Hyaluronan

Neurofibromatosis type 2 (NF-2) is associated with mainly three types of recurrent benign tumors restricted to the central nervous system: schwannoma, meningioma and ependymoma. The absence of the protein NF2/Merlin causes an uninterrupted cell proliferation cascade originating from an abnormal interaction between an extracellular mucopolysaccharide, hyaluronan (HA), and schwann cell surface CD44 receptor, which has been identified as one of the central causative factors for schwannoma. Most tumors in NF-2 have a predilection to originate from either arachnoid cap cells or schwann cells of the cisternal portion of nerve rootlets that share a continuous exposure to cerebrospinal fluid (CSF).

Ariyannur et al. hypothesized that the CSF HA may play a role in tumorigenesis in NF-2. In a prospective analysis over a period of one year, the levels of medium to low molecular weight HA (LMW HA) was estimated in the CSF of three subjects with central schwannomas and compared against that of age-sex matched controls, using Cetyltrimethylammonium bromide coupled turbidimetric assay and found to be seventeen-fold higher in the schwannoma subjects compared to the controls. HA was observed to be actively secreted by cultured schwannoma cells isolated from tumor tissues commensurate with their proliferation rate. On cell viability index analysis to compare the cell proliferation of astrocytoma cells with LMW HA vs. oligomeric HA (OHA), we found a decrease in cell proliferation of up to 30% with OHA. The study provides initial evidence that CSF HA may have a central role in the tumorigenesis of schwannoma in NF-2 [1)].

Hyaluronan (HA)-grafted lipid-based nanoparticles (LNPs). These LNPs having an ionized lipid were previously shown to be highly effective in delivering small interfering RNAs (siRNAs) into various cell types. LNP's surface was functionalized with hyaluronan (HA), a naturally occurring glycosaminoglycan that specifically binds the CD44 receptor expressed on GBM cells.

Cohen et al. found that HA-LNPs can successfully bind to glioblastoma GBM cell lines and primary neurospheres of GBM patients. HA-LNPs loaded with Polo-Like Kinase 1 (PLK1) siRNAs (siPLK1) dramatically reduced the expression of PLK1 mRNA and cumulated in cell death even under shear flow that simulate the flow of the cerebrospinal fluid compared with control groups. Next, a human GBM U87MG orthotopic xenograft model was established by intracranial injection of U87MG cells into nude mice. Convection of Cy3-siRNA entrapped in HA-LNPs was performed, and specific Cy3 uptake was observed in U87MG cells. Moreover, convection of siPLK1 entrapped in HA-LNPs reduced mRNA levels by more than 80% and significantly prolonged survival of treated mice in the orthotopic model. Taken together, this results suggest that RNAi therapeutics could effectively be delivered in a localized manner with HA-coated LNPs and ultimately may become a therapeutic modality for GBM [2)].

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Ariyannur PS, Vikkath N, Pillai AB. Cerebrospinal Fluid Hyaluronan and Neurofibromatosis Type 2. Cancer Microenviron. 2018 Aug 25. doi: 10.1007/s12307-018-0216-2. [Epub ahead of print] PubMed PMID: 30145722.
2)
Cohen ZR, Ramishetti S, Peshes-Yaloz N, Goldsmith M, Wohl A, Zibly Z, Peer D. Localized RNAi Therapeutics of Chemoresistant Grade IV Glioma Using Hyaluronan-Grafted Lipid-Based Nanoparticles. ACS Nano. 2015 Jan 8. [Epub ahead of print] PubMed PMID: 25558928.