SAHA-induced TRAIL-sensitisation of Multiple Myeloma cells is enhanced in 3D cell culture

A. Arhoma, A.D. Chantry, S.L. Haywood-Small, N.A. Cross

www.elsevier.com/locate/yexcr

PII: S0014-4827(17)30488-3
DOI: http://dx.doi.org/10.1016/j.yexcr.2017.09.012
Reference: YEXCR10734

To appear in: *Experimental Cell Research*

Received date: 15 December 2016
Revised date: 5 September 2017
Accepted date: 6 September 2017

Cite this article as: A. Arhoma, A.D. Chantry, S.L. Haywood-Small and N.A. Cross, SAHA-induced TRAIL-sensitisation of Multiple Myeloma cells is enhanced in 3D cell culture, *Experimental Cell Research,* http://dx.doi.org/10.1016/j.yexcr.2017.09.012

SAHA-induced TRAIL-sensitisation of Multiple Myeloma cells is enhanced in 3D cell culture.

Arhoma, A, Chantry, AD[#], Haywood-Small, SL, Cross, NA*
Biomolecular Sciences Research centre, Sheffield Hallam University
[#]Mellanby Centre for Bone Research, University of Sheffield
*Corresponding author

Abstract

Background: Multiple Myeloma (MM) is currently incurable despite many novel therapies. Tumour Necrosis Factor-Related Apoptosis-Inducing Ligand (TRAIL) is a potential anti-tumour agent although effects as a single agent are limited. In this study, we investigated whether the Histone Deacetylase (HDAC) inhibitor SAHA can enhance TRAIL-induced apoptosis and target TRAIL resistance in both suspension culture, and 3D cell culture as a model of solid disseminated MM lesions that form in bone.

Methods: The effects of SAHA and/or TRAIL in 6 Multiple Myeloma cell lines were assessed in both suspension cultures and in an Alginate-based 3D cell culture model. The effect of SAHA and/or TRAIL was assessed on apoptosis by assessment of nuclear morphology using Hoechst 33342/Propidium Iodide staining. Viable cell number was assessed by CellTiter-Glo luminescence assay, Caspase-8 and -9 activities were measured by Caspase-Glo™ assay kit. TRAIL-resistant cells were generated by culture of RPMI 8226 and NCI-H929 by acute exposure to TRAIL followed by selection of TRAIL-resistant cells.

Results: TRAIL significantly induced apoptosis in a dose-dependent manner in OPM-2, RPMI 8226, NCI-H929, U266, JJN-3 MM cell lines and ADC-1 plasma cell leukaemia cells. SAHA amplified TRAIL responses in all lines except OPM-2, and enhanced TRAIL responses were both via Caspase-8 and -9. SAHA treatment induced growth inhibition that further increased in the combination treatment with TRAIL in MM cells. The co-treatment of TRAIL and SAHA reduced viable cell numbers all cell lines. TRAIL responses were further potentiated by SAHA in 3D cell culture in NCI-H929, RPMI 8226 and U266 at lower TRAIL + SAHA doses than in suspension culture. However TRAIL responses in cells that had been selected for TRAIL resistance were not further enhanced by SAHA treatment.