

Correspondence

Mcl-1 levels need not be lowered for cells to be sensitized for ABT-263/737-induced apoptosis

R Yamaguchi¹* and G Perkins²

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Dear Editor,

In light of new findings, a small adjustment should be made in our understanding of the relationship between Mcl-1 and ABT-263/737.

ABT-263 and ABT-737 (ABT) are Bcl-2 antagonists that bind to Bcl-2 family members with high affinity, but do not bind to Mcl-1. As single agents, they induce apoptosis in lymphomas and small cell lung carcinomas with varied efficacy. In an attempt to explain this varied efficacy, it has been suggested that the presence of Mcl-1 protein is hindering the apoptosis-inducing power of these agents.^{1,2} Indeed, in numerous studies, the Mcl-1 expression levels inversely correlated with sensitivity to ABT-737 in small lymphomas and cell lung carcinomas with a few notable exceptions. One of the exceptions is a promyelocytic leukemia cell line, HL-60. These cells express reasonably large amounts of Mcl-1, but they are nevertheless sensitive to ABT-737.³ In most cells, Bak is normally sequestered by Mcl-1 and Bcl-xL, and only when Bak is freed from both, can it induce apoptosis.⁴ In HL-60 cells, however, Mcl-1 does not co-precipitate with Bak, suggesting that the real determinant of ABT sensitivity is how much Bak is sequestered in its association with Mcl-1, and not the presence of Mcl-1 protein *per se*. Interestingly, we found that the strength of this association can be weakened without lowering the Mcl-1 expression levels by pre-incubating cancer cells with deoxyglucose for only 1–3 h.⁵ Unlike apoptosis induced by glucose depletion,^{6–8} during the short time that it took deoxyglucose to prime cells for apoptosis, similar amounts of Mcl-1 remained. However, we could no longer co-precipitate Mcl-1 with Bak, and the sensitivity of these cells to ABT increased by 10-fold.

A short exposure to deoxyglucose sensitizes all sorts of cancer cells for ABT-induced apoptosis.⁵ It can also induce apoptosis in untransformed cells such as NIH3T3 cells if they become highly glycolytic by culture conditions, suggesting that deoxyglucose can prime even normal healthy cells if they become highly glycolytic. Besides cancer cells, some brain cells are known to be highly glycolytic. However, because ABT does not cross the blood–brain barrier, in animals treated with the deoxyglucose and ABT combination, the only cells exposed to both agents would be highly glycolytic cancer cells outside the brain. Indeed, in our experiments using cancer-bearing mice, the deoxyglucose-ABT-263 combination effectively treated tumor cells located outside the brain, with very little harm to the animals.⁵

Conflict of Interest

The authors declare no conflict of interest.

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¹Department of Molecular Biology, Kyushu University Medical School, Fukuoka, Japan and ²Center for Research in Biological Systems, UCSD, La Jolla, CA, USA
*Corresponding author: R Yamaguchi, Department of Molecular Biology, Kyushu University Medical School, Collaboration Station2/room 425, 1-3-1 Maidashi, Higashi-ku, Fukuoka, 812-8582, Japan. Tel: +81 66 532 3627; E-mail: rudy.yamaguchi@gmail.com