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Isaac Yang and Michael Lim

Biologic Principles of Immunotherapy for Malignant Gliomas

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Seunggu J. Han, Gurvinder Kaur, Isaac Yang, and Michael Lim

The most common primary brain neoplasm is glioblastoma multiforme, which is associated with a dismal prognosis. Despite the recommended treatment regimen of aggressive surgical resection, radiation, and chemotherapy, the median survival remains approximately only 14 months. Due to these minimal improvements in survival of patients despite recent advances in conventional treatments, new modalities such as immunotherapy are being investigated and studied. A hurdle to developing effective immunotherapy is the immunosuppressive characteristics that are the hallmark of malignant gliomas. Effective therapeutic strategies will require overcoming these mechanisms, by augmenting tumor antigen presentation, perhaps in a setting isolated from the tumor microenvironment. The heterogeneity of potential glioma antigens warrants potential targeting of multiple tumor-specific antigens, and discovery and investigation of additional antigens. This article describes the current strategies and principles of immunotherapy for malignant gliomas.

Mechanisms of Local Immunoresponse in Glioma

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Emilia Albesiano, James E. Han, and Michael Lim

Even though the central nervous system (CNS) was conventionally defined as “immunologically privileged”, new discoveries have demonstrated the role of the immune system in neurologic disease and illness, including gliomas. Brain tumor immunotherapy is an exciting and revived area of research, in which neurosurgeons have taken a major position. Despite the ability to induce a tumor-specific systemic immune response, the challenge to effectively eradicate intracranial gliomas remains mainly because of tumor-induced immunoresponse. This article gives an overview of the immunologic responses that occur in the CNS and their potential role in brain tumors. The main cellular and molecular mechanisms that mediate tumor escape from natural immune surveillance are also covered in this article. Glioma cells have been shown to diminish the expression of danger signals necessary for immune activation and to increase the concentration of immunosuppressive factors in the tumor microenvironment, which results in T-cell anergy or apoptosis. Finally, the authors discuss most of the over-expressed oncogenic signaling pathways that cause tumor tolerance.

Glioblastoma-Derived Mechanisms of Systemic Immunosuppression

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Allen Waziri

Abnormalities of cellular immunity are commonly seen in patients with glioblastoma (GBM), and the subsequent relative immunosuppression likely contributes to poor tumor-specific responses in affected individuals. Endogenous immune regulation is likely to limit the efficacy of a wide array of immunotherapeutic strategies, therefore mandating consideration in the continued development of novel treatments for

GBM. Various tumor-associated factors have been implicated as potential generators of the immunosuppressive effect. This article outlines relevant experimentation exploring the nature of immune defects in patients with GBM, including a critical discussion of tumor-secreted factors, cell-surface proteins, and more recently described populations of immunoregulatory leukocytes that have potential roles in the subversion of cellular immunity.

Microglia and Central Nervous System Immunity

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Gurvinder Kaur, Seunggu J. Han, Isaac Yang, and Courtney Crane

The central nervous system (CNS) has evolved as an immune-privileged site to protect its vital functions from damaging immune-mediated inflammation. There must be a CNS-adapted system of surveillance that continuously evaluates local changes in the nervous system and communicates to the peripheral immune system during an injury or a disease. Recent advances leading to a better understanding of the CNS disease processes has placed microglia, the CNS-based resident macrophages, at center stage in this system of active surveillance. Evidence points to microglia cells contributing to the immunosuppressive environment of gliomas and actually promoting tumor growth. Microglia accumulation exists in almost every CNS disease process, including CNS tumors. This article discusses the role of microglia in CNS immunity and highlights key advances made in glioma immunology.

Immunostimulants for Malignant Gliomas

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Nicholas Butowski

Several immunostimulant approaches have been studied in the treatment of gliomas. The advent of recombinant DNA technology led to a nonspecific immunostimulation via systemic administration of cytokines. Recently, in attempts to more closely mimic their natural activity, cytokines have been delivered by implanting genetically transduced cells or by using in vivo gene transfer techniques. The latest efforts have focused on immunostimulatory agents that act directly on antigen-presenting cells and effector cells of the immune system via pattern recognition receptors. Combining these strategies with more than one mode of immunotherapy may provide better clinical results.

Passive Antibody-Mediated Immunotherapy for the Treatment of Malignant Gliomas

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Siddhartha Mitra, Gordon Li, and Griffith R. Harsh IV

Despite advances in understanding the molecular mechanisms of brain cancer, the outcome of patients with malignant gliomas treated according to the current standard of care remains poor. Novel therapies are needed, and immunotherapy has emerged with great promise. The diffuse infiltration of malignant gliomas is a major challenge to effective treatment; immunotherapy has the advantage of accessing the entire brain with specificity for tumor cells. Therapeutic immune approaches include cytokine therapy, passive immunotherapy, and active immunotherapy. Cytokine therapy involves the administration of immunomodulatory cytokines to activate the immune system. Active immunotherapy is the generation or augmentation of an immune response, typically by vaccination against tumor antigens. Passive immunotherapy connotes either adoptive therapy, in which tumor-specific immune cells are expanded ex vivo and reintroduced into the patient, or passive antibody-mediated therapy. In this article, the authors discuss the preclinical and clinical studies that have used passive antibody-mediated immunotherapy, otherwise known as serotherapy, for the treatment of malignant gliomas.

