Documents

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Combination of hyaluronic acid conjugates with immunogenic cell death inducer and CpG for glioblastoma local chemo-immunotherapy elicits an immune response and induces long-term survival

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Abstract
The efficacy of standard glioblastoma (GBM) treatments has been limited due to the highly immunosuppressive tumor immune microenvironment, interpatient tumor heterogenicity and anatomical barriers, such as the blood brain barrier. In the present work, we hypothesized that a new local therapy based on the combination of doxorubicin (DOX) as an immunogenic cell death (ICD) inducer and CpG, a Toll-like receptor (TLR)-9 agonist, would act synergistically to eradicate GBM. DOX and CpG were first tested in an orthotopic GL261 GBM model showing enhanced survival. To improve the outcome with a reduced dose, we designed bioresponsive hyaluronic acid (HA)-drug conjugates for effective in situ chemoimmunotherapy. HA was derivatized with CpG. The new HA-CpG conjugate showed high efficacy in re-educating protumoral M2-like microglia into an antitumoral M1-like phenotype, inducing the expression of immune-stimulatory cytokines. DOX was also conjugated to HA. DOX conjugation increased ICD induction in GL261 cells. Finally, a combination of the conjugates was explored in an orthotopic GL261 GBM model. The local delivery of combined HA-DOX + HA-CpG into the tumor mass elicited antitumor CD8+ T cell responses in the brain tumor microenvironment and reduced the infiltration of M2-like tumor-associated macrophages and myeloid-derived suppressor cells. Importantly, the combination of HA-DOX and HA-CpG induced long-term survival in >66% of GBM-bearing animals than other treatments (no long-term survivor observed), demonstrating the benefits of conjugating synergistic drugs to HA nanocarrier. These results emphasize that HA-drug conjugates constitute an effective drug delivery platform for local chemoimmunotherapy against GBM and open new perspectives for the treatment of other brain cancers and brain metastasis. © 2023 Elsevier Ltd

Author Keywords
Chemoimmunotherapy; Glioblastoma; Hyaluronic acid conjugates; Immunogenic cell death; Local treatment; Microglia; Polymer-drug conjugates; Tumor immune microenvironment

Index Keywords
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