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The Role of LKB1 in the Pathogenesis of Skin and Other Epithelial Cancers

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Abstract

LKB1 acts as a master kinase, with its major protein targets being the family of AMPKs. Through activation of multiple signaling pathways, LKB1's main physiologic functions involve regulating cellular growth, metabolism, and polarity. Germline mutations in *LKB1* result in Peutz-Jeghers Syndrome, a rare cancer susceptibility syndrome. In addition, multiple *LKB1* mutations have been identified in sporadic cancers, especially those of the lung. Recent studies from a variety of murine models have helped characterize LKB1's role in the pathogenesis of epithelial cancers. In some tumor types, LKB1 might function chiefly to suppress cell growth or invasion, while in other cases, it may serve to prevent metastasis. Moreover, molecular signatures of individual tumors likely influence LKB1's operational role, as multiple studies have shown that LKB1 can synergize with other tumor suppressors and/or oncogenes to accelerate tumorigenesis. To date, LKB1 has been considered mainly a tumor suppressor; however, some studies have suggested its potential oncogenic role, mainly through the suppression of apoptosis. In short, LKB1 is a tissue and context-specific kinase. This review aims to summarize our current understanding of its role in the pathogenesis of epithelial cancers.

Keywords

LKB1; STK11; epithelial cancer; tumor suppressor

Introduction

The tumor suppressor Liver Kinase B1 (*LKB1*) encodes a serine threonine kinase, which forms a complex with two other proteins, namely the pseudokinase STRAD and the scaffold protein MO25. These proteins regulate LKB1's stability, kinase activity, and sub-cellular localization [1;2]. The physiologic function of this protein complex is to regulate multiple biological pathways involving p53-dependent and independent apoptosis, cell cycle arrest and proliferation, chromatin remodeling, angiogenesis, energy metabolism, fatty acid

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Conflicts of Interest Statement

None Declared

biosynthesis, Wnt signaling, and control of cell polarity [3;4;5;6;7]. LKB1 has been termed a “master kinase,” given its ability to phosphorylate at least 14 downstream proteins [8]. AMP-activated protein kinase (AMPK), the most studied of this target group acts as a cellular energy checkpoint, coordinating catabolic and anabolic activities [9;10;11]. Under conditions of low cellular energy and stress, it is thought that the binding of AMP to a regulatory subunit of AMPK induces a conformational change that permits the phosphorylation and activation of AMPK by LKB1 [10]. Activated AMPK in turn induces cell cycle arrest, upregulates genes involved in catabolism, downregulates those involved in gluconeogenesis and lipogenesis, and halts protein synthesis through inhibition of mammalian target of rapamycin (mTOR) [10;12;13]. Loss of *Lkb1* leads to decreased AMPK activity, and thus relieves these growth constraints, which in the correct context may result in tumorigenesis.

Inherited germ line mutations of *LKB1* result in Peutz-Jeghers Syndrome (PJS), a rare cancer susceptibility syndrome characterized by mucocutaneous pigmentation and the early development of multiple intestinal hamartomas [14;15]. Although initial studies proposed that between 30–70% of PJS patients harbor inactivating germline mutations of *LKB1*, more recent studies using improved mutational detection methods have suggested that closer to all cases of PJS may be due to *LKB1* inactivation [16;17;18;19;20]. *LKB1* has also been implicated in multiple sporadic cancers [21;22], especially those of the lung [23;24]. These clinical data coupled with LKB1’s known role in growth suppression support its function as a potent tumor suppressor.

