Melanoma Cells Show Enhanced Cytotoxicity in the Presence of Disintegrin Eristostatin

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Eristostatin¹, 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, SBC12 radial growth phase human melanoma cells were incubated with 500 nM disintegrin for 3 days and radiolabeled with ⁵¹Cr for 1 hour at 37°C. These labelled cells were used as targets in a cytotoxicity assay where the effector cells were MHC-non-restricted TALL-104 cells⁵ (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, SBC12 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 SBC12 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 cells³, 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 expression⁴. 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

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