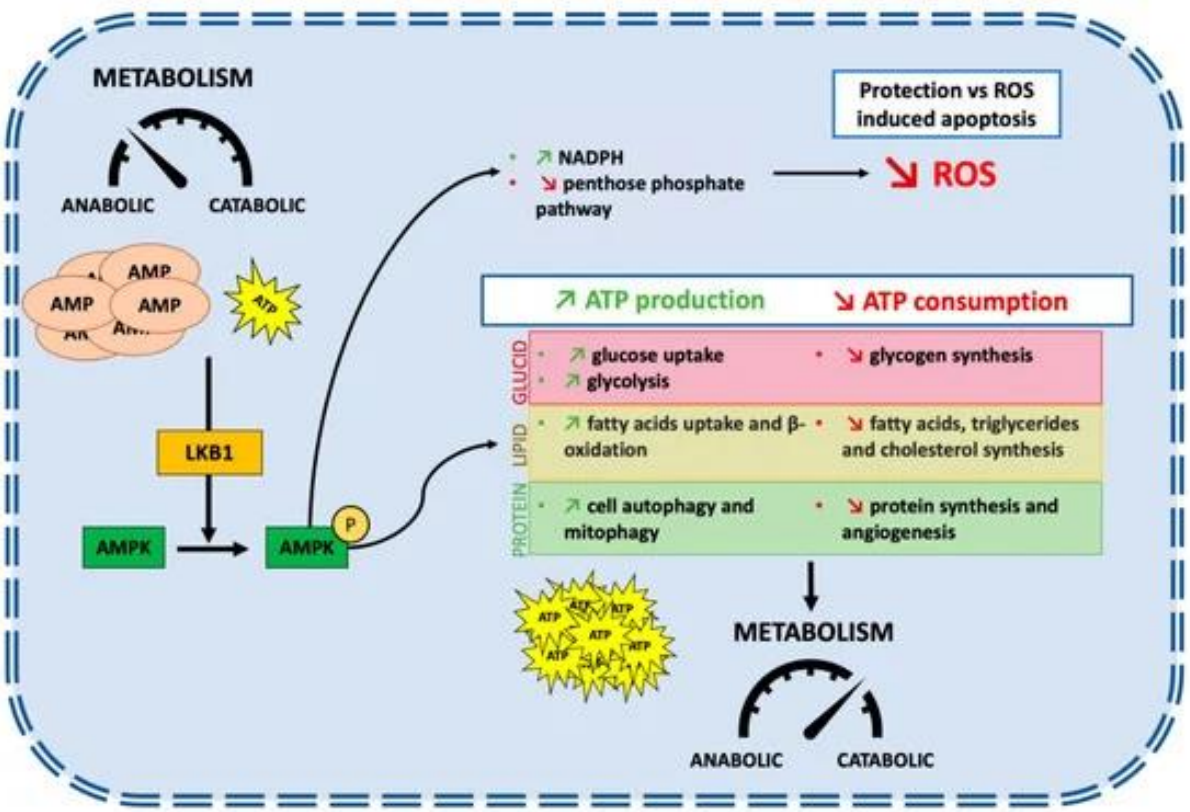

Figure 1: STK11/LBK1 facilitates the transition of a cell's metabolism from anabolic to catabolic, which increases cell survival under stressful situations(27)

Protein Synthesis Regulation and Cellular Adaptation

Protein synthesis in cells is an essential yet energy-intensive activity that uses up a large amount of a cell's ATP stores(28). Strict control of protein synthesis is necessary to preserve energy balance. AMPK activation by STK11/LKB1 results in suppression of the mTOR pathway, which in turn suppresses protein synthesis and limits ATP consumption. The mTOR also functions as a central hub to integrate signals from growth factors, nutrients, and energy sources to regulate protein translation(29). Furthermore, LKB1 has the ability to directly block the signaling pathways Wnt/β-catenin and mTORC1 (serves as a downstream effector for several commonly disrupted oncogenic pathways, including the PI3K/AKT and MAPK pathways), which promote cell growth and proliferation(14, 30). Interestingly, a common feature of a lot of solid tumors is mTOR dysregulation(31). AMP-activated protein kinase (AMPK), which is triggered by the tumor suppressor LKB1, is an important upstream regulator of mTOR(32). There are other, greater consequences of this signaling cascade. According to Huang et al. AMPK activation promotes angiogenesis, which in turn adversely regulates hypoxia-inducible factor 1α (HIF-1α), a transcription factor essential for cellular adaptation to low oxygen environments(33). AMPK has the ability to restrict tumor development and vascularization by blocking HIF-1α(34). Referring to Kim et al., STK11/LKB1-induced AMPK activation further stimulates autophagy and mitophagy, two cellular degradation mechanisms for recycling cellular components and producing metabolic precursors under nutritional limited availability(35). This adaptive response may increase a cancer cell's ability to survive by improving its ability to produce energy reserves under stressful circumstances(36, 37).