Another important physiologic role of LKB1 is in regulating cell polarity [25]. LKB1 establishes cell polarity in cortical neurons [26] and colonic epithelium in mice [6]. Importantly, disrupted cell polarity resulting from loss of LKB1 function may also contribute to tumor invasion and metastasis [27]. Loss of cell polarity is both a general feature of adenocarcinomas [28], and it strongly correlates with aggressive and invasive malignant growth in some tumor types [7]. Interestingly, although multiple proteins, such as the microtubule affinity-regulating kinases 1–4 (MARK1-4 proteins) have been shown to control cell polarity through LKB1 [8], AMPK may also partially direct this regulation. In addition to its ability to act as an energy checkpoint, AMPK may also be critical for maintaining normal cellular architecture and polarity [29;30]. Similar developmental defects in mitosis and cell polarity have been observed in AMPK-null and *Lkb1*-null mutant flies. Moreover, genetic reconstitution of AMPK in *LKB1* knockouts rescued the mutant phenotype, suggesting a redundant or overlapping role of these two kinases in controlling cell polarity [29]. In another study, AMPK, in an LKB1-dependent fashion was shown to control the assembly of epithelial tight junctions, thereby helping maintain epithelial cell polarity [31]. In short, through the control of both energy regulation and cell polarity, the LKB1-AMPK signaling axis appears to be critically important in tumor suppression.

LKB1 protein is widely expressed in both embryonic and adult tissues, although at different levels. In murine embryos, LKB1 expression is highly ubiquitous, but during development, expression becomes more prominent in the heart, lung, pancreas, kidney, and gastrointestinal tract [32]. In adults, skeletal muscle, glial cells, seminiferous tubules of the testes, follicles and corpus leuteum of the ovary, and most epithelial tissues show the highest levels of LKB1 protein expression [33]. To some extent, the pattern of tumor susceptibility in PJS patients correlates with the expression of *Lkb1* in normal adult and embryonic tissues. For example, gastrointestinal tract tumors are the most common cancer type documented in PJS, and LKB1 immunostaining is moderately high in epithelia from normal human adult small intestine, colon, and pancreatic islet cells, and very high in human embryo small intestine and stomach [32;33].

Considering the pathogenesis of PJS-associated cancers, a central question is whether biallelic inactivation of *LKB1* is required for promoting carcinogenesis in target tissues [34;35]. While multiple studies have suggested that single allelic inactivation is sufficient for hamartomatous polyp formation [36;37;38;39;40], other data demonstrate that biallelic loss may be a driving force in tumorigenesis. When comparing the frequency of loss of heterozygosity (LOH) in polyps to carcinomas from PJS patients, LOH was detected in between 25% and 38% of polyps and between 64% and 100% of carcinomas, respectively [35;41;42;43]. Moreover, several studies examining liver, colorectal, breast, pancreatic, and sex cord tumors have reported biallelic loss of *LKB1*, and on certain genetic backgrounds, *Lkb1* heterozygous mice have been shown to develop hepatic carcinomas and squamous cell carcinomas that exhibit *Lkb1* LOH [42;44;45;46;47;48]. These data suggest that complete loss of *LKB1* may contribute to tumorigenesis in multiple tissue types, but *LKB1*'s exact function is likely tissue and context specific. Indeed, to better elucidate *LKB1*'s role in tumor development, numerous mouse models have been generated. Studies in these animals suggest varying contributions of cell polarity control, AMPK activity, mTOR repression, and other downstream protein targets in the pathogenesis of multiple cancer types. This review aims to summarize the current understanding of *LKB1*'s role in the development and progression of epithelial cancers.

Breast

Clinical evidence suggests that *LKB1* plays a tumor suppressive role in breast cancer. Compared to the general population, patients with PJS have a 54% increased risk of developing breast cancer and low expression of *LKB1* has been documented in approximately 30% of breast cancer patients [49]. Loss of *LKB1* expression has been linked to particular cancer subtypes, including papillary carcinomas [50], and subsets of both high-grade in situ and invasive carcinomas [51]. Moreover, low expression of *LKB1* has been correlated with higher tumor histological grade, larger tumor size, the presence of lymph node metastasis, and overall decreased patient survival [49]. To better understand these clinical findings, both *in vitro* and *in vivo* studies have been performed to characterize *LKB1*'s molecular role in breast cancer. Initial work demonstrated that over-expression of *LKB1* in *LKB1*-null cell lines resulted in growth inhibition, which was mediated by G1 cell cycle arrest and p21 induction [49]. More recently, *LKB1* over-expression was shown to inhibit breast cancer cell migration and invasion and to reduce pulmonary metastases. These changes were associated with the down-regulation of matrix metalloproteinases MMP-2 and MMP-9. In addition, *LKB1* over-expression also correlated with decreased micro vessel density (MVD) and down-regulation of VEGF and bFGF [52], implying that loss of *LKB1* might contribute to angiogenesis. In breast cancer patients, both MVD and angiogenesis have been linked to poorer patient prognosis [53;54;55].

