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Archives in Cancer Research
ISSN 2254-6081

2016
Vol.4 No.3:93

DOI: 10.21767/2254-6081.100093

TH588 Potently Kills Melanoma Cells Grown in 3-Dimensional Culture Through Apoptosis Induced by ROS

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Received: 21 July 2016; **Accepted:** 25 July 2016; **Published:** 30 July 2016

Citation: Wang JY, Jiang CC, Yan XG, et al. TH588 Potently Kills Melanoma Cells Grown in 3-Dimensional Culture Through Apoptosis Induced by ROS. Arch Can Res. 2016, 4: 3.

3D Culture Performed Using the Hanging Drop Technique

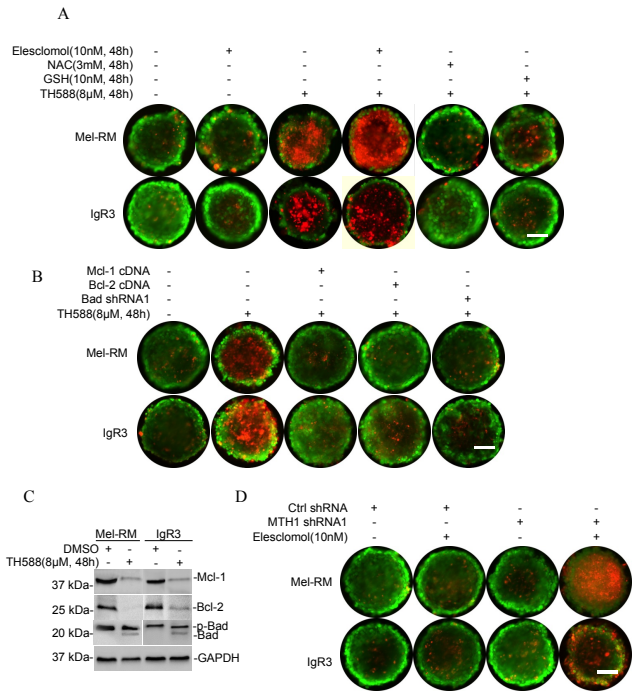

Figure 1 TH588 kills melanoma cells in 3D culture through apoptosis induced by ROS. [Green: viable cells; Red: dead cells. A and B: melanoma cells grown in 3D cultures were treated as indicated. C: whole-cell lysates from 3D cultured melanoma cells treated as indicated were subjected to Western Blotting. D: melanoma cells grown in 3D cultures were treated as indicated (n=3, Data shown are representatives)].

MutT homolog 1 sanitizes oxidized dNTP pools through converting 8-oxo-deoxy-guanine (8-oxo-dGTP) and 2-OH-deoxy-adenosine (2-OH-dATP) into the corresponding monophosphates, thus protecting cells from DNA damage caused by reactive oxygen species (ROS).

As one of the first-in-class MutT homolog 1 (MTH1) inhibitors, TH588 has been reported to kill cancer cells leading to impressive therapeutic responses in various human cancer xenografts [1]. However, our resent results and those reported by others have raised concerns about the potential of MTH1 as therapeutic target and the specificity of TH588 as a MTH1 inhibitor [2-4]. Nevertheless, our results demonstrating TH588 kills melanoma cells but did not impinge on the survival of melanocytes suggest that it remains a promising candidate for melanoma treatment [2]. Here, we report that TH588 indeed potently kills melanoma cells grown in 3-dimensional (3D) culture, and that is mediated by ROS and is related by activation of the BH3-only protein Bad and downregulation of the anti-apoptotic protein Bcl-2 and Mcl-1 **(Figure 1)**.

3D culture was performed using the hanging drop technique as previously described [5]. Cells were stained with calcein AM and ethidium homodimer-1 for 24 h followed by the treatment.

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