Letter to the Editor

Proposal for a Synthetic Lethality Therapy Using the Paralog Dependence of Cancer Cells—Response

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We thank Dr. Thompson and colleagues for their insightful comments about our article (1). We have now reevaluated our finding based on their comments.

Recently, two studies sought to identify synthetic lethal partners for BRG1 using the same (and other) cancer cell lines as used by us (2, 3); their conclusions were in agreement with our own. Hoffman and colleagues (2) used a deep-coverage design shRNA (DECODER) library targeting 262 epigenetic regulators to examine the effect of gene ablation on the growth of 58 cancer cell lines. They found that BRM is essential for the growth of cancer cells harboring loss-of-function mutations in BRG1. Wilson and colleagues (3) used genome-wide shRNA screening of 11,194 genes to compare the susceptibility of eight cancer cell lines harboring inactivating mutations in BRG1 and 144 cancer cell lines without these mutations with gene ablation and found that BRM was the most specifically essential gene in BRG1-mutant cancer cells. Taken together, the results of these studies strongly support our finding that BRG1-deficient cancer cells are susceptible to BRM depletion.

Data about the restoration of BRG1 or BRM in deficient cell lines and the knockout of BRG1 and/or BRM alleles strongly indicate that BRG1 and BRM genes have tumor-suppressive activity; thus, a therapy designed to suppress BRM function appears paradoxical at first glance. However, cancer cells that developed through a BRG1 deficiency might, in turn, have acquired a specific cellular context that needs BRM as an essential survival factor (we believe that this may correspond to one of the “cell type and environmental conditions” mentioned by Thompson and colleagues). Indeed, a recent study shows that BRM is necessary for the assembly of intact SWI/SNF complexes in BRG1-deficient cancer cells (3). Therefore, we believe that our results (and those of other authors; refs. 1–3) indicate that BRG1-deficient cancer cells harbor a specific vulnerability, which largely depends on the BRG1 paralog, BRM, and we do not deny the tumor-suppressive nature of BRG1 and BRM. A similar vulnerability is also observed in ARID1A/BAF250A-deficient cancer cells (which largely depends on its paralog, ARID1B/BAF250B; ref. 4), supporting the applicability of a paralog-dependence-based approach to synthetic lethality therapy for cancer cells with a genetic deficiency.

Reisman and colleagues (5, 6) identified a subset of primary lung tumors that lack expression of both BRG1 and BRM. These tumor cells proliferated independent of BRM; thus, the carcinogenic processes and the chromatin remodeling machinery are thought to be different from those in tumor cells lacking only BRG1. Therefore, therapeutic strategies based on reversing epigenetically silenced genes (7) or the introduction of microRNAs (as proposed by Thompson and colleagues) will be applicable to such tumors (which have a poor prognosis; ref. 5) because therapies based on BRM depletion are not effective.

We agree that epigenetic silencing of BRG1 and BRM in primary tumors is an important avenue that should be pursued because it is a major mode of BRG1/BRM deficiency in primary tumors. We showed that a lung cancer cell line, II-18, which harbors the wild-type BRG1 gene but lacks expression of the BRG1 protein, is susceptible to BRM depletion (1). Therefore, therapies that target BRM might also be effective against cancer cells harboring epigenetically silenced BRG1. However, more cancer cell lines should be examined to draw firm conclusions.

As pointed out by Thompson and colleagues, the induction of p21 by BRM depletion was investigated only in a single BRG1-deficient cell line (1). However, we observed the induction of senescence by BRM depletion (indicated both by senescence-associated β-galactosidase staining and G1 arrest) in three BRG1-deficient cancer cell lines (H1299, A549, and H157). Hoffman and colleagues (2) also made similar observations in another cell line NCI-H838. Therefore, senescence is likely to be a major mode of growth arrest induced by BRM depletion in BRG1-deficient cancers, although p21 induction remains as a possible mechanism. Based on the fact that senescence is an irreversible phenomenon, and that growth arrest caused by BRM depletion continues after BRM reexpression (1), we consider that the results of the colony formation assay are reasonable.

We would like to propose a synthetic lethality therapy approach based on BRM dependence, which is a specific characteristic of BRG1-deficient cancer cells. This strategy can also be applied to cancers with other genetic deficiencies (if the gene in question has a complementary paralog).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

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