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TITLE

Nano-RNAi–functionalized polyvalent gold nanoparticles as novel anti-glioma therapeutics

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Glioblastoma (GBM) is a lethal brain tumor characterized by resistance to extant chemo-, radiation and targeted therapies. Bcl2L12 (for Bcl2-Like 12) is a cytoplasmic and nuclear glioma oncoprotein that is over-expressed in >90% of primary GBM and confers resistance toward therapy-induced apoptosis. On the molecular levels, Bcl2L12 binds and inhibits caspase-7 and blocks caspase-3 maturation through up-regulation of the small heat shock protein and caspase-3-specific inhibitor αB-crystalline. In addition, nuclear Bcl2L12 physically interacts with the p53 tumor suppressor and robustly represses p53 transactivational activities. To therapeutically suppress Bcl2L12's diverse and potent gliomagenic activities, we employed a gene silencing approach using small interfering RNA (siRNA)-conjugated polyvalent gold nanoparticles (RNA-Au-NPs) to knockdown and inactivate Bcl2L12 signaling in glial cells. Our studies document that RNA-Au-NPs exhibit superior biological stability, highly significant knockdown efficacies, robust cellular uptake, and biocompatible intratumoral delivery upon systemic i.v., and local administration, reduced off-target effects, and diminished activation of innate immune responses compared to conventional, lipoplex-delivered RNAi. In particular, we could show that RNA-Au-NPs are single entity agents, which are 500 times more effective in knocking down Bcl2L12 than conventional RNAi-based methods and do not require auxiliary transfection agents. MRI studies using Gd (III)-conjugated RNA-Au-NPs confirmed that these nanomaterials penetrate intracranial brain tumors highly effectively without the need for convection-based enhanced delivery. Nano-RNAi-mediated knockdown of Bcl2L12 resulted in sensitization of cells toward apoptosis, and prolonged survival of glioma-bearing mice. Thus, silencing Bcl2L12 signaling by nano-RNAi represents a novel therapeutic approach to restrain GBM pathogenesis.

Biography

Dr. Stegh obtained his Ph.D from the University of Chicago, and the Leibniz University of Hannover, and did his postdoctoral studies at the Dana-Farber Cancer Institute/Harvard Medical School. His research program is aimed at understanding the genetic program that underlies the pathogenesis of Glioblastoma (GBM), the most prevalent and malignant form of brain cancer, and to drive these basic discoveries toward pharmaceutical opportunities using nanotechnology and high-throughput medicinal chemistry. He is an Assistant Professor at Northwestern University, and authored 20 publications. His work has recently been awarded with the prestigious Sidney Kimmel and James S. McDonnell 21st century science awards.