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REVIEW

BRG1 and *LKB1*: tales of two tumor suppressor genes on chromosome 19p and lung cancer

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Losses of heterozygosity (LOH) of the short arm of chromosome 19 are frequent in lung cancer, suggesting that one or more tumor suppressor genes are present in this region. The *LKB1* gene, also called *STK11*, is somatically inactivated through point mutations and large deletions in lung tumors, demonstrating that *LKB1* is a target of the LOH of this chromosomal arm. Data from several independent groups have provided information about the profiles of lung tumors with *LKB1* inactivation and it is generally agreed that this alteration strongly predominates in non-small cell lung cancer, in particular adenocarcinomas, in smokers. The LKB1 protein has serine–threonine kinase activity and is involved in the regulation of the cell energetic checkpoint through the phosphorylation and activation of adenosine monophosphate-dependent kinase (AMPK). LKB1 is also involved in other processes such as cell polarization, probably through substrates other than AMPK. Interestingly, another gene on chromosome 19p, *BRG1*, encoding a component of the SWI/SNF chromatin-remodeling complex, has emerged as a tumor suppressor gene that is altered in lung tumors. Similar to *LKB1*, *BRG1* is somatically inactivated by point mutations or large deletions in lung tumors featuring LOH of chromosome 19p. These observations suggest an important role for *BRG1* in lung cancer and highlight the need to further our understanding of the function of Brahma/SWI2-related gene 1 (BRG1) in cancer. Finally, simultaneous mutations at *LKB1* and *BRG1* are common in lung cancer cells, which exemplifies how a single event, LOH of chromosome 19p in this instance, targets two different tumor suppressors.

Loss of heterozygosity of chromosome 19p in lung cancer: one hit—two targets

Screening for regions with loss of heterozygosity (LOH) in tumors is widely used to search for novel tumor suppressor genes in cancer. Over the past decade, this type of screening has been done using highly polymorphic microsatellite markers, but nowadays, faster and more informative genome-wide high-throughput analytical approaches, such as single-nucleotide polymorphism-based microarray, are quickly substituting traditional methods (1,2). In the particular case of lung cancer, LOH at 9p and 17p is especially common, targeting well-known tumor suppressors such as *P16/INK4A* at 9p or *TP53* at 17p. In addition to these, LOH in chromosome 19 is an extremely frequent event in tumors of non-small cell lung cancer (NSCLC), the most common type of lung cancer. Using microsatellite markers to test for genome-wide LOH in lung cancer cell lines with matched normal tissue, Virmani *et al.* (3) reported that as many as 80% of NSCLCs had LOH at chromosome 19p compared with <30% of small cell lung cancers (SCLCs). The high frequency of LOH on this chromosomal arm was later confirmed in lung primary tumors (4). These observations strongly suggested that chromosome 19p, specifically the 19p13 region, contained one or more tumor suppressor genes. Later, also by means of microsatellite markers on the entire short arm of chromosome 19, we isolated a minimal region of LOH within 19p13.3 that contained the *LKB1* tumor suppressor (5). Germ line-inactivating mutations at *LKB1* (also named *STK11* for serine–threonine kinase 11) are responsible for the cancer-prone Peutz–Jeghers syndrome (PJS) (OMIM 175200), an autosomal dominant inherited disorder (6,7). Individuals with PJS typically show mucocutaneous melanin pigmentation and suffer from hamartomatous polyps in the gastrointestinal tract (8,9). However, among the most important health-related concerns is the increased risk of cancer development (8). We screened for mutations in the entire coding region of *LKB1* in a set of lung primary tumors and lung cancer cell lines and found that it was indeed biallelically inactivated in these and predominantly so in those of the NSCLC type with LOH (5,10,11). The presence of inactivating biallelic mutations of *LKB1* in lung cancer has since been confirmed by others (12–16), unequivocally attesting to its important tumor suppressor role in lung cancer. While the prevalence of LOH on chromosome 19p in NSCLC is close to 80%, *LKB1* mutations, including large deletions, occur in about half of lung cancers of this type. This leaves open the possibility that there is another tumor suppressor gene in the region.

To identify novel tumor suppressors, Teng *et al.* (17) screened for regions of homozygous deletions in cancer cell lines and found that the *BRG1* gene (also called *SMARCA4*) was biallelically deleted in a subset of cell lines of different types of tumor. Later, they identified inactivating mutations of *BRG1* in a variety of cancer cell lines, including those of the lung, albeit at low frequency (18). *BRG1* is located on chromosome 19p13.2, only ~10 Mb from *LKB1*. Our recent observations have demonstrated that *BRG1* inactivation in lung cancer is not occasional because as many as one-third of lung cancer cell lines of NSCLC origin carry mutations of this tumor suppressor gene (19). Simultaneous alterations of *BRG1* and *LKB1* are quite common in lung cancer cell lines and are an example of how a single event, LOH at chromosome 19p in this instance, can target two different tumor suppressor genes. This is one of the few known examples of this phenomenon. Figure 1 represents the chromosomal location of those tumor suppressor genes found to be disrupted in lung cancer.