In addition to its possible role in cell cycle arrest and prevention of metastasis, *LKB1* may also play a role in estrogen receptor (ER) signaling. Intriguingly, *LKB1* has been shown to act as a coactivator in ER α signaling by directly binding to the ER α and transactivating gene expression [56]. Given that enhanced ER α expression has been associated with increased breast cancer risk, it seems paradoxical that a tumor suppressor would act as an ER α coactivator, although other tumor suppressors including Rb, p21, TSC2, and Brg1 have been shown to function as similar nuclear coactivators in specific contexts [57;58;59;60;61;62;63]. Further studies are needed to clarify the role of *LKB1* in regulating ER signaling related to breast cancer pathogenesis.

Finally, the *LKB1*-AMPK signaling pathway might serve as a therapeutic target in breast cancer. Through upregulation of *LKB1*, subsequent activation of AMPK and suppression of mTOR, the adipocytokine adiponectin has been shown to inhibit breast cancer cell adhesion,

invasion, and migration [64]. Then too, LKB1 driven AMPK activation by metformin has been shown to inhibit aromatase expression [65]. Aromatase is a key protein involved in estrogen synthesis, and high levels of estrogen in breast tissue have been correlated with increased breast cancer risk [65]. Together, these studies imply that adiponectin analogues and/or LKB1/AMPK activators might have efficacy as breast cancer therapeutics.

Gastrointestinal

A recent analysis of 419 patients with PJS demonstrated that cumulative cancer risks were highest for gastrointestinal tumors, including esophageal, stomach, small bowel, colorectal, and pancreatic cancers, and that the risk for these tumor types at ages 30, 40, 50, and 60 years was 1%, 9%, 15%, and 33%, respectively [66]. Given that one of the hallmarks of PJS is the early development of benign gastrointestinal hamartomas, studies have focused on how *LKB1* allele status relates to gastrointestinal tumorigenesis. Several lines of evidence in both human and mouse models have suggested that hamartoma formation and carcinogenesis are distinct processes [35;36;37;38;41;42;43;67]. Indeed, the gastrointestinal hamartomas that PJS patients develop are remarkable in that they are well differentiated and exhibit normal morphology and grade, features that clearly distinguish them from pre-malignant lesions [68]. Interestingly, while biallelic loss of *LKB1* does occur in some liver, colorectal, and pancreatic tumors, alternate lines of evidence have shown that biallelic loss is not necessarily required in the development of all gastrointestinal tumors [42;44;46;47;69]. In the pancreas of mice, for instance, complete loss of LKB1 has been shown to result in markedly disrupted acinar cell polarity, decreased AMPK/MARK/SAD kinase activity, and the development of unusual but benign serous cystadenomas [70;71]. On the other hand, *Lkb1* haploinsufficiency coupled with oncogenic K-RAS mutations has been shown to result in malignant ductal adenocarcinomas [71]. In this particular study, it was proposed that decreased LKB1 protein expression synergized with K-Ras over-activation through reduced p21/p53-mediated growth arrest. Similar results have been observed in some human pancreatic ductal adenocarcinomas. LKB1 expression was found to be decreased in approximately 20% of samples analyzed, all of which also showed depressed levels of p21 [71]. Given that decreased levels of both LKB1 and p21 correlated with worsened prognosis, this signaling axis might represent an important therapeutic target in a subset of *Lkb1*-deficient, K-Ras over-expressing pancreatic cancers.

