The LKB1 serine/threonine kinase is a tumour suppressor responsible for the inherited familial cancer disorder Peutz-Jeghers syndrome and is inactivated in a large percentage of human lung cancers. LKB1 acts as a master kinase, directly phosphorylating and activating a family of 14 AMPK (AMP-activated protein kinase)-related kinases which control cell metabolism, cell growth and cell polarity. In this issue of the Biochemical Journal, Hardie and colleagues discover an alternative splice form of LKB1 that alters the C-terminus of the protein containing a few known sites of post-translational regulation. Although widely expressed, the short isoform (LKB1s) is the sole splice isoform expressed in testes, and its expression peaks at the time of spermatid maturation. Male mice lacking the LKB1s isoform have dramatic defects in spermatocozoal, resulting in sterility.

Key words: alternative splicing, AMP-activated protein kinase (AMPK), kinase, LKB1, spermatogenesis.
The authors next examined whether the short LKB1 isoform displays altered function relative to the standard long isoform in a number of assays. First, they examined whether the short isoform is altered in its ability to activate AMPK, or several of the AMPK-related kinases. The authors took advantage of the fact that HeLa cells lack LKB1 to introduce each isoform in the absence of the other. No significant difference was observed, although in vitro kinase assays using purified recombinant AMPKα1 or the BRSK (brain-specific kinase)/SAD kinases as substrates both revealed increased catalytic activity of the LKB1 isoform. Strikingly, despite lacking the farnesylation site and C-terminal phosphorylation site, no difference was observed for the subcellular localization of each isoform in HeLa cells. Further studies will be required to determine whether, in some cell types, there may be a differential localization for either isoform in response to specific stimuli, particularly those that result in increased phosphorylation of Ser428 or farnesylation of Cys430.

To directly investigate a requirement for the LKB1 isoform, the authors took advantage of a genetically engineered mouse bearing a conditional floxed allele of LKB1 in which the middle five exons to Drosophila. Both isoforms of LKB1 appear to activate all the tested members of the AMPK-related family of kinases, many of which have well-established roles in the control of cell polarity (SAD/MARK subgroups) as well as in cell growth and/or the control of glucose metabolism [AMPK, SIKs (self-inducible kinases)]. Little is known about the function of SNRK or the Aik5/SNARK (SNF1/AMPK-related kinase) subgroup, and many of these kinases may share overlapping substrates; therefore designing some as regulating cell polarity and others as regulating cell growth/metabolism is somewhat arbitrary.

**REFERENCES**


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