Characteristics of *LKB1* inactivation in lung cancer

LKB1 inactivation is characteristic of NSCLCs, especially lung adenocarcinomas, while alterations are rare in SCLCs (5,10,14). This is fully consistent with the reported percentages of LOH on chromosome 19p, which are significantly higher in NSCLC than in SCLC (3,4). *LKB1* inactivation in lung cancer occurs mainly as a result of non-sense mutations, indels or large intragenic deletions at one allele plus large chromosomal deletions of the other, leading to a complete absence of LKB1 protein (20). Only a few missense mutations have been reported to date, most of which affect the kinase domain, while gene promoter hypermethylation is rare (5). In agreement with the classic definition of a *bona fide* tumor suppressor gene, mutations of *LKB1* in lung cancer of sporadic origin are tumor specific and homozygous (20). A list of the alterations found in *LKB1* in lung cancer is provided in a recent review (20). *LKB1* mutations occur preferentially in lung tumors of smokers and are found concomitantly with *KRAS*

Abbreviations: AMPK, adenosine monophosphate-dependent kinase; ATP, adenosine triphosphate; BRG1, Brahma/SWI2-related gene 1; BRM, Brahma; LOH, loss of heterozygosity; NSCLC, non-small cell lung cancer; PJS, Peutz–Jeghers syndrome; SCLC, small cell lung cancer; TSC, tuberous sclerosis complex.