In addition to its role in pancreatic adenocarcinoma, LKB1 may also contribute to the pathogenesis of other gastrointestinal tumors. Mice heterozygous for *Lkb1* develop hepatocellular adenomas and carcinomas beginning at 30 weeks of age [72]. Furthermore, cooperation with additional genes may accelerate carcinogenesis. For instance, *Lkb1* heterozygous mice with either *p53* homozygous mutations or overexpression of beta-catenin manifest earlier onset of hepatic tumors than mice carrying mutant *Lkb1* alone [73;74]. In addition, double heterozygous (for both *Lkb1* and *p53*) mice show increased incidence of gastric tumors and dramatically reduced life spans. Together, these studies suggest that either total or partial loss of LKB1 can contribute to tumorigenesis in the gastrointestinal tract and that deregulation of other signaling pathways may accelerate this process.

Lung

Sporadic mutations in *LKB1* are common in non-small cell lung carcinoma [75;76], and studies demonstrate that it is the third most commonly mutated gene behind *p53* and *K-RAS*. Gene inactivation mainly results from non-sense mutations or a combination of indels or large intragenic deletions on one *LKB1* allele plus large chromosomal deletions on the other allele [75]. Demographically, *LKB1* mutations in lung tumors are more common in male Caucasian smokers, and these tumors tend to be more poorly differentiated [23;77;78].

Moreover, *LKB1* inactivating mutations are more frequent with the occurrence of concomitant activating *K-RAS* mutations, but not *EGFR* mutations. Patients harboring compound mutations suffer a poorer prognosis than those with *K-RAS* mutations alone [77;79]. Interestingly, mouse models have corroborated these observations. Whereas loss of *LKB1* alone did not yield pulmonary pathology and *K-RAS* activation alone produced lung tumors with long latency, the combination of both mutations produced a more aggressive tumor phenotype with higher tumor multiplicity and more frequent metastases [76]. In addition, these animals developed tumors with a spectrum of histologies, including pulmonary squamous cell carcinoma (SCC), which is one of the most lethal human malignancies [76].

An integrated genomic and phosphoproteomic analysis was performed to better define the cooperation between *LKB1* inactivation and *K-RAS* activation in these animals [24]. The analysis also aimed to identify the most relevant signaling pathways. Primary murine tumors showed increased expression of genes associated with the FAK/SRC and PI3K/AKT pathways, while metastatic tumors showed increased expression in epithelial-mesenchymal transition, stem cell, and growth factor pathways [24]. Activation of the FAK/SRC pathway is particularly interesting, since *LKB1* and SRC are involved in both mTOR signaling and cell migratory processes through p21-activated kinase (PAK1). It is known that *LKB1* negatively regulates mTOR through AMPK, while SRC positively regulates it through PI3K/AKT signaling [80;81]. Thus, loss of *LKB1* coupled with increased SRC activity implies both a relief of growth constraints and a drive of cell growth, supporting possible cooperation between these two pathways. Turning to PAK1 signaling, *LKB1* and SRC might similarly act in concert, this time by disrupting cell polarity, which could impact cell migratory and metastasis processes. Functional *LKB1* has been shown to be essential for maintaining normal lung cell polarity through an *LKB1*-cdc42-PAK1 pathway [82]. Therefore, its loss might contribute to augmented cellular migration and invasion. In this regard, loss of *LKB1* has been correlated with increased PAK1 activity and subsequent PAK1-mediated cell migration, while ectopic expression of *LKB1* in *LKB1*-null cells resulted in the reversal of this activity [82]. In contrast, FAK/SRC signaling drives PAK1 activation, which in turn promotes cell migration [83]. Together, inactivation of *LKB1* with overactivation of FAK/SRC provides a compound mechanism for cell invasion. For patients harboring dual *LKB1* and *K-RAS* mutations, the potential clinical implications of these studies include the use of 1.) FAK/SRC kinase inhibitors such as Dasatinib, a multi-targeted inhibitor of Src family kinases, 2.) AMPK activators such as metformin, and/or 3.) mTOR inhibitors like rapamycin. Inhibitors of mTOR have already been used in the treatment of some patients with lung cancer with clear evidence of anti-cancer activity [84;85].

