Nanocell-mediated delivery of miR-34a counteracts temozolomide resistance in glioblastoma

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1. 簡述論文的概要與重大發現

Glioblastoma (GBM)是最具有侵襲能力、最難治療的癌症，積極治療的情況下平均壽命也不到一年，在腦癌中常見的治療藥物是 Temozolomide，在治療的過程未殺死的癌細胞會產生出新的抗藥性，使腫瘤產生 ITH，而在 GBM 中也因 blood–brain barrier (BBB) 跟 intra-tumor heterogeneity (ITH) 的存在，使治療藥物的傳遞有限，是突破 GBM 治療的最大障礙，所以作者希望使用 microRNA 去調節多個信號路徑，並提高存活率。作者在過去的研究中，找到一些細菌具有 LPS 的外膜層，可將細菌改造以後將更小分子的藥物，送進腫瘤細胞中.接著作者從 glioma 的 cell lines 中透過 KEGG database 找到 microRNA-34a，和三個核心訊號 Retinoblastoma gene (RB gene)、P53 tumor-suppressor gene、receptor tyrosine kinase 的活性有關.並利用 Nanocells 當作載體送進 nude 體內。結果顯示 overexpression microRNA-34a 會降低三個核心訊號活化的狀態，在 microRNA-34a 的幫忙下，增強了 GBM 細胞對 TMZ 的反應。因此，TMZ 搭配 microRNA-34a 並且使用 Nanocell 的聯合治療，可以作為 GBM 患者的新型療法。

2. 對內容的疑問

在以往的研究表明，MGMT 在 TMZ 治療的過程中是一個很重要的角色，MGMT 是一個修復蛋白，他會把在 DNA 上甲基化的 guanine 去甲基化，進行 DNA 的修復，會讓 TMZ 藥物治療失敗，產生抗性．而在本篇實驗當中作者卻做出在 TMZ 治療當中 MGMT 是沒有相連性的，而此疑惑有待探討。

3. 論文的缺點與評論

從此篇研究中發現 miR-34a 可以有效廣泛抑制 glioma 中不同 subtype 的 cell lines 的 proliferation，即使對 TMZ 產生高度抗性的 cell lines 也可以被抑制，之後利用細菌衍生的 nanocell 去攜帶 mir-34a，並且搭配 TMZ 藥物使用，明顯增加了小鼠的存活率，假設未來有機會突破臨床試驗，或許是一種新穎的治療方式。

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Abstract

Background: Glioblastoma is the most common primary brain tumor and remains uniformly fatal, highlighting the dire need for developing effective therapeutics. Significant intra- and inter-tumor heterogeneity and inadequate delivery of therapeutics across blood–brain barrier continue to be significant impediments towards developing therapies which can significantly enhance survival. We hypothesize that microRNAs have the potential to serve as effective therapeutics for glioblastoma as they modulate the activity of multiple signaling pathways, and hence can counteract heterogeneity if successfully delivered.

Methods: Using a computational approach, we identified microRNA-34a as a microRNA that maximally reduces the activation status of the three core signaling networks (the receptor tyrosine kinase, p53 and Rb networks) that have been found to be deregulated in most glioblastoma tumors. Glioblastoma cultures were transfected with microRNA-34a or control microRNA to assess biological function and therapeutic potential in vitro. Nanocells were derived from genetically modified bacteria and loaded with microRNA-34a for intravenous administration to orthotopic patient-derived glioblastoma xenografts in mice.

Results: Overexpression of microRNA-34a strongly reduced the activation status of the three core signaling networks. microRNA-34a transfection also inhibited the survival of multiple established glioblastoma cell lines, as well as primary patient-derived xenograft cultures representing the proneural, mesenchymal and classical subtypes. Transfection of microRNA-34a enhanced temozolomide (TMZ) response in in vitro cultures of glioblastoma cells with primary TMZ sensitivity, primary TMZ resistance and acquired TMZ resistance. Mechanistically, microRNA-34a downregulated multiple therapeutic resistance genes which are associated with worse survival in glioblastoma patients and are enriched in specific tumor spatial compartments. Importantly, intravenous administration of nanocells carrying miR-34a and targeted to epidermal growth factor receptor (EGFR) strongly enhanced TMZ sensitivity in an orthotopic patient-derived xenograft mouse model of glioblastoma.

Conclusions: Targeted bacterially-derived nanocells are an effective vehicle for the delivery of microRNA-34a to glioblastoma tumors. microRNA-34a inhibits survival and strongly sensitizes a wide range of glioblastoma cell cultures

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