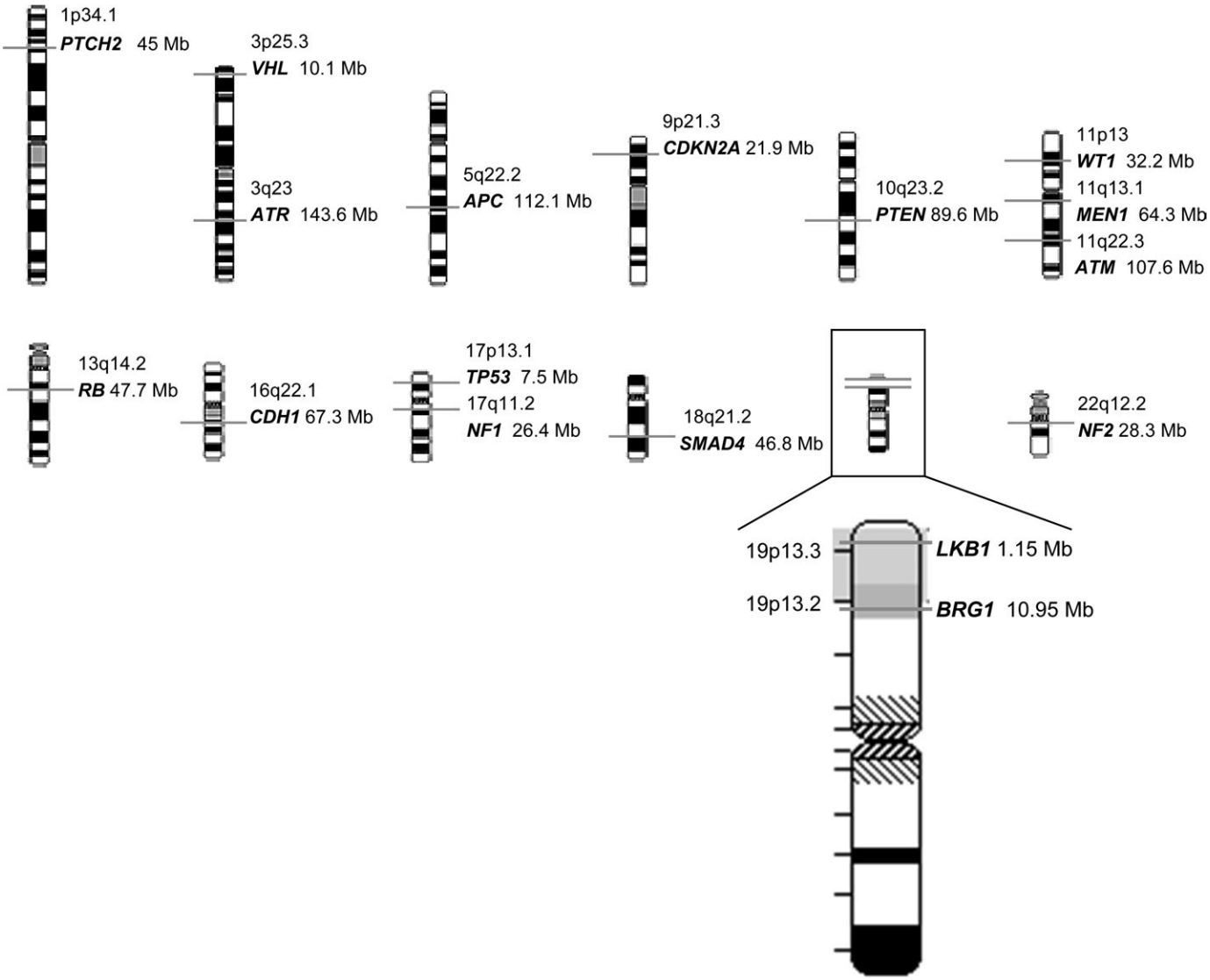

Fig. 1. Chromosomal location of tumor suppressor genes found to be altered in lung cancer. Included are only those tumor suppressor genes reported to be somatically inactivated in lung tumors in the Catalog of Somatic Mutations in Cancer database (http://www.sanger.ac.uk/genetics/CGP/cosmic/) and carrying at least one truncated mutation. It has to be remembered that, except for *TP53*, *CDKN2A*, *LKB1*, *RB* and *BRG1*, most of the depicted genes, though they may be frequently inactivated in other types of cancer, are only occasionally altered in lung cancer.

but not with *EGFR* mutations (5,13,16). Moreover, *LKB1* inactivation is less frequent in lung adenocarcinomas from patients of Asian origin (14,15), who exhibit a significantly higher frequency of *EGFR* alterations than found in lung adenocarcinomas arising in patients from western countries. Corroborating this observation, it has recently been reported in mouse models that *Kras* and *Lkb1* mutations cooperate in lung carcinogenesis since combination of somatically activatable mutant *Kras* with *Lkb1* rendered more lung tumors and higher rates of distant metastasis than *Kras* alone or *Kras/p16* or *Kras/p53* double mutants (12). Recently, it has been reported that *LKB1* is the third most commonly altered gene in lung adenocarcinomas, after *TP53* and *KRAS* (21). Taken together, this represents consistent evidence that *LKB1* inactivation is a major event in lung carcinogenesis. Mutations of *LKB1* are found concomitantly with alterations of many oncogenes and tumor suppressors such as *KRAS*, *P16*, *TP53*, *MYC*, *BRG1* and *PIK3CA*, implying that *LKB1* has an independent biological effect on tumorigenesis (5,10,14). Thus, *LKB1*-inactivated lung tumors are typified by the following characteristics: (i) NSCLC type, especially adenocarcinoma; (ii) from an individual with a smoking habit; (iii) concomitant presence of mutations at several well-known oncogenes/tumor suppressors but not at *EGFR* and (iv) individuals of non-Asian origin. It is also known that *LKB1* mutations accumulate in less-differentiated tumors. The reports that provide information about the characteristics of *LKB1*-mutant tumors are summarized in Table I. Although *LKB1* alterations appear to be uncommon in tumors other than those of the lung, the use of highly sensitive approaches to detecting mutations in primary tumors coupled with multiplex ligation-dependent probe amplification assay or other methodologies for identifying intragenic large deletions are now required to gather definitive information about how general *LKB1* inactivation is in other types of cancer.

Given its relevance in tumorigenesis, it seems plausible that other components or targets of LKB1 activity could also be mutated in cancer. For example, *STRAD* and *MO25*, which encode the two components of the LKB1 functional complex, and tuberous sclerosis complex (*TSC*) 1 and TSC2, which encode downstream effectors of LKB1 signaling through adenosine monophosphate-dependent kinase (AMPK), are some of the candidates (22,23). Although the formers do not appear to be mutated in PJS patients without detectable *LKB1* alterations (24), the possibility that there are mutations of these genes in tumors of sporadic origin has not yet been ruled out. On the other hand, germ line mutations of the *TSC1* and *TSC2* genes are known to