While murine studies suggest that FAK/SRC signaling is important for tumorigenesis in *Lkb1-K-Ras* double mutant mice, it is unknown if this pathway is relevant to lung cancers harboring mutations in other genes, such as *p53*, *PTEN*, or *BRAF*. Then too, given *LKB1*'s numerous downstream targets, pathways other than those involving AMPK are likely to be important in the development and progression of carcinogenesis. In fact, the ability of *LKB1* to increase the stability of Polyomavirus Enhancer Activator 3 (PEA3), which, in turn, increases transcription of genes involved in metastasis, such as *COX-2*, *MMP-9*, and *MMP-14* has been documented in some non small cell lung cancers [86]. Interestingly, increased *COX-2* has been correlated with decreased survival of patients with adenocarcinoma, implying that *COX-2* inhibitors might offer therapeutic benefit in a subset of this population [87]. Others studies also indicate a possible link between *LKB1* and c-MYC in lung carcinogenesis. In this regard, ectopic *LKB1* expression in an *LKB1*-null lung cancer cell line was shown to down-regulate c-MYC protein, leading to a G1 cell cycle arrest and an induction of apoptosis. In addition, over-expression of *LKB1* was shown to

inhibit the activation of ERK 1/2 and STAT3 signaling pathways, which act upstream of c-MYC and contribute to cell proliferation [88].

Reproductive Tissues

LKB1 may also play a tumor suppressive role in epithelial cancers of the reproductive system. Although prostate cancer incidence is not increased in PJS patients, this is not surprising, since their average life expectancy is 57 years while prostate cancer is typically diagnosed in the seventh decade [3]. Based on the analysis of a limited number of cell lines, LKB1 does appear to be mutated in at least some prostate cancers [89]. Moreover, male mice engineered to lack LKB1 in prostate epithelium showed predisposition to prostatic intraepithelial neoplasia (PIN) and reduced longevity [90]. In these animals loss of LKB1 positively correlated with beta-catenin nuclear translocation and upregulation of the WNT and PI3K/AKT/PTEN signaling cascades, suggesting the importance of these pathways in prostate tumorigenesis. In addition, the LKB1 deficient prostate phenotype mirrored aspects of both PTEN loss and WNT deregulation. Interestingly, PIN development seemed to be independent of mTOR signaling. Loss of LKB1 correlated with an unexpected surge in AMPK and a decrease in mTOR signaling, implying that either LKB1 does not regulate AMPK within prostate epithelium or that an alternative AMPK kinase compensates for loss of LKB1 expression. PIN foci also exhibited loss of cell polarity, evidenced by aberrant expression of ZO-1, a tight junction protein that is typically highly organized in normal prostate tissue.

In addition to its role in prostate epithelium, LKB1 may also function in female reproductive tract tumorigenesis. PJS patients have a significantly increased risk of developing gynecological cancers, and tumors show clinical and histopathologic distinctions [91]. In the endocervix, for example, PJS patients develop extremely well differentiated adenocarcinomas, which contrary to expectation, tend to be large, invasive, and clinically aggressive [92]. Murine studies have recapitulated LKB1's role in endometrial carcinogenesis. Female mice carrying heterozygous endometrial *Lkb1* inactivation develop focal tumors with long latency, while those with homozygous *Lkb1* inactivation undergo diffuse malignant transformation of their entire endometrium with rapid extrauterine spread and death [92]. Although these tumors showed intact cell polarity, levels of AMPK were markedly decreased. Interestingly, despite LKB1 loss, mTOR expression in these tumors was not significantly decreased. When mTOR was inhibited with rapamycin, disease progression was substantially slowed and pre-existing tumors showed striking regression, underscoring the potential benefit of this therapeutic agent in LKB1-deficient endometrial cancers. In cervical cancer, somatic mutations of *LKB1* have been found in 20% of tumors, and loss of LKB1 has been associated with accelerated disease progression [93]. Similar to endometrial cancer, suppression of mTOR signaling has also been shown to exert an anti-proliferative effect in LKB1-deficient cervical cancer cell lines [94].

