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COMMENTARY

Does the BCL-2 family member BIK control lung carcinogenesis?

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ABSTRACT

Hyperplastic airway epithelial cells may be the cause for increased risk for lung cancer in patients with chronic lung diseases. The B-cell lymphoma **2** (Bcl-2) family member, Bcl-2-interacting killer (BIK), triggers cell death specifically in these hyperplastic cells because of adequate presence of Death-associated Protein Kinase 1 (DAPk1), BCL-2 Antagonist Killer (BAK), and Extracellular Signal-regulated Kinase 1/**2** (ERK1/2). Therefore, BIK may be a useful tool to control the development of lung cancer in patients with chronic diseases.

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BIK (Bcl-2 interacting killer) is the founding member of BH3-only family proteins in which the cell death activity was first linked to the conserved Bcl-2 homology domain 3 (BH3).[1] Although *BIK* is widely expressed in hematopoietic and in endothelial cells of the venous lineages, loss of *Bik* does not increase the numbers of such cells in mice or protect hematopoietic cells *in vitro* from apoptosis induced by cytokine withdrawal or other cytotoxic stimuli.[2] In mouse embryo fibroblasts, *Bik* overexpression causes only 10% cell death but up to 60% in AECs,[3] suggesting specificity to cell type-dependent susceptibility.

The airway epithelium is very efficient in regulating cell numbers. Following exposure to environmental pollutants or viral or bacterial infections, existing and proliferating epithelial cells produce mucins to protect the lung from further injury. This hyperplastic response involves a 30% increase in epithelial cell number per mm basal lamina.[4] When the injury stops, up to 30% of hyperplastic cells are eliminated by apoptotic mechanisms and the epithelium returns to the original cell numbers.[4] If this resolution process is dysfunctional hyperplastic mucous cells are sustained for longer periods, as is frequently observed in the airways of patients with allergic asthma and cigarette smokers. Secreted mucins can be the basis for airflow obstruction.[5]

We observed that during prolonged exposure to allergens, the resolution of hyperplastic mucous cells is mediated by Bik-induced apoptosis of airway epithelial cells.[6] In the absence of Bik, mice fail to resolve mucous cell hyperplasia during prolonged exposure to allergen. This finding was validated in humans, as *BIK* mRNA levels in epithelial cells from patients with asthma were reduced compared with those from normal control subjects.[6] Similarly, cigarette smoke (CS) suppresses Bik levels and thereby induces mucous cell hyperplasia.[3] CS-induced hyperplastic mucous cells are reduced when Bik levels are restored. These results were further confirmed in humans where *BIK* expression was reduced in lung autopsy samples from former-smokers with chronic bronchitis compared with those without,[3] suggesting that individuals who express high levels of *BIK* may be protected from chronic bronchitis. Therefore, factors that differentially regulate *BIK* expression in subjects with chronic bronchitis could be closely related to the susceptibility factors that cause permanent changes in former smokers with chronic bronchitis.

Recently, we focused on elucidating the mechanisms by which BIK causes cell death in airway epithelial cells. Bik antagonizes the pro-proliferative activity of activated Extracellular Signal-regulated Kinase1/2 (ERK1/2) by interacting with and retaining this kinase in the cytosol and blocking its nuclear localization.[6] BIK is predominantly localized to the endoplasmic reticulum (ER) and mediates apoptosis signaling to mitochondria. BIK displaces BCL-2 Antagonist Killer (BAK) from Bcl-2 and thereby increases BAK levels by delaying its degradation.[7] The enhanced BAK translocates to the ER and interacts with Death Associated Protein Kinase 1 (DAPk1). BIK also activates DAPk1 to facilitate the formation of the BIK–DAPk1–ERK1/2–BAK (BDEB) complex. This ER-anchored BDEB complex also binds to mitochondria and increases the contact sites between ER and mitochondria. BIK by interacting with BCL-2 also disrupts BCL-2 and IP_3R interaction. Because BCL-2/IP_3R complex retains ER-Ca^{2+},[8] the disruption of this complex by BIK elicits ER-Ca^{2+} release. The ensuing transfer of ER-Ca^{2+} to the mitochondria elicits mitochondrial outer membrane permeability (MOMP). Therefore, the main role of BIK appears to be based on its high affinity to BCL-2. In fact, mutations that mimic phosphorylation (Thr(33), Ser(35)→Asp) enhance the cell death activity of BIK and interaction with BCL-2,[9] while mutations that prevent phosphorylation reduce the cell death activity. Thus, BIK disrupts the interaction of BCL-2 with BAK, IP_3R, and possibly DAPk1 to initiate the BDEB complex formation. Therefore, the cell-type-specific

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effect of BIK may be due the presence/absence of proteins that form the BDEB complex and may explain why cells of the hematopoietic system and endothelial cells of the venous lineages are less sensitive to BIK-induced death. In fact, our data show that cells expressing low levels of DAPk1 or BAK are less susceptible to BIK-induced cell death. The number of ER-mitochondria contact sites likely determines whether the cell undergoes apoptosis, because even reduced levels of Bak as found in heterozygous mice protects from BIK-induced cell death.[7]

A double hydrocarbon-stapled peptide modeled after the BIK BH3 helix causes efficient BAK activation and cell death to reduce allergen- or CS-induced epithelial and mucous cell hyperplasia in primary human AECs in culture and *in vivo*. Similarly, transgenic expression of *Bik* in the airways of adult *Bik* knockout mice resolves allergen- or CS-induced mucous cell hyperplasia.[7] In cancer cells, proteasome inhibitors such as Bortizomib increase the level of BIK,[10] suggesting that BIK protein is targeted by the proteasomal machinery. While BIK itself is regulated by proteasomal system, BIK also interacts with and displaces BAK from BCL-2 to inhibit proteasomal degradation of BAK. Thus, this close relationship of BIK with the proteasomal function needs further investigation.

Hyperplastic airway epithelial cells can be the source for neoplastic lesions during carcinogenesis, suggesting that the normal function of BIK may be to remove cancerous cells before hyperplasias form tumors. Cigarette smokers with emphysema and chronic bronchitis are at 2–4-fold higher risk of developing lung cancer. Therefore, BIK by specifically targeting hyperplastic airway cells may have implications in controlling the early stages of lung carcinogenesis. The sustained suppression of BIK in airway epithelial cells of smokers could be the initial signal for insensitivity to evading growth-arrest signals and apoptosis via unopposed nuclear translocation of activated ERK1/2[6] and BDEB-mediated ER-Ca^{2+} release,[7] respectively. Future studies need to investigate whether increased BIK expression can protect susceptible smokers from developing lung cancer.

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