Table I. Characteristics of *LKB1* mutant lung tumors

Characteristics		Number (%) of tumors carrying *LKB1* mutations						
Patient								
Ethnicity		Asian	Caucasian					Comments
Onozato *et al.* (15)		2 (25%)	3 (33%)					CL (NSCLC)
Onozato *et al.* (15)		3 (3%)	ND					PT (NSCLC)
Koivunen *et al.* (16)		9 (5%)	25 (17%)**					PT (NSCLC)
Smoking habit		Non-smokers	Smokers					
Matsumoto *et al.* (14)		0 (0%)	7 (8%)*					PT (NSCLC)
Koivunen *et al.* (13)		2 (3%)	26 (14%)**					PT (NSCLC)
Histology								
Tumor differentiation		Well	Moderate	Poor				
Matsumoto *et al.* (14)		1 (1%)	0 (0%)	6 (18%)** (W or M versus P)				PT (NSCLC)
Histological subtype		NSCLC	SCLC	AC	SCC			
Carretero *et al.* (10)		6 (33%)	0 (0%)	ND	ND			CL
Matsumoto *et al.* (14)		20 (39%)	1 (5%)**	13 (42%)	3 (27%)			CL
Onozato *et al.* (15)		5 (30%)	0 (0%)	3 (60%)	1 (11%)			CL
Onozato *et al.* (15)		ND	ND	3 (4%)	0 (0%)			PT
Ji *et al.* (12)		ND	ND	27 (34%)	8 (19%)			PT
Koivunen *et al.* (16)		ND	ND	27 (13%)	5 (5%)*			PT
Genetic								
Association with other gene alterations								
		KRAS−	*KRAS*+	*EGFR*−	*EGFR*+	*TP53*−	*TP53*+	
Sanchez-Cespedes *et al.* (5)	*LKB1*−	9	7	ND	ND	9	7	PT+CL
	LKB1+	4	4	ND	ND	3	5	
Matsumoto *et al.* (14)	*LKB1*−	134	14	94	54	78	49	PT
	LKB1+	6	1	7	0	1	3	
	LKB1−	45	4**	46	3	10	39	CL
	LKB1+	13	8	19	2	4	17	
Koivunen *et al.* (16)	*LKB1*−	237	39*	207	69**	ND	ND	PT
	LKB1+	24	10	33	1	ND	ND	
Association with the presence of *BRG1* mutations								
		BRG1−	*BRG1*+					
Medina *et al.* (19)	*LKB1*−	17	5					CL
	LKB1+	7	8					

*$P < 0.05$; **$P < 0.01$. No differences have been found with age, gender or clinical parameters such as tumor stage or patient's survival. AC, adenocarcinoma; CL, cell lines; M, moderately differentiated; ND, not determined; P, poorly differentiated; PT, primary tumors; SCC, squamous cell carcinoma; W, well differentiated; −, absence of mutation; +, presence of mutation.

cause the tuberous sclerosis syndrome. The proteins encoded by *TSC1* and *TSC2* act downstream of LKB1, modulated by AMPK (25). This is a disease that, though not apparently conferring an increased risk of cancer, shares some similarities with PJS, including the presence of hamartomas (26).

Biological role of *LKB1*: energy control checkpoint, cell polarity and others

LKB1 encodes for a protein of 433 amino acids with serine–threonine kinase activity. In addition to a kinase domain (residues 49–309), the protein has several conserved motifs, including a nuclear localization signal in the N-terminal non-catalytic region (residues 38–43) (27). LKB1 functions in a heterotrimeric complex with the inactive pseudokinase, STE20-related adapter and the armadillo repeat scaffolding-like protein, MO25 (22,23). These proteins are required not only to enable the full kinase activity of LKB1 but also to ensure its subcellular localization. The tumor suppressor role of the LKB1 protein was first observed from its ability to suppress colony formation after being re-introduced in *LKB1*-deficient cancer cells (28–30). Mice homozygous for mutant *Lkb1* die during embryonic development but $Lkb1^{+/-}$ mice survive, although they develop multiple gastrointestinal polyps and have a significantly increased predisposition to cancer, similar to what happens in the human PJS (12,31–34).

To date, the best-known substrate for LKB1 is AMPK, a sensor of cellular energy status (35,36). AMPK becomes activated through phosphorylation by LKB1 when the intracellular adenosine monophosphate:adenosine triphosphate (ATP) ratio rises above a threshold, leading to the modulation of multiple downstream targets to normalize ATP levels (37). Thus, in addition to the abilities proposed by Hanahan *et al.* (38), the abrogation of energetic checkpoints may also be required for a normal cell to become cancerous because it allows the maintenance of the highly energy-consuming processes such as DNA replication and cell division in circumstances of compromised ATP availability. One of the AMPK substrates is the tuberin protein, encoded by the gene *TSC2*, which, once activated, represses mammalian target of rapamycin (25,39). This has been verified in several types of cell, including lung cancer cells, which require wild-type LKB1 to modulate AMPK activity under conditions of energetic stress (40).

