INTRODUCTION

Gene and viral therapy for glioblastoma multiforme

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IN this issue of *Neurosurgical Focus*, the reviews and papers present state-of-the-art preclinical and clinical experiences utilizing viral vector-mediated gene therapies and oncolytic viruses for the treatment of glioblastoma (GBM). Over the past 3 decades, this field has evolved from experimentation in vitro and in mouse models of GBM to multiple clinical trials, several of which have been advanced to phase 2 and 3 studies. In general, progress in the field has been spurred on by FDA approval of one oncolytic virus (Imlygic, Amgen) for melanoma in 2015 and several viral vector-mediated gene therapies for neurologic, hematologic, and ophthalmologic disease. Current vaccines against coronavirus utilize gene therapy approaches as well. Therefore, the promise that this science can also be harnessed as a treatment for GBM remains alive but not yet fully realized.

The mode of action of this therapy depends on expression of genes (be it from gene therapy or viral genes from an oncolytic virus) in the GBM microenvironment to cause cytotoxic and immunogenic cell death, leading to an adaptive immune response against tumor. The reports in this issue encompass a snapshot of the field: approaches such as oncolytic herpes simplex virus 1-mediated delivery, oncolytic adenovirus, oncolytic Newcastle disease virus, and oncolytic vesicular stomatitis virus. The strategies discussed in these papers represent a few of the many approaches for GBM that are being tested, some in clinical trials. Novel delivery methods (such as intra-arterial delivery) are also discussed. To provide the reader with an appreciation of the plethora of approaches currently under investigation, several review articles on the topic are also included.

It is becoming clear from clinical studies that viral-mediated therapies provide a rapid avenue to increase inflammation and infiltration of cytotoxic T cells in GBM. The question remains whether the strength of this effect, repertoire and potency of infiltrating immune cells, and both quantity and availability of diverse tumor antigen-reacting T cells are sufficient for potent and long-lasting immunity against this cancer. Even if such immunity develops, it remains to be determined whether the frequency of tumor cell escape from such immune surveillance will prevent ultimate cure or even long-term survival after these treatments.

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Disclosures

Dr. Chiocca reports being a consultant for Advantagene, DNAtrix, Immunomic, Seneca, and Insightec; direct stock ownership in DNAtrix and Seneca; and being a patent holder in Oncolytic HSV. Dr. Lang reports being a patent holder in DNAtrix. Dr. Markert reports having been an equity owner in Catherex (< 8%), which underwent structured buyout by Amgen; being an owner of Aettis Inc. and Trevor Inc., being a consultant for Imugene; and being a patent holder of Mustang Biotech.

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