Additionally, LKB1 controls adhesion and cell polarity via processes that include the PAR protein complex and the crumbs complex(38); similarly like epithelial cadherin (E-cadherin or cadherin1 or E-cad) (39).

STK11 as a Tumor Suppressor

One common genetic change seen in a number of cancers is inactivation of STK11/LKB1. These

inactivating events mostly take the form of somatic mutations in the STK11 gene, which might include insertions, nonsense mutations, chromosomal deletions, loss of heterozygosity (LOH), and insertions(40-45).

STK11 changes were discovered to be present in 1.35% of more than four thousands patients with solid tumors in a paper published recently(46). As seen in colorectal cancer, hypermethylation of the STK11 promoter region can negatively influence STK11/LKB1 expression(47). These non-mutational mechanisms need to be taken into account when characterizing cancers since they may resemble STK11-mutant tumors in terms of growth and aggressiveness. As a consequence, mutation analysis of the STK11 gene may not be sufficient to identify individuals with decreased oncosuppressive STK11/LKB1 function, even though sequencing has been applied to the majority of clinical investigations to describe STK11 status(48).

Clinical Significance of STK11 Mutations

Patients with intestinal cancer may benefit from knowing if they have STK11 mutations as a predictive factor. Studies indicate that these mutations can be linked to a more aggressive tumor phenotype and worse clinical results.(49).