In addition to cell energetic control, it is now clear that LKB1 regulates other processes, such as cell polarity. Among the first observations linking LKB1 and polarity in mammals are those reported by Baas *et al.* (41), whereby LKB1 can induce complete polarization of intestinal epithelial cells in a cell-autonomous fashion. This effect was noticed, upon activation of LKB1, by the formation of an apical brush border coupled with the position of junctional proteins surrounding this brush border and with the correct sorting of apical and basolateral membrane markers. Although these investigations failed to detect LKB1 protein in a polarized form in intestinal cells, we and others have observed that LKB1 may have a marked apical distribution in some lung cancers and normal tissues (42,43). These differences may be the consequence of tissue-specific biology. We do not yet understand whether the role of LKB1 in cell polarity is mediated by AMPK or other substrates (44) (see refs 45,46 for reviews on this matter).

LKB1 has also been associated with the transforming growth factor beta pathway. In this regard, *Lkb1*-deficient mice have reduced transforming growth factor beta pathway activity in endothelial cells and in the stroma, which some have suggested contributes to polyposis by generating a permissive microenvironment for epithelial expansion (47,48). Other processes that may be controlled by LKB1 through the regulation of the transcription factor PEA3 include angiogenesis (34) and cyclooxygenase 2 levels (33,49). Table II and Figure 2A include a summary of the genetic and biological tumor suppressor characteristics of LKB1.

The *BRG1* tumor suppressor

The tumor suppressor gene *BRG1* (also called *SMARCA4*) is located in the 19p13.2 chromosomal region, where it spans a total length of ~100 kb. The mature transcript is comprised of 34 coding exons and codes for the protein BRG1 (Brahma/SWI2-related gene 1), a central component of the SWI/SNF chromatin-remodeling complex that features a bromodomain and helicase/ATPase activity. Depending on the cellular context, the complex can regulate transcriptional transactivation or repression by remodeling the chromatin structure, upon disturbing DNA–histone interactions at the nucleosomes in an ATP-dependent manner. Within this complex, BRG1 coexists with several BRG1-associated factors, which have variable composition. The functions and components of the SWI/SNF complex have been thoroughly reviewed elsewhere (60,61). In addition to BRG1, the protein BRM (Brahma) (SMARCA2) can substitute BRG1 and fulfill the helicase/ATPase function of the complex. Despite the high degree of homology between them, BRG1 and BRM do not seem to have interchangeable biological functions, as was revealed by knockout experiments in mice. Thus, while *Brg1* knockouts are lethal before implantation and heterozygous mice are prone to developing epithelial tumors (53), *Brm* knockouts are viable and do not develop tumors (62). In addition, double $Brg1^{+/-}$ and $Brm^{-/-}$ mice do not have greater tumor susceptibility than $Brg1^{+/-}$ alone (55). Thus, to date there has been no conclusive evidence to support the existence of a role for BRM in

Table II. Description of the genetic evidences supporting the tumor suppressor characteristics of *BRG1* and *LKB1*

Type of evidence	*LKB1*	*BRG1*
Human cancer		
Frequent LOH	Yes (refs 3–5)	Yes (refs 3–5)
Associated cancer syndrome	Peutz–Jeghers (refs 6,7)	n.d.
Cancer predisposition syndrome of components of the complex	n.d.	*SNF5/INI1* (nervous system and soft tissue sarcomas) (ref. 50)
Sporadic tumors with mutations	Lung, prostate, pancreas, cervix, head and neck (ref. 20)	Lung, prostate, breast, pancreas (refs 18,19)
Components of the complex mutated in sporadic cancer	n.d.	SNF5/INI1 (refs 51,52)
Type of mutations[a]	Frameshift, non-sense, large deletions, missense (ref. 20)	Frameshift, non-sense, large deletions, missense (refs 18,19)
Mouse models		
Knockouts (KO)	Embryonically lethal (refs 31,32)	Embryonically lethal (ref. 53)
Heterozygous	Gastrointestinal hamartomas (refs 32,33)	
	Hepatocellular carcinomas (ref. 54)	Epithelial tumors (ref. 53)
	Lung cancer (NSCLC) (ref. 12)	Mammary tumors (ref. 55)
	Endometrial adenocarcinomas (ref. 56)	
Tissue-specific KO	Lung cancer (NSCLC) (ref. 12)	
	Prostate intraepithelial neoplasia (ref. 57)	Lung cancer (NSCLC) (ref. 58)
	Pancreatic serous cystadenomas (ref. 59)	

n.d., no data.
[a]The reported mutations are homozygous indicating the loss of the remaining allele.

