The Executioner Protein: Targeting BAX to Induce Apoptosis in Anaplastic Thyroid Cancer Cells

Di Cristofano, Francesca (School: Pelham Memorial High School)

While chemotherapy and targeted therapy are common cancer treatments, both have limitations. Induced apoptosis is an attractive alternative. Mitochondrial apoptosis is controlled by the BCL-2 family of proteins. The BH3-only members of this family activate BAX, which irreversibly triggers apoptosis. At the same time, anti-apoptotic members (BCL-XL, BCL-2), sequester and inhibit both BH3-only proteins and BAX. Cancer cells are often addicted to anti-apoptotic proteins. BH3-mimetics such as ABT-263 have been developed to bind to and inhibit BCL-2/XL, allowing BH3-only proteins to activate BAX. While BH3-mimetics have had success in hematological tumors, solid tumors are more genetically complex, often overexpressing multiple anti-apoptotic proteins and rendering BH3-mimetics ineffective. Direct BAX activation with a small molecule would bypass these problems. EGAV1 is a novel BAX activator that has been only tested in hematological tumors. The response of solid tumors to this approach is a major gap in our field. We used anaplastic thyroid cancer (ATC) as a model to determine whether EGAV1 is effective in inducing apoptosis in solid tumors. We found that ATC cell lines have limited sensitivity to ABT-263 and EGAV1 as single agents. We hypothesized that high levels of BCL-2 and BCL-XL still sequester EGAV1-activated BAX, limiting its efficacy. In fact, addition of ABT-263 dramatically sensitizes ATC cell lines to EGAV1-mediated apoptosis. Our data provide support for a novel approach to the treatment of incurable solid tumors such as ATC, which, thanks to the low concentration of compounds required, is likely to be more effective and tolerable than current treatments.

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