Skin

The role of LKB1 in skin carcinogenesis is currently under investigation. Initial studies have hinted at its tumor suppressive role in cutaneous squamous cell carcinoma (SCC). Murine models with LKB1 selectively deleted in the epidermis have been shown to develop SCCs spontaneously, although at a very low rate [48]. However, these animals manifested markedly accelerated tumorigenesis after topical application of DMBA, a chemical carcinogen [48]. In these studies, it was shown that the pathogenesis of SCCs did not involve *RAS* mutations, which are induced by DMBA treatment, suggesting that SCC associated with LKB1 loss may involve pathways distinct from those in H-RAS-induced SCCs. Loss of LKB1 also had little impact on mTOR signaling. Interestingly, when LKB1

was re-introduced in tumor-derived SCC cell lines, a senescence-like growth arrest was observed, involving the RB, but not p53 and AMPK pathways. An induction of p38 was also observed, suggesting that *wildtype* LKB1 might thus function to provoke an acute stress response, potentiating senescence, which may be lost when LKB1 is mutated.

It is also likely that LKB1 plays a tumor suppressive role in the nonepithelial skin cancer, melanoma. PJS patients have characteristic melanin freckling on the lips and oral mucosa, and occasionally on the digits, palms, soles, and axillae, but the etiology of these pigmented lesions is unknown [33]. Although they have been generally considered lentigines, an alternate theory hypothesizes that these lesions are actually benign neoplasm of melanocytes [95]. Since PJS freckles are typically not biopsied, histological verification is lacking, yet this pigmentation inspires the possibility of LKB1's role in the pathogenesis of melanoma. While PJS patients haven't been shown to develop excess skin tumors, one study has identified *LKB1* somatic mutations in both a melanoma cell line and a small number of primary tumors [96]. More recently, two independent groups have implicated LKB1 in a BRAF-AMPK signaling "axis" that allows for cell proliferation under metabolic stress [97;98]. It was shown that in melanoma cells harboring the specific BRAFV600E mutation, signaling was rewired allowing two kinases, ERK and RSK to inhibit LKB1 via phosphorylation. It was proposed that this inhibition of LKB1, which dampened AMPK signaling, thus potentiated mTOR activity and ultimately enhanced cell growth and proliferation. These findings suggest that BRAF inhibitors, possibly in combination with AMPK activators may have clinical benefit in a subset of melanoma patients. Moreover, future research should be directed to determine if similar post-translational inhibition of LKB1 occurs in other cancers, such as colon, thyroid, and ovarian, which also frequently harbor the BRAFV600E mutation [99].

Conclusion

When examining the function of LKB1 in multiple epithelial cell cancers, it becomes clear that this protein plays many context specific roles. This is not unexpected, given its multiple downstream targets. In some instances, LKB1 might function chiefly to suppress cell growth or invasion, while in other cases, it may serve to prevent metastasis. Moreover, molecular signatures of individual tumors likely influence LKB1's operational role, as multiple studies have shown that LKB1 can synergize with other tumor suppressors and/or oncogenes to accelerate tumorigenesis (Figure 1). In *Lkb1* heterozygous mice, p53 deficiency accelerated polyposis, conferred shorter tumor latency, and altered the spectrum of carcinomas observed [100]. The too, double mutant mice designed with low LKB1 expression and *PTEN* heterozygosity showed significantly accelerated tumorigenesis compared to counterparts expressing low LKB1 or PTEN alone [101]. In other contexts, K-RAS has been shown to cooperate with LKB1. In both lung and pancreatic cancer models, mice with compound *Lkb1* and *K-ras* mutations developed more aggressive tumors more quickly [24;48;76]. Finally, recent research has suggested that LKB1 might synergize with c-MYC to prevent the later's oncogenic signalling. For example, in the presence of *wildtype* LKB1, c-MYC was unable to induce epithelial cell proliferation in a mammary model, but when LKB1 was silenced, cells instantly re-entered the cell cycle [102]. Interestingly, by taking advantage of a newly engineered 3-dimensional epithelial cell culture model, the authors of this study showed that in addition to preventing c-MYC oncogenic signaling, cell polarity was maintained in cells harboring *wildtype* LKB1, but not mutant LKB1. This study well exemplified the likely overlapping roles of LKB1 in repressing cell growth and in maintaining cell polarity, both of which are important in tumor suppression. To date, multiple murine models have demonstrated tissue-specific deregulation of both cell growth pathways, such as mTOR signaling and cell polarity (Table 1).