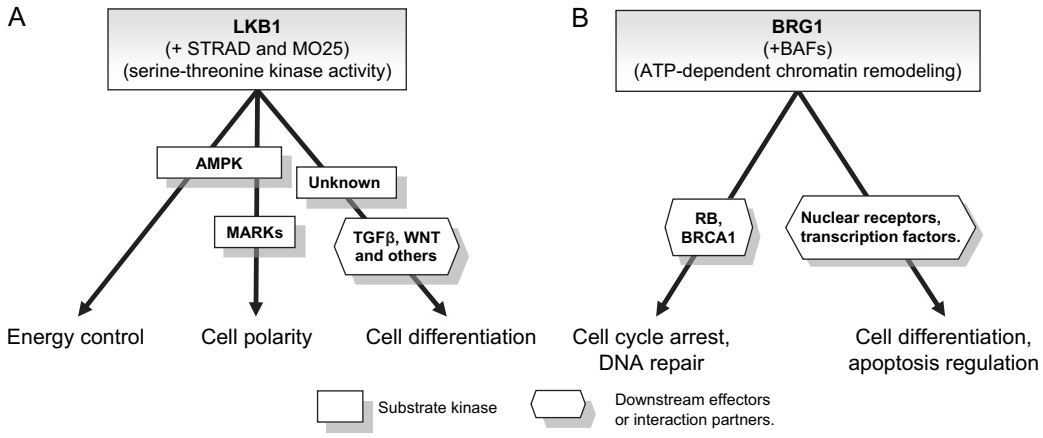

Fig. 2. Schematic representation of the LKB1 and BRG1 functions. (**A**) LKB1 association with STE20-related adapter (STRAD) and the scaffolding protein MO25 promotes cytosolic localization and activation of LKB1 serine–threonine kinase activity. Thus, LKB1 can activate downstream kinases and effectors such as AMPK and MARKs that eventually regulate different biological functions including the control of the cell energetic status, polarity and differentiation. (**B**) BRG1, with ATPase activity, interacts with its associated factors [BRG1-associated factors (BAFs)] constituting the SWI/SNF complex. The SWI/SNF complex functions, including regulation of gene transcription, occur through the remodeling of the chromatin structure. Direct interaction of BRG1, or other components of the complex, with different proteins such as retinoblastoma (RB), BRCA1, nuclear receptors and transcription factors play a role in orchestrating different biological pathways including arrest of the cell cycle, DNA repair, as well as cell differentiation and regulation of apoptosis.

tumor suppression nor have any inactivating mutations of this gene been found. Complexes containing BRG1 or BRM may play distinct roles in nucleosome remodeling or regulate the expression of different downstream genes (53). It is also possible that both ATPases play similar roles in adult organisms but display heterogenous and tissue-specific patterns of expression. Further studies are required to understand the specific functions of each ATPase in normal cellular physiology and in tumorigenesis. As stated above, animal models demonstrate that BRG1 function is required for mammalian development and that its heterozygous ablation predisposes to tumor development. Complementary to these data, lung *Brg1*-targeted conditional knockout mice develop fewer tumors than their heterozygous littermates in response to carcinogens (58), possibly due to the antiapoptotic protection conferred by a single *Brg1* allele.

As mentioned above, SWI/SNF is a multimeric complex of proteins of variable composition (63). Thus, any protein of the complex is a potential target for gene alterations that may disrupt its function. In fact, mutations of various components of SWI/SNF have been described in primary tumors and cancer cell lines of human origin. In particular, germ line or somatic mutations of the gene *hSNF5/INI1* (also known as *SMARCAB1* or *BAF47*) were detected in malignant rhabdoid tumors (51,52), although they were absent from cancers of the lung (64). Aside from the tumor predisposition observed in $Brg1^{+/-}$ mice, other research using tumor-derived cell lines has associated BRG1 deficiency with cancer development. First, reintroduction of *BRG1* in deficient MEFs reverted the transformed phenotype. This observation may be explained by the ability of BRG1 to arrest the cell cycle through the activity of the retinoblastoma protein (65–67). Second, several cancer-related proteins such as P21 (66,68), BRCA1 (69), LKB1 (70), SMADs (71), CFOS (72), CMYC (73) and FANCA (74) have been associated with BRG1 or other components of the SWI/SNF complex.

Biological role of BRG1: chromatin remodeling for gene expression, survival and repair

