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REVIEW ARTICLE

LKB1 tumor suppressor: Therapeutic opportunities knock when LKB1 is inactivated

Wei Zhou*, **Jun Zhang**, **Adam I. Marcus**

Department of Hematology and Medical Oncology, The Winship Cancer Institute, Emory University School of Medicine, Atlanta, Georgia

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Abstract LKB1 is commonly thought of as a tumor suppressor gene because its hereditary mutation is responsible for a cancer syndrome, and somatic inactivation of LKB1 is found in non-small cell lung cancer, melanoma, and cervical cancers. However, unlike other tumor suppressors whose main function is to either suppress cell proliferation or promote cell death, one of the functions of LKB1-regulated AMPK signaling is to suppress cell proliferation in order to promote cell survival under energetic stress conditions. This unique, pro-survival function of LKB1 has led to the discovery of reagents, such as phenformin, that specifically exploit the vulnerability of LKB1-null cells in their defect in sensing energetic stress. Such targeted agents represent a novel treatment strategy because they induce cell killing when LKB1 is absent. This review article summarizes various vulnerabilities of LKB1-mutant cells that have been reported in the literature and discusses the potential of using existing or developing novel reagents to target cancer cells with defective LKB1.

Introduction

The current cancer treatment paradigm is to inhibit biological pathways that are hyperactive in cancer cells with pharmaceutical reagents. While these approaches have proven successful in the clinic, they share two common limitations. First, the targeted proteins or pathways are likely to play important physiological roles in some normal tissues, and their inhibition thus leads to toxic side effects. Second, cancer cells have defective DNA damage/repair checkpoint(s) which make them genetically unstable.[1] Consequently, cancer cells are genetically heterogeneous, and each cell contains numerous pre-existing mutations that are not normally selected. Systemic therapy creates an environment for the selection of cancer cells with mutated target proteins that no longer interact with the drug. Therefore, side effects and secondary mutation-related

* Corresponding author. Departments of Hematology and Medical Oncology, Emory University School of Medicine, 1365 Clifton Road, NE, Suite C4084, Atlanta 30322, Georgia. Tel.: +995 404 778 2134; fax: +995 404 778 5530.
E-mail address: wzhou2@emory.edu (W. Zhou).
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drug-resistance are two inevitable consequences of current cancer treatment approaches.

Tumor suppressor genes are not normally perceived as viable drug targets, and a common quote from pharmaceutical companies is "how can you target something that is not there?" It is important to note that even though Dr. Frank McCormick pioneered the concept of killing p53-null cells with the ONYX virus, the most successful clinical study of this virus was accompanied by evidence that ONYX-015 kills cancer cells through a mechanism that is not related to p53 inactivation.[2,3] Recent studies have indicated that defects in the LKB1-AMPK signaling pathway make tumors vulnerable to varieties of stress, which can be exploited therapeutically.

Liver kinase 1 (LKB1 also known as STK11) is a tumor suppressor gene that is inactivated by bi-allelic mutation in non-small cell lung cancer (NSCLC), malignant melanoma and cervical cancer.[4–6] Our knowledge of the biological roles of LKB1 has rapidly expanded over the past decade. Initial research focused on its roles in cell polarity, cell motility, protein translation and energy metabolism, and recent advances indicated that LKB1 is also involved in the regulation of other cellular process, such as DNA damage checkpoint, liposome function, and various signal transduction pathways. Hence, the inactivation of LKB1 in human tumors will lead to the de-regulation of multiple cellular processes, but it is still unclear which of them is related to tumorigenesis. From a treatment perspective, the lack of proper regulation should make cancer cells vulnerable to reagents that specifically inhibit these pathways. A therapeutic approach that can specifically eliminate LKB1-deficient cells will have at least two advantages. First, LKB1 is ubiquitously expressed in all tissue types, and therapeutic approaches against LKB1-null cells should have less toxic effects on normal tissues (i.e. fewer side effects). Second, LKB1 is frequently inactivated by bi-allelic genetic inactivation. Because the genetic codes for LKB1 are lost in these cancer cells, they are unlikely to be restored by genetic instability. Even if cancer cells find another way to restore LKB1 function, its tumor suppressor function should inhibit the growth of these cells. This review article will focus on the nature of these vulnerabilities and recent advances in the development of clinical reagents that target these vulnerabilities in LKB1-null cancer cells (Table 1).

LKB1 as a serine/threonine kinase

LKB1 protein has a central kinase domain, two N-terminal nuclear leading sequences, and a C-terminal regulatory motif. The protein also contains a CAAX motif at C-terminal end and can be farnesylated. The formation of an LKB1/Strad/MO25 complex is essential for LKB1's kinase activity,[7] and there are at least 13 known substrates of LKB1, which includes AMPKs, BRSKs, and MARKs.[8] LKB1 is ubiquitously expressed in all tissues, so the mere presence of this protein does not inhibit cell proliferation.[9] Existing data indicate that LKB1 kinase activity can be regulated either by post-translational modification of LKB1 itself or by the regulation of conformational configuration of its downstream targets. The upstream regulators of LKB1

Table 1 | A summary of agents may be used to target LKB1 mutants and their stages of development.

Class	Agents	Targets / Mechanisms that are *LKB1 independent*	Stage of development	Comments	Refs
AMPK activators/ stress inducers	Metformin	Inhibits mitochondria complex 1 and induces higher AMP/ATP ratio in LKB1 mutants[25–27]	Multiple phase 1 to 3 trials in malignancy and diabetes. Some of them included AMPK in the outcome measures (e.g. the phase 2 trial *NCT01266486*)	The phase 2 *NA_00052073* also included LKB1 status in the secondary outcome measures	25–27
	Phenformin	Targets mitochondria complex 1 and induces more severe energy stress in LKB1 mutants[27]	Was withdrawn from market in 1978 due to rare but severe lactic acidosis in diabetic pts. Not currently in clinical trial	LKB1 farnesylation is required for activation of AMPK by phenformin[30]	27,30
	AICAR	Induces apoptosis in LKB1-null MEF cells and ovarian cancer cells[34,35]	Phase 1-2, but none for malignancies at this moment		34,35
mTOR/HIF-1α/ LOX inhibitors	Rapalogues (Everolimus, sirolimus, temsirolimus)	mTORC1	Now in multiple phase 1-3 clinical trials	*NCT01178151* is a phase 2 trial specifically for PJS	32,42,43

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