At present, most all investigations of LKB1 support its function as a tumor suppressor. But, are there any contexts where its expression might actually promote growth in an oncogenic fashion? Although its downstream target AMPK certainly prevents growth through multiple pathways, AMPK also facilitates some events which may prove beneficial to tumor cells. Under nutrient deprivation or oxidative stress, AMPK stimulates glucose uptake and upregulates the expression of key glycolytic enzymes, both of which may allow large tumors to continue growing when they have exhausted immediate nutrient and oxygen supplies [103]. This suggests that perhaps re-activation or even overexpression of LKB1 may be advantageous in larger, more advanced tumors. Recent research has also suggested that LKB1 can function to prevent apoptosis in times of stress, which might similarly provide tumors with a growth advantage. Under energy-deprived conditions, for example, LKB1-deficient fibroblasts were shown to undergo greater degrees of cell death than wild type counterparts [104]. Moreover, they were both more sensitized to cell death after exposure to AIMCAR, an AMP analogue, and more sensitive to chemotherapeutic agents after exposure to AMPK inhibitors [104]. In addition, *wildtype* LKB1 has also been shown to be required for preventing apoptosis in cells over-expressing AKT [105]. AKT is thought to contribute to tumorigenesis in part by preventing apoptosis by phosphorylation and inactivation of FOXO transcription factors [106;107]. AKT activation led to increased FOXO phosphorylation in LKB1 *wildtype*, but not LKB1-null cells, and when LKB1 was re-introduced, phosphorylation was restored [105]. In sum, these data indicate that *wildtype* LKB1 can promote growth through the suppression of apoptosis. As tumors expand and develop areas of hypoxia, LKB1 might thus promote cell survival through this mechanism. In conclusion, although LKB1 has been traditionally considered a tumor suppressor, it might in fact play an oncogenic role in certain contexts. Whereas loss of LKB1 may be important in initial tumor cell growth, invasion, and metastasis, perhaps re-establishment of its expression may promote tumor survival when growth outstrips nutrient supplies. Future studies exploring LKB1's functional status in tumors at different stages will certainly be informative.

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Figure 1. Lkb1 may cooperate with other oncogenes and/or tumor suppressors in carcinogenesis

Both *in vitro* and *in vivo* studies have demonstrated that LKB1 may cooperate with additional mutated genes or deregulated signaling pathways to accelerate tumorigenesis. Although most *in vivo* studies have used murine models to assess gene cooperation, these findings may also be relevant humans.

1. Based on decreased LKB1 expression (5–10 fold reduction) using hypomorphic mice.
2. Based on LKB1 expression ablation using a shRNA approach.
3. Based on studies using *Lkb1* heterozygous mice.
4. Based on LKB1 expression ablation using an adenovirus delivering Cre recombinase strategy.
5. Based on analysis of human non-small cell lung tumors with mutated *LKB1*.
6. Based on ectopic and overexpression of LKB1 in LKB1-null cell lines.
7. Based on melanoma cell lines harboring the BRAFV600E mutation. In this case, LKB1 was inactivated post-translationally through rewired signaling.

Table 1
mTOR signaling and cell polarity defects in tissue-specific Lkb1-deficient tumor models

To suppress tumorigenesis, LKB1 likely plays overlapping roles in repressing cell growth and in maintaining cell polarity in multiple epithelial cancer types. To date, murine models with tissue-specific deletion of LKB1 have identified deregulation in both cell growth pathways, such as mTOR signaling and in cell polarity.

Cancer Type	mTOR Signaling	Cell Polarity
Non small cell lung	deregulated	defective (<i>in vitro</i>)
Skin: SCC (DMBA-induced)	independent	no significant defects
Skin: Melanoma (BRAFV600E+)	deregulated	<i>unknown</i>
Breast	deregulated	defective (<i>in vitro</i>)
Endometrial	independent	defective (<i>in vivo</i>)
Prostate	independent	no significant defects
Pancreatic	independent	Defective (<i>in vivo</i>)