

Therapeutic activation of macrophages and microglia to suppress brain tumor-initiating cells

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Background

Glioblastoma is a ferociously expanding form of tumor with a grim prognosis even after surgical removal. The tumor most frequently returns after surgery, which may point to a population of cells that have the capacity to initiate a relapse. Resident macrophage population of the brain should tame tumor growth but glioma seems to be interfering with their normal response hence growing even in their presence. Artificial activation of macrophages has been shown to decelerate the growth of glioma in mouse model.¹ There are reports of interaction between cells that have the capacity to initiate tumors and macrophages, mostly these interactions lead to diminished activity of macrophages² and increased invasiveness of cells that initiate tumor.³ These interactions do give us an opportunity to explore the possibility of activating macrophages and differentiating cells that initiate tumor and as a result curb brain tumor.

The author's objective in this study was to investigate the use of a drug already in human use to activate macrophages present in the brain tumor environment. These macrophages, upon activation, theoretically may differentiate cells that initiate brain tumor and hence render them ineffective for relapse. The drug used in this study was amphotericin B.

Study design

Cells initiating brain tumor were isolated from glioma patients undergoing surgery. Microglia were isolated from epilepsy patients. After verification of the stem cell like properties of tumor initiating cells through *in vivo* and *in vitro* assays these were cultured in serum free media. Sphere formation was observed in these cultures as is the norm with stem cells.

Microglia cells were also cultured in serum free media as a preparation for co-culturing them with tumor initiating cells. Upon co-culturing, there was a marked reduction in sphere formation due to cell differentiation. In addition, there was also marked reduction in sphere formation from just addition of microglia conditioned media. To account for this effect, micro-

array of tumor initiating cells and multiplex protein assay of microglia conditioned media was performed. IL-8 and MCP-1 were found to be potential factors for differentiation of tumor initiating cells.

Amphotericin B was selected from a pool of 1040 compounds as an microglia activator. Its activity was checked through amount of TNF- α being secreted by activated microglia.

Its activity was further checked on microglia isolated from glioma patients, where it caused microglia activation and hence caused differentiation of tumor initiating cells.

Finally, levels of IL-8 and MCP-1 being secreted by glioma patient microglia were analysed and found to be reduced.

Implications

This study elucidates a link between the innate immune system and the stem cell like tumor initiating cells. The path described in this study to manipulate the tumor initiating cells would make them incapable of a certain relapse if applied in actual disease scenario. The drug choice puts this possible therapeutic procedure on a fast track as amphotericin B is already used against fungal infection in humans.

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