VIDEO ARTICLE

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mRNA and Exosome-mediated Directed Gene Therapy of Cancer with no Side Effects

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Abstract

Chemotherapy with no or minimal side effects is an urgent need. One means of attaining it is through gene-delivered prodrug therapies (GDEPTs). Prodrugs are harmless until activated by a bacterial or viral gene product; they can kill tumors without side effects if the activating gene is specifically delivered to cancer. Previous have been hampered mainly from low gene delivery and expression and use of viruses as gene delivery vehicles. Further, the need to inject the gene directly into the tumor required by these approaches minimized usefulness as many cancers, particularly cancer metastases, are not amenable to direct gene injection. My collaborators and I have addressed these problems. The use of the prodrug CNOB (C16H7CIN2O4) that we discovered facilitated this because its activated drug MCHB (C16H9CIN2O2) can be quantitatively visualized in living mice; and by using exosomes (EVs) for gene delivery. The enzyme HChrR6 that we discovered, improved and humanized was used to activate CNOB. Use of mRNA, instead of the commonly used DNA, in gene delivery proved highly advantageous: mRNA is translated directly upon cytosol entry unlike DNA; the latter must first enter the nucleus, hampering gene expression as DNA nuclear entry is highly inefficient. Copious and prolonged gene expression increases the prodrug levels in tumors, their killing and prevention of drug resistance. We have now enhanced the clinical transfer prospect of this approach by using: the prodrug CB1954 (tretazicar, also activated by HChrR6) for which safe human dose is established, and loading exosomes with in vitro transcribed HChrR6 mRNA, eliminating the use of a plasmid we previously used, which can potentially harm the patients. This loading required several steps through which we ascertained HChrR6 mRNA translated product's competence for tretazicar activation by a facile test that we developed. Systemic administration of the HChrR6 mRNA-loaded exosomes that displayed anti-HER2 scFv (termed "IVT-EXODEPTs") and tretazicar killed HER2+ breast cancer xenografts in athymic mice. This occurred without injury to other organs. This, along with the elimination of the need for direct gene injection into the tumor, moves our GDEPT closer to clinical transfer. The approach is generic and can treat any disease in which a receptor/ ligand is over-expressed.

Biography of the Presenting Author

A. C. Matin is an Indian-American microbiologist, immunologist, academician and researcher. He is a professor of microbiology and immunology at Stanford University School of Medicine. He has published over 100 research papers plus several reviews and has many patents registered in his name. His research is focused on bio-molecular engineering, cellular resistance and virulence, drug discovery, biology of microgravity, bioremediation, stress promoters, stress sensing, and biotechnology. He has made pioneering research contributions in biology and physiology of mixotrophy, starvation responses at the cellular and genetic levels, bacterial multidrug and biofilm resistance, role of G proteins in starvation and motility, discovery of an imageable cancer prodrug, specific drug targeting and the development of heritable contrast agent for molecular resonance imaging. Matin's work on antibiotic resistance along with his work as a principal investigator on E. coli AntiMicrobial Satellite (EcAMSat) system resulted in NASA sending E. coli to space for astronaut health protection in 2017. He is the recipient of NASA honor award for the ECAMSAT Project. He was the editor-in-chief of Open Access Journal of Applied Sciences.

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