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Apoptosis

Major finding: An NMR-based fragment screen identified a BAX-interacting compound, BIF-44, that enhances BAX activity.

Mechanism: BIF-44 binds to a deep hydrophobic pocket to induce conformation changes that sensitize BAX activation.

Impact: Allosteric BAX sensitization may represent a therapeutic strategy to promote apoptosis of cancer cells.

BAX CAN BE ALLOSTERICALLY SENSITIZED TO PROMOTE APOPTOSIS

The proapoptotic BAX protein is comprised of nine α-helices (α1–α9) and is a critical regulator of the mitochondrial apoptosis pathway. In the conformationally inactive state, BAX is primarily cytosolic and can be activated by BH3-only activator proteins, which bind to ab α6/α6 "trigger site" to induce a conformational change that activates BAX and promotes its oligomerization. Conversely, antiapoptotic BCL2 proteins or the cytomegalovirus vMIA protein can bind to and inhibit BAX. Efforts to therapeutically enhance apoptosis have largely focused on inhibiting antiapoptotic proteins. Pritz, Wachter, and colleagues took the opposite approach and sought to identify compounds that directly activate the proapoptotic BAX protein to potentially promote cancer cell death. An NMR spectroscopy–based fragment screen to discover molecules that interact with full-length human BAX identified the BAX-interacting compound BIF-44. BIF-44 bound specifically to BAX and enhanced BAX activation triggered by the α-helical BH3 motif of the BIM protein. BIF-44 bound competitively to the same region as vMIA, in a deep hydrophobic pocket formed by the junction of the α3–α4 and α5–α6 hairpins that normally maintain BAX in an inactive state. Binding of BIF-44 induced a structural change that resulted in allosteric mobilization of the α1–α2 loop, which is involved in BH3-mediated activation, and the BAX BH3 helix, which is involved in propagating BAX oligomerization, resulting in sensitization of BAX activation. In addition to identifying a BAX allosteric sensitization site and mechanism of conformational regulation of BAX, these findings suggest the potential for therapeutic enhancement of BAX activity to reduce the apoptotic threshold and promote apoptosis of cancer cells. ■

Pritz JR, Wachter F, Lee S, Luccarelli J, Wales TE, Cohen DT, et al. Allosteric sensitization of proapoptotic BAX. Nat Chem Biol 2017 Jul 10 [Epub ahead of print].

Tumor Antigens

Major finding: Renal clear cell carcinomas have the highest proportion of indels, which are linked to immune activation.

Concept: Frameshift indels are associated with a greater response to anti–PD-1 than nonsynonymous SNVs.

Impact: Frameshift indels may be potential biomarkers of response to immune checkpoint inhibitors.

FRAMESHIFT INDELS GENERATE HIGHLY IMMUNOGENIC TUMOR NEOANTIGENS

Tumor-specific neoantigens are the targets of T cells in the context of checkpoint inhibitors or adoptive T-cell transfer. However, analyses of tumor-specific antigens have focused on single nucleotide variants (SNV), and the effects of small-scale insertions and deletions (indel) are less well understood. It has been hypothesized that frameshift indels may produce a large quantity of mutagenic neoantigenic peptides distinct from self, prompting Turajlic, Litchfield, and colleagues to investigate the effect of indels on the immunogenic phenotype. Analysis of whole-exome sequencing data from 5,777 solid tumors across 19 tumor types from The Cancer Genome Atlas (TCGA) revealed that renal clear cell carcinoma had the highest proportion of coding indels, 2.4 times higher than the pan-cancer average, and this observation was validated in two independent cohorts. Renal papillary cell carcinoma and chromophobe renal cell carcinoma also had elevated indel frequencies, suggesting a tissue-specific mutational process. Analysis of TCGA indels predicted 2 neoantigens per frameshift mutation in contrast to 0.64 neoantigens per nonsynonymous SNV and a 9-fold enrichment of mutant-specific neoantigens. Consistent with increased neoantigen generation, patients with melanoma harboring frameshift indel mutations exhibited a greater response to anti–PD-1 therapies than patients with nonsynonymous SNVs or in-frame indels. Similarly, RNA sequencing of tumors from patients with renal clear cell carcinoma revealed that a high load of frameshift neoantigens was associated with high expression of genes linked to immune activation, including genes involved in MHC class I antigen presentation and $CD8^+$ T-cell activation. The finding that indels are a highly immunogenic mutation class that generate abundant neoantigens and may be associated with response to checkpoint inhibitors suggests that frameshift indels may serve as potential biomarkers of response to checkpoint blockade and as targets of tumor vaccines and cell therapies. ■

Turajlic S, Litchfield K, Xu H, Rosenthal R, McGranahan N, Reading JL, et al. Insertion-and-deletion-derived tumour-specific neoantigens and the immunogenic phenotype: a pan-cancer analysis. Lancet Oncol 2017;18:1009–21.

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AACR American Association for Cancer Research

CANCER DISCOVERY

BAX Can Be Allosterically Sensitized to Promote Apoptosis

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