Melanoma Cells Show Enhanced Cytotoxicity in the Presence of Disintegrin Eristostatin

McLane MA[1]*, Tian J*[2]*, Paquette-Straub CA*[2]*, Hailey S*[1]

[1]University of Delaware, Newark, Delaware, USA
[2]Royal Brisbane Hospital, Brisbane, Australia

Eristostatin[1], a 5.4 kDa disintegrin derived from the viper venom of *Eristocophis macmahoni*, is a potent inhibitor of human and murine melanoma metastases in mouse model systems. This study was initiated as a follow-up to the observation that treatment of melanoma cells with 4000 nM eristostatin for 5 days showed no difference in cell proliferation when compared to control cells, thus suggesting eristostatin does not have a direct cytotoxic effect. To investigate other possible mechanisms, SBCl2 radial growth phase human melanoma cells were incubated with 500 nM disintegrin for 3 days and radiolabeled with ^{51}Cr for 1 hour at 37^0C. These labelled cells were used as targets in a cytotoxicity assay where the effector cells were MHC-non-restricted TALL-104 cells[2] (CD8+, CD56+, CD16-, CD161+). The melanoma cells treated with eristostatin showed higher susceptibility to specific killing by TALL-104 cells. Simultaneous treatment of the target and effector cells with eristostatin did not change this result. In parallel studies, SBCl2 melanoma cells were incubated for 3 days with 500nM eristostatin, then assessed for expression of various cell surface markers by flow cytometry. The eristostatin-treated cells showed a significant increase in FAS expression. These results indicate that eristostatin increases the susceptibility of SBCl2 to apoptotic death induced by the cytotoxic cell TALL-104. Additional studies using vertical growth phase WM164 and metastatic MV3, 1205Lu, M24met and C8161 human melanoma cells in the presence of human natural killer (NK) cells showed a significant variability in the cytotoxic effect on the melanoma cells[3], suggesting differences related to cancer stage. This variability could not be attributed to changes in cell surface expression of MHC class I molecules, integrins, nor in MICA/B expression[4]. Our hypothesis is that eristostatin may inhibit metastasis by increasing susceptibility of melanoma cells to cytotoxic cells *in vivo* and will be investigated in future studies.

References
(1) Tian J, Paquette-Straub C, Sage EH, Funk S, McLane MA. Toxicon 49: 899-908, 2007.
(2) McLane MA, Zhang X, Tian J, Paquette-Straub C. Toxin Reviews 26: 47-76, 2007.
(3) Butera D, Piazza RMF, Toxicon 46: 178-184, 2005.
(4) McLane MA, Kuchar, MA, Brando C, Miele ME. Haemostasis 31: 3-6, 177-182, 2001.

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