The chromatin-remodeling complexes enable gene transcription by contributing to a transcriptionally permissive environment through the modulation of the chromatin structure and its ability to help coordinate the binding of transcription factors to promoters and enhancers. The BRG1-containing SWI/SNF complex in mammals is involved in the transcriptional modulation of hormone-responsive promoters through the binding of the complex to various nuclear receptors and its recruitment to gene-specific promoters. In this regard, specific components of the complex can bind to glucorticoid (75), estrogen (76), progesterone (77), retinoic acid (78) and vitamin D3 (79) receptors, among others. Supporting this, the use of gene expression microarrays combined with chromatin immunoprecipitation led to the identification of several targets whose transcription was mediated by BRG1 in lung cancer cells. Such is the case of *CYP3A4* (80). CYP3A4 belongs to the P450 (CYP) family of proteins, which are involved in metabolizing a variety of endogenous and xenobiotic substances. Transcription of *CYP3A4* is triggered by several nuclear receptors such as the pregnane X receptor, the orphan receptor constitutive androstane receptor, and the vitamin D3 and glucocorticoid receptors (81). Other target promoters of the BRG1-dependent SWI/SNF complex have been identified, including those of *CSF1*, *P21* and *ZNF185* (66,68,80,82). The involvement of the SWI/SNF complex in the transcriptional activation of these promoters could relate to earlier research that demonstrates the participation of the SWI/SNF complex in the regulation of cell growth and differentiation (83–85) as well as to early embryonic development and cancer progression (50,60,84,86).

Recent reports highlight the relevance of SWI/SNF to the regulation of apoptosis in response to DNA damage-induced genotoxic stress. Depending on the cell type and the nature of the insult, the complex may enhance or repress apoptosis. Mammalian cells exhibit complex cellular responses to DNA damage, including cell cycle arrest, DNA repair and apoptosis. An intact SWI/SNF complex might be crucial for orchestrating the onset of the DNA damage response. Recruiting of BRG1/BRM to E2F1-responsive promoters by direct interaction with DNA topoisomerase II-binding protein 1 (87) represses the proapoptotic activity of E2F1 (88) (but not E2F2 or 2F3) by a retinoblastoma protein-independent mechanism in response to radiomimetic drug-induced DNA damage. This negative regulation seems to be essential in the control of E2F1-dependent apoptosis during normal cell growth and DNA damage. Dominant-negative mutants of BRG1/BRM derepress E2F1 activity during DNA damage, facilitating apoptosis. BRG1 restoration in deficient cancer cells may also give rise to apoptosis protection from ultraviolet-induced DNA damage via prolongation of cell cycle checkpoints by enhancing the expression of DNA damage-responsive genes such as *Gadd45a* and p21 (89) or by reducing the prolonged p53 activity that may lead to apoptosis (90). The proapoptotic function of SWI/SNF is illustrated by the effect of restoring BAF57 expression into deficient BT549 human breast cancer cells. This leads to slow growth, promoted contact inhibition as well as cell cycle arrest and apoptosis, presumably by upregulating proapoptotic genes (91). Thus, a functional SWI/SNF complex can protect cells against the deleterious consequences of DNA damage by ensuring timely DNA repair and, eventually, progression through the cell cycle. Furthermore, the SWI/SNF complex may have an auxiliary function in the context of DNA repair since it contributes to homologous recombination-mediated DNA repair by its interaction with BRCA1 (92). During homologous recombination after DNA damage, the repair machinery must gain access to the damaged DNA in an intricate environment of highly organized chromatin. Through its remodeling action, SWI/SNF activity prompts the access of homologous recombination to the chromatin during the early phases of DNA damage repair (93). Table II and Figure 2B include a summary of the genetic and biological tumor suppressor characteristics of BRG1.

In conclusion, it is worth investing effort into elucidating the role of BRG1 and how its inactivation influences cancer development. It will also be of interest to investigate how its status or level of expression in a particular tumor may influence the prognosis of the disease upon treatment with current DNA-damaging agents or radiation. This is an important consideration at least for some tumors with aberrant BRG1/BRM expression (94) since acquired resistance of tumor cells to the activation of apoptosis (95) is a serious drawback of current anticancer therapies.

The *BRG1* tumor suppressor in lung cancer

Wong *et al.* thoroughly screened for regions of homozygous deletions in cancer cell lines and found that *BRG1* was biallelically deleted in a subset of cell lines of different tumor origins, including those from lung. They found, for the first time, the presence of inactivating mutations in pancreatic, prostate, breast, lung and colon cancer cell lines and demonstrated that reintroducing BRG1 into cells lacking BRG1 expression was sufficient to reverse their transformed phenotype, inducing growth arrest and flattened phenotype (18). Furthermore, we recently reported a high incidence of inactivating mutations of *BRG1* in lung cancer cell lines (19), whereby about a quarter of the lines screened featured *BRG1* inactivation. Similar to what is observed for *LKB1*, the presence of *BRG1* alterations was significantly more frequent in the NSCLC-type cell lines, harboring about one-third of the identified mutations compared with the only 5% in the SCLC type. These observations are in contrast with the seemingly low initial rate of inactivating mutations of *BRG1* detected in tumors from human biopsies (96). However, the presence of *BRG1* inactivation in lung primary tumors has probably been underestimated. In this regard, results of an earlier study used immunohistochemical staining to evaluate the levels of BRG1 and BRM in lung primary NSCLCs, revealing that 30% of the tumors had no detectable protein, suggesting *BRG1* inactivation (97). Furthermore, loss of nuclear expression of either one or both BRG1 or BRM was associated with poorer survival rate in NSCLC patients than in those in which both proteins were present (98).