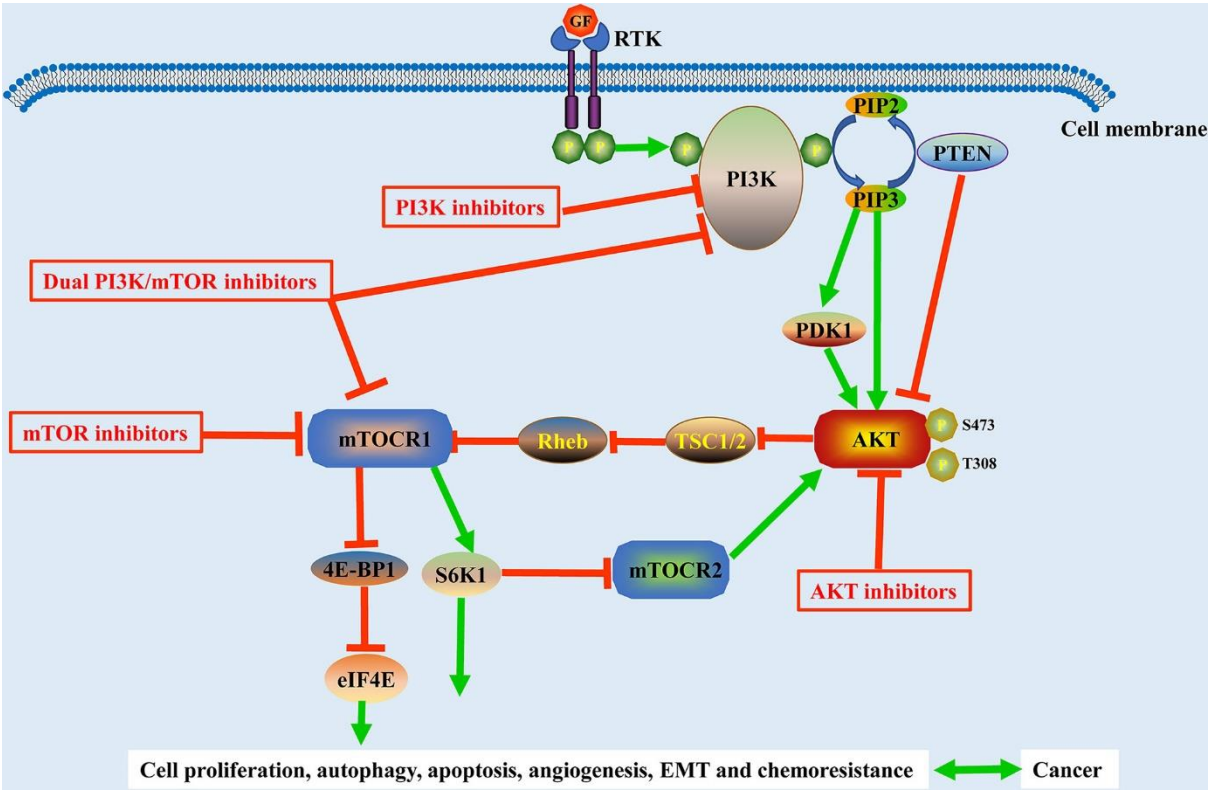

Figure 2: Schematic representation of the PI3K/Akt/mTOR pathway and its related inhibitors in solid tumors(50).

STK11/ LKB1 and Gastrointestinal Cancer

1. Colorectal Cancer (CRC)

Researches have well documented that LKB1 mutations are commonly seen in CRC particularly in sporadic and hereditary cases(51-53). They, also, indicate that the deletion of LKB1 stimulates the growth of CRC by triggering the PI3K/AKT/mTOR pathway, which limits apoptosis and increases cell division(37, 54, 55). Furthermore, through stimulation of the Wnt/β-catenin pathway, LKB1 loss interferes with cellular adhesion and polarity, increasing invasiveness and metastasis(56, 57). According to recent studies, LKB1 restoration in colorectal cancer cells has the ability to inhibit tumor development and metastasis, suggesting that it may be a promising target for therapy(17, 58).

2. Gastric Cancer (GC)

Patients with GC have a worse prognosis when their LKB1 expression is reduced(59). Through blocking the nuclear translocation of Yap and β-

catenin, two important transcriptional regulators involved in cell migration and proliferation, LKB1 suppresses tumors in GC(59, 60). Furthermore, by preventing lipogenesis and encouraging fatty acid oxidation, LKB1 activation of AMPK inhibits the development of GC cells(61). These results imply that one potential therapy approach for GC may involve LKB1 function restoration.

3. Peutz-Jeghers Syndrome (PJS)

People with Peutz-Jeghers syndrome (PJS), an autosomal dominant condition marked by mucocutaneous hamartomas and an elevated risk of gastrointestinal malignancies, are predisposed by germline mutations in STK11(62-64). LKB1 mutations in PJS patients cause abnormal AMPK signaling, which in turn causes dysregulated cell growth and proliferation, which in turn contributes in the development of tumors(65-68).

STK11 and Therapeutic Implications

Therapeutic implications may result from the detection of STK11 mutations. Patients with STK11 mutations may benefit from medications that target the AMPK signaling pathway, as LKB1 controls this system. In cancer models lacking LKB1, preclinical research has demonstrated the potential of AMPK activators. The critical role of LKB1 in GI cancer pathogenesis makes it a promising target for therapeutic strategies, especially those of the gastrointestinal tract(69).

Several approaches are being explored, including:

- AMPA activators: Medication that mimics LKB1 function by activating AMPK may be able to inhibit tumor development in GI malignancies lacking LKB1(65, 69-72).
- mTORC1 inhibitors: Preclinical models of GI malignancies lacking LKB1 have demonstrated potential in response to rapamycin and its analogs, which block mTORC1 signaling(67, 73, 74).
- Inhibitors of the Wnt/β-catenin pathway: One possible treatment approach for GI tumors with LKB1 mutations might include focusing on the Wnt/β-catenin pathway, which is dysregulated due to LKB1 deletion(75-77).
- The potential application of medications that target additional elements of the LKB1 signaling network to prevent tumor development are being researched as well(17, 58, 67, 78).

However, translating scientific findings into useful therapies requires the development of efficient medication formulations and delivery mechanisms. To ensure the best possible bioavailability, stability, and targeted administration, more research is required to improve the pharmacokinetics and pharmacodynamics of prospective therapies

Conclusion

Serine/threonine kinase 11 (STK11) plays a multifaceted role in maintaining gut health and acts as a guardian against GI cancers. Its involvement in AMPK signaling and interaction with other key pathways highlight its importance in regulating cellular processes. Understanding the mechanisms by which STK11/LKB1 dysfunction contributes to GI tumorigenesis paves the way for developing novel diagnostic and therapeutic strategies. Future research focusing on restoring LKB1 function or targeting its downstream signaling pathways holds promise for improving clinical outcomes in GI cancers.

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