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Apoptosis

Major finding: Activity of the proapoptotic BAX protein is regulated by formation of inactive cytosolic dimers.

Mechanism: BAX dimers are resistant to activation by BH3-only activator proteins.

Impact: Identification of BAX dimers and their structure may aid development of BAX-modulating drugs.

CYTOSOLIC BAX CAN FORM AUTOINHIBITED DIMERS TO SUPPRESS APOPTOSIS

The proapoptotic BAX protein triggers apoptosis via the intrinsic pathway by inducing mitochondrial outer membrane permeabilization (MOMP). BAX largely exists in an inactive conformation in the cytoplasm, but under cellular stress BAX is activated by BH3-only proteins and translocates to the mitochondrial outer membrane to induce MOMP. Structural studies have revealed conformational changes at the N-terminal surface and C-terminal α9 helix that are required for BAX activation by BH3 proteins and MOMP induction, but suggest that additional mechanisms may stabilize BAX in the inactive cytosolic conformation. Garner, Reyna, and colleagues identified an autoinhibited dimeric BAX conformation in addition to the inactive monomer conformation. The BAX dimers did not induce membrane permeabilization, and, in contrast to BAX monomers, were resistant to BH3-mediated activation. Moreover, BAX dimers failed to translocate to the membrane upon BH3-induced stimulation. Crystallization studies indicated that the BAX dimer exhibited an asymmetric conformation; the N-terminal BAX activation site of one BAX monomer interacted with the C-terminal surface (including C-terminal helix α9) of the other BAX monomer. BAX monomers are activated by BH3 binding to the N-terminal activation site, triggering a conformational change, but in the BAX dimer, helix α9 from one monomer bound to the N-terminal activation site of the other, maintaining a closed and inactive conformation refractory to BH3 activation. Dissociation of the BAX dimer into monomers was required for BH3 binding and BAX activation. In mouse embryonic fibroblasts, wild-type BAX dimers reduced apoptosis, whereas dimerization-impaired BAX exhibited increased apoptosis, pointing to a role for inactive BAX dimers in regulation of BAX-dependent apoptosis. The identification of cytosolic autoinhibited BAX dimers reveals an additional mechanism by which BAX activation and apoptosis can be regulated, and may be useful in developing pharmacologic BAX modulators. ■

Garner TP, Reyna DE, Priyadarshi A, Chen HC, Li S, Wu Y, et al. An autoinhibited dimeric form of BAX regulates the BAX activation pathway. Mol Cell 2016;63:485–97.

Pancreatic Cancer

Major finding: The NRF2-driven antioxidant program shields translation-related proteins to drive PDAC maintenance.

Mechanism: NRF2 inhibits oxidation of translational regulatory factors and drives autocrine EGFR signaling.

Impact: Combined inhibition of AKT and glutathione synthesis may be a potential therapy for PDAC.

NRF2-MEDIATED TRANSLATION PROMOTES PANCREATIC CANCER MAINTENANCE

Oncogenic *KRAS* and loss of *TP53* are two of the most frequent genetic alterations that drive pancreatic ductal adenocarcinoma (PDAC). Having recently shown that mutant *KRAS* expression upregulates the transcription factor nuclear factor, erythroid 2 like 2 (NRF2, encoded by *NFE2L2*)–driven transactivation of antioxidant-regulated genes to drive PDAC initiation, Chio and colleagues further characterized the role of NRF2 in PDAC tumorigenesis. NRF2/*NFE2L2* expression was elevated in patient PDAC-derived (hT) organoids, and NRF2 ablation resulted in organoid death or highly elevated reactive oxygen species (ROS) levels and decreased proliferation. Similarly, engraftment of mutant *Kras* (K) organoids derived from the pancreata of *NFE2L2*-deficient mice was decreased compared to K organoids derived from wild-type *NFE2L2* mice. NRF2-deficient K and mutant *Kras*/*Trp53*$^{R172H/+}$ (KP) organoids exhibited decreased glutathione (GSH) and increased ROS compared to NRF2-proficient counterparts. Analysis of the cysteine proteome in KP organoids showed that NRF2 deficiency resulted in elevated cysteine oxidation of translation-related proteins, including regulators of translation. Consistent with these findings, hT, K, and KP organoids deficient of NRF2 all exhibited decreased cap-dependent mRNA translation of prosurvival proteins and reduced autocrine EGFR activation, which is critical for promoting the initiation of cap-dependent mRNA translation. *In vitro*, treatment of hT and KP organoids with the pan-AKT inhibitor MK2206 resulted in decreased protein synthesis and inhibition of translation initiation, the effect of which was further augmented through combined treatment with the GSH synthesis inhibitor buthionine sulfoximine (BSO). Similarly, combination treatment with BSO and MK2206 was significantly more efficacious than single-drug treatment in inhibiting growth of a PDAC xenograft and a genetically engineered mouse model of PDAC. Together, these findings elucidate a mechanism by which antioxidants promote PDAC tumorigenesis and suggest that combined targeting of GSH synthesis and AKT may be a potential therapy for patients with PDAC. ■

Chio II, Jafarnejad SM, Ponz-Sarvise M, Park Y, Rivera K, Palm W, et al. NRF2 promotes tumor maintenance by modulating mRNA translation in pancreatic cancer. Cell 2016 Jul 28 [Epub ahead of print].

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CANCER DISCOVERY

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