The nature of *BRG1* mutations detected in lung cancer cell lines includes loss of one allele plus frameshift, indels, non-sense or

missense mutations in the remaining allele or large homozygous deletions, most of them yielding a truncated protein (99). Inactivation of *BRG1* by different mechanisms, such as promoter hypermethylation, appears to be uncommon (96). A recent review provides a comprehensive list of alterations found in *BRG1* in cancer (99). Although infrequent, among the most interesting mutations detected in *BRG1* are highly conserved amino acid substitutions within or near the helicase/ATPase domain, which are required to couple ATP hydrolysis to chromatin-remodeling activity (100). In addition, a GG>TT tandem base substitution was also particularly intriguing because alterations of this kind are believed to be caused by exposure to acetaldehyde, a compound that is present in tobacco smoke and automotive exhaust gases (101). Thus, similar to *LKB1*, *BRG1* inactivation may be associated with smoking habit. Mutations at *BRG1* frequently coexisted with alterations at other commonly altered genes in lung cancer, such as *TP53*, *KRAS*, *CDKN2A* and *LKB1*, among others (19). Intriguingly, alterations at *BRG1* and *MYC* amplification appeared in a mutually exclusive manner in tumors. Although these observations are still preliminary, their confirmation in a large number of tumors might indicate a similar biological function for MYC and BRG1 during tumorigenesis. Providing further support for this, Cheng *et al.* (73) reported that the SWI/SNF complex is required in CMYC-mediated gene transactivation and that recruitment of SWI/SNF to the promoters regulated by MYC depends on MYC–INI1 interaction.

Previous studies have shown that LKB1 can bind and regulate BRG1 chromatin-remodeling activity *in vivo* (70,102) and that such interaction is dependent on the N-terminal region of LKB1 and the helicase domain of BRG1. Although LKB1 is not required for BRG1 function or to regulate BRG1-containing SWI/SNF complexes, in the presence of LKB1, whether it is active or not, the ATPase activity of BRG1 is enhanced. Interaction between functionally active LKB1 and BRG1 promotes BRG1-dependent cell cycle arrest and senescence of SL26 cells, presumably through the retinoblastoma pathway (70,83,103). However, no new evidence has yet emerged that definitely demonstrates the connection between LKB1 and BRG1. To date, the fact that BRG1 and LKB1 inactivation occur concomitantly at a relatively high frequency in cancer cells indicates that the two alterations are not equivalent and cooperate in cancer development. In conclusion, further efforts are necessary to clarify the biological consequences of the LKB1–BRG1 interaction and how it can affect not only known but also as yet uncharacterized LKB1 potential functions (44).

What lies ahead?

The compelling data regarding *LKB1* inactivation in cancer coupled with information about functional and biochemical characteristics of the encoded protein as well as the characterization of animal models leave little doubt that LKB1 is a key tumor suppressor involved not only in the inherited PJS but also in lung tumors of sporadic origin. Likewise, we believe that *BRG1* will soon come to be considered a highly relevant tumor suppressor in lung tumors, even though few *BRG1* mutations have been identified in lung primary tumors to date, in contrast to the relatively high frequency reported in lung cancer cell lines. In spite of all the genetic information available, important questions remain to be answered. First, are *LKB1* and *BRG1* somatic inactivation specific to lung cancer? Alternatively, as seems more probably, are there other sporadic tumor types that carry mutations at these tumor suppressor genes? If so, what are they? Inactivation of *BRG1* and *LKB1* is so common, at least in lung cancer, that other components of the biological pathways to which these tumor suppressors belong are also potential targets for genetic alterations in cancer. This needs to be explored. In addition to these genetic questions, there are a number of unresolved issues regarding the functional role of these tumor suppressors that require intense investigation. What is the entire set of LKB1 substrates? Does LKB1 regulate cellular processes other than cell energetic control and cell polarity? What is the involvement of BRG1 in cancer development? Does BRG1 mediate the transcriptional activity of MYC? Does BRG1 participate in processes other than chromatin remodeling?

In conclusion, *BRG1* and *LKB1* are two tumor suppressor genes located on the short arm of chromosome 19 that show frequent concomitant inactivation in lung cancer. The relatively high frequency of mutations found in lung cancer cell lines attests to their importance in the development of this type of cancer and indicates that it is worth putting intense effort into investigating their biological role, especially in regard to cancer. Finally, the possible uses of this genetic information for clinical purposes, especially to improve cancer therapies, should also be considered.

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