Correspondence re: DC Lev et al., Dacarbazine causes transcriptional up-regulation of interleukin 8 and vascular endothelial growth factor in melanoma cells: A possible escape mechanism from chemotherapy. Mol Cancer Ther, 2003;2(8):753–63.

Letter

Is Photodecomposition More Important Than Metabolic Activation for the Antitumor Activity of Dacarbazine?

Lev et al. (1) clearly demonstrate that the antitumor agent dacarbazine (DTIC) causes melanoma cells to secrete interleukin (IL)-8 and vascular endothelial growth factor (VEGF). The authors suggest that cytokine overexpression might render tumor cells resistant to DTIC, which is presently considered the reference drug for the treatment of malignant melanoma.

The study has been entirely conducted using light-activated DTIC without considering that DTIC requires metabolic activation by liver microsomes to generate 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide (MTIC), which is responsible for the alkylation of nucleic acids (2). In particular, O⁶-methylguanine is regarded as the major cytotoxic lesion produced by the active metabolite of DTIC (2). In fact, tumor cells expressing high levels of the O⁶-alkylguanine DNA alkyltransferase (AGT) are resistant to DTIC and to temozolomide, which spontaneously decomposes in aqueous solution to generate the methylating species MTIC (3, 4).

Although the importance of light protection for DTIC, to avoid toxicity due to photodecomposition products, is still controversial, it is instead well established that the antitumor activity of DTIC is mainly the result of DNA methylation.

Therefore, to assess whether IL-8 and VEGF expression in melanoma cells might limit the efficacy of DTIC, it would have been certainly more interesting to evaluate the influence of MTIC-induced DNA methylation rather than analyzing the effects of photodecomposition products, which might not substantially contribute to the antitumor effects of DTIC.

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References

Reply

Drs. Tentori and Graziani (1) raised an important point regarding our recently published paper (2). It is indeed well recognized that dacarbazine (DTIC) is a chemotherapeutic...
agent that requires processing by the liver enzymatic complex (cytochrome P450) in vivo to generate its active compound, 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide (MTIC). However, our results demonstrated that the drug exhibited a strong antitumor cytotoxic effect in vitro without the need for microsomal activation (Fig. 1 in the manuscript; Ref. 2). Moreover, other investigators have previously used the drug without activation demonstrating various cytotoxic effects such as the induction of tumor cell apoptosis (3). We hypothesized that in our model, using melanoma cell lines, the activation of the drug and the production of MTIC is induced by cytochrome P450 expressed by the tumor cells. It has previously been shown that a wide range of tumor cell types overexpress cytochrome P450 to a level that enables the activation of several prodrug antitumor agents, including DTIC (4).

We exposed the drug to white light for an hour before usage because previous data had demonstrated that the activation of DTIC by white light was a viable alternative to using a microsome plus cofactor system for bioactivation (5). Although this form of activation is still in debate, we assumed that augmentation of the drug efficacy by light in our model was not due to photodecomposition product because their production requires prolonged light exposure (>24 h) of the drug (6). Nevertheless, the possibility that light-induced conversion of the prodrug DTIC to its active form MTIC may still exist although it is yet to be proven.

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