Interferon-gamma in Brain Tumor Immunotherapy

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Ari Kane and Isaac Yang

Interferon-gamma (IFN γ) is a cytokine that acts on cell-surface receptors, activating transcription of genes that offer treatment potential by increasing tumor immunogenicity, disrupting proliferative mechanisms, and inhibiting tumor angiogenesis. However, abnormally low levels of IFN γ are produced by tumor cells and local T cells in the glioma microenvironment. Current investigations into the immunomodulating effects of IFN γ suggest that IFN γ has the potential to be used clinically in the treatment of brain tumors and as a promising adjunct to other immunotherapeutic modalities. Here the authors review the published literature that highlights the potential role of IFN γ in the treatment and immunotherapy of malignant gliomas.

The Epidermal Growth Factor Variant III Peptide Vaccine for Treatment of Malignant Gliomas

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Gordon Li, Siddhartha Mitra, and Albert J. Wong

Epidermal growth factor variant III (EGFRvIII) is the most common alteration of the epidermal growth factor (EGF) receptor found in human tumors. It is commonly expressed in glioblastoma multiforme (GBM), where it was initially identified. This constitutively active mutant receptor leads to unregulated growth, survival, invasion, and angiogenesis in cells that express it. EGFRvIII results from an in-frame deletion of exons 2 to 7 resulting in the fusion of exon 1 to exon 8 of the EGF receptor gene creating a novel glycine at the junction in the extracellular amino terminal domain. The juxtaposition of ordinarily distant amino acids in combination with the glycine that forms at the junction leads to a novel tumor-specific epitope that would make an ideal tumor-specific target. A peptide derived from the EGFRvIII junction can be used as a vaccine to prevent or induce the regression of tumors. This peptide vaccine has now proceeded to phase 1 and 2 clinical trials where it has been highly successful and is now undergoing investigation in a larger human clinical trial for patients who have newly diagnosed GBM. In this article, the authors discuss the pre-clinical data that led to the human trials and the exciting preliminary data from the clinical trials.

Clinical Applications of a Peptide-Based Vaccine for Glioblastoma

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Charles W. Kanaly, Dale Ding, Amy B. Heimberger, and John H. Sampson

Glioblastoma multiforme is a malignant, relentless brain cancer with no known cure, and standard therapies leave significant room for the development of better, more effective treatments. Immunotherapy is a promising approach to the treatment of solid tumors that directs the patient's own immune system to destroy tumor cells. The most successful immunologically based cancer therapy to date involves the passive administration of monoclonal antibodies, but significant antitumor responses have also been generated with active vaccination strategies and cell-transfer therapies. This article summarizes the important components of the immune system, discusses the specific difficulty of immunologic privilege in the central nervous system, and reviews treatment approaches that are being attempted, with an emphasis on active immunotherapy using peptide vaccines.

Heat Shock Proteins in Glioblastomas

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Isaac Yang, Shanna Fang, and Andrew T. Parsa

Glioblastoma multiforme is the most common primary central nervous system tumor. The prognosis for these malignant brain tumors is poor, with a median survival

of 14 months and a 5-year survival rate below 2%. Development of novel treatments is essential to improving survival and quality of life for these patients. Endogenous heat shock proteins have been implicated in mediation of both adaptive and innate immunity, and there is a rising interest in the use of this safe and multifaceted heat shock protein vaccine therapy as a promising treatment for human cancers, including glioblastoma multiforme.

The Role of Tregs in Glioma-Mediated Immunosuppression: Potential Target for Intervention

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William Humphries, Jun Wei, John H. Sampson, and Amy B. Heimberger

The role of regulatory T cells (Tregs) in mediating immune suppression of anti-tumor immune responses is increasingly appreciated in patients with malignancies—especially within the malignant glioma patient population. This article discusses the role and prognostic significance of Tregs within glioma patients and delineates potential approaches for their inhibition that can be used alone or in combination with other immune therapeutics in clinical trials and in the clinical settings of recurrent or residual disease.

Dendritic Cell Vaccines for Brain Tumors

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Won Kim and Linda M. Liao

Over the past decade, dendritic cell-based immunotherapy for central nervous system tumors has progressed from preclinical rodent models and safety assessments to phase I/II clinical trials in over 200 patients, which have produced measurable immunologic responses and some prolonged survival rates. Many questions regarding the methods and molecular mechanisms behind this new treatment option, however, remain unanswered. Results from currently ongoing and future studies will help to elucidate which dendritic cell preparations, treatment protocols, and adjuvant therapeutic regimens will optimize the efficacy of dendritic cell vaccination. As clinical studies continue to report results on dendritic cell-mediated immunotherapy, it will be critical to continue refining treatment methods and developing new ways to augment this promising form of glioma treatment.

Glioma Stem Cell Research for the Development of Immunotherapy

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Jianfei Ji, Keith L. Black, and John S. Yu

Glioma, especially high-grade glioblastoma multiforme (GBM), is the most common and aggressive type of brain tumor, accounting for about half of all the primary brain tumors. Despite continued advances in surgery, chemotherapy, and radiotherapy, the clinical outcomes remain dismal. The 2-year survival rate of GBM is less than 30%. Better understanding of GBM biology is needed to develop novel therapies. Recent studies have demonstrated the existence of a small subpopulation of cells with stemlike features called cancer stem cells (CSCs). These GBM CSCs are self-renewable and highly tumorigenic. They not only are chemo-radio resistant but also often contain multidrug resistance genes and drug transporter genes. These characteristics enable GBM CSCs to survive standard cytotoxic therapies. Among GBM CSCs, CD133⁺ cells are a well-defined population and are prospectively isolated by their cell-surface marker. Increasing data show that the presence of CD133⁺ CSCs highly correlates with patient survival, making these cells an ideal immunotherapy target population. The authors have reviewed recent studies related with GBM CSCs (particularly CD133⁺ CSCs) and the novel therapeutic strategies targeting these cells.

Virally Mediated Immunotherapy for Brain Tumors

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Pankaj K. Agarwalla, Zachary R. Barnard, and William T. Curry Jr

Brain tumors are a leading cause of mortality and morbidity in the United States. Malignant brain tumors occur in approximately 80,000 adults. Furthermore, the average 5-year survival rate for malignant brain tumors across all ages and races is approximately 30% and has remained relatively static over the past few decades, showing the need for continued research and progress in brain tumor therapy. Improved techniques in molecular biology have expanded understanding of tumor genetics and permitted viral engineering and the anticancer therapeutic use of viruses as directly cytotoxic agents and as gene vectors. Preclinical models have shown promising antitumor effects, and generation of clinical grade vectors is feasible. In parallel to these developments, better understanding of antitumor immunity has been accompanied by progress in cancer immunotherapy, the goal of which is to stimulate host rejection of a growing tumor. This article reviews the intersection between the use of viral therapy and immunotherapy in the treatment of malignant gliomas. Each approach shows great promise on its own and in combined or integrated forms.

Distinguishing Glioma Recurrence from Treatment Effect After Radiochemotherapy and Immunotherapy

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Isaac Yang, Nancy G. Huh, Zachary A. Smith, Seunggu J. Han, and Andrew T. Parsa

Recent advancements have made radiation and chemotherapy the standard of care for newly diagnosed glioblastomas. The use of these therapies has resulted in an increased diagnosis of pseudoprogression and radiation-induced necrosis. Standard MRI techniques are inadequate in differentiating tumor recurrence from posttreatment effects. Diagnosis of a posttreatment lesion as glioma recurrence rather than radiochemotherapy or immunotherapy treatment effect is critical. This increase in accuracy plays a role as newer immunotherapies incurring posttreatment effects on MRI emerge. Advancements with magnetic resonance spectroscopy, diffusion-weighted imaging, and functional positron emission tomography scans have shown promising capabilities. Further investigations are necessary to assess the imaging algorithms and accuracy of these modalities to differentiate true glioma recurrence from radiotherapy or immunotherapy treatment effect.

Immunotherapy Combined with Chemotherapy in the Treatment of Tumors

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James L. Frazier, James E. Han, Michael Lim, and Alessandro Olivi

This article provides a broad overview of the data, including laboratory and clinical studies, currently available on the combination of immunotherapy and chemotherapy for treating cancer. The various forms of immunotherapy combined with chemotherapy include monoclonal antibodies, adoptive lymphocyte transfer, or active specific immunotherapy, such as tumor proteins, irradiated tumor cells, tumor cell lysates, dendritic cells pulsed with peptides or lysates, or tumor antigens expressed in plasmids or viral vectors. This discussion is not limited to malignant brain tumors, because many of the studies have been conducted on various cancer types, thereby providing a comprehensive perspective that may encourage further studies that combine chemotherapy and immunotherapy for treating brain tumors.

Monitoring Immune Responses After Glioma Vaccine Immunotherapy

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Brian Jian, Isaac Yang, and Andrew T. Parsa

Immunotherapy provides the ideal candidate of therapeutic attack against malignant gliomas because it allows for targeting of cancer cells without the potential for

nonspecific toxicity. This is important when glial tumor cells spread far through normal brain tissue. Current vaccine therapies are in clinical trials and are showing beneficial responses. Given that the inflammatory response may make serial radiographic imaging more difficult to interpret, newer methodologies of immunomonitoring must be developed to assess the biologic efficacy of these immunotherapies. This article reviews methods of monitoring the immune system after vaccination against malignant gliomas. Improvements in immunomonitoring should lead to an increase in the efficiency of identifying viable avenues of therapeutic research, and assess the efficacy of those currently employed.

Challenges in Clinical Design of Immunotherapy Trials for Malignant Glioma 201

Cleo E. Rolle, Sadhak Sengupta, and Maciej S. Lesniