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Potential for Thermal Enhancement by Quercetin Mediated Mechanisms Targeting p53 Antagonists in Human Melanoma Cells

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Introduction
Recently Temozolomide (TMZ) has become the more commonly used analog of DTIC-related oral agents. Although the response rates achieved by TMZ alone are less than satisfactory, there is great interest in identifying compounds that could be used in combination therapy. We have previously demonstrated that the bioflavonoid quercetin (Qct) promotes a p53-mediated response in melanoma and sensitizes melanoma to DTIC. Here we demonstrate that Qct also sensitizes cells to TMZ by a mechanism that involves the modulation of a truncated p53 family member, ΔNp73.

Methods
DB-1 (p53 wild type), and SK Mel 28 (p53 mutant) human melanoma cell lines were treated with TMZ (400 μM) for 48 hr followed by exposure to Qct (75 μM) for 24 hr. Cell death was determined by Annexin V-FITC staining, and immunocytochemical analysis was carried out to determine protein translocation.

Results
After treatment with TMZ, DB-1 cells demonstrated increased phosphorylation of mutated ATM and p53. However, the cells were resistant to TMZ-induced apoptosis and the resistance was associated with an increase in nuclear localization of ΔNp73. Qct treatment in combination with TMZ abolished drug insensitivity and caused a more than additive induction of apoptosis compared to either treatment alone. Treatment with Qct caused redistribution of ΔNp73 into both the cytoplasm and nucleus, which has been associated with increased p53 transcriptional activity. Knockdown of ΔNp73 restored PARP cleavage in the TMZ treated cells, confirming its anti-apoptotic role. The response to treatment was predominantly p53 mediated, as the p53 mutant SK Mel 28 cells did not show significant enhancement of apoptosis.

Conclusion
This study demonstrates that Qct can sensitize cells to TMZ and that the mechanisms of sensitization involve modulation of p53 family members. These results strongly suggest combination with hyperthermia in this treatment scheme. The inhibition of heat-induced p53/HSF1 by inhibiting p53 would diminish HSP70 levels thereby enhancing the heat sensitization of DNA-damage induced cell death [Sharma A, et al. Cancer Sci. 2010 Jan 28. Epub ahead of print].

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