Cathepsin B Inhibition Abrogates the Invasive Phenotype of Medulloblastoma

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Introduction

Medulloblastoma is the most common malignant brain tumor of children. Poor prognosis is associated with an invasive phenotype, characterized by proliferation and the ability to invade surrounding tissue. Our laboratory and colleagues have identified that activity of the protease cathepsin B is strongly associated with the invasive phenotype. We hypothesized that inhibition of cathepsin B would result in a reduction of these tumor-related activities. In this study, we investigated the therapeutic potential of a cathepsin B inhibitor, CA074ME, in medulloblastoma.

Methods

Established human medulloblastoma cell lines were grown and baseline proliferation and invasion characteristics were quantitated using the Cell Counting Kit-8 (CCK8) assay for proliferation and the trans-well invasion assay was used for invasion. Cell lines were then treated with increasing concentrations of CA074ME, with changes in proliferation and invasion measured then subjected to standard statistical analysis.

Results

Inhibition of cathepsin B with CA074ME produced a dose-dependent reduction, up to 4-fold in magnitude, of proliferation of medulloblastoma cell lines (with the exception of extremely low doses, which had a paradoxical effect on proliferation). Similarly, invasion was significantly reduced by ~75% in a dose-dependent manner.

Conclusions

Inhibition of cathepsin B markedly influences medulloblastoma phenotype, reducing both proliferation and invasion in a dose-dependent manner. These data suggest a novel method to pharmacologically target clinically significant tumor activity.

Figure 1

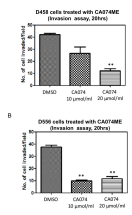

Figure 1. Effect of cathepsin B inhibitor on invasion of medulloblastoma cell lines. A. Dose dependent response of D458 cell cell lines to cathepsin B inhibitor on invasion. B. Response of D556 cell lines to cathepsin B inhibitor on invasion.

Learning Objectives

By the conclusion of this session, participants should be able to (1) discuss the importance of the invasive phenotype in medulloblastoma, (2) describe the influence of proteases on the invasive phenotype of medulloblastoma and (3) identify the potential utility of pharmacologic blockade of cathepsin B in this tumor type

Figure 2

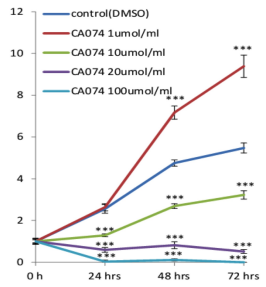

Figure 2. Dose dependent response of medulloblastoma cell line to cathepsin B inhibitor on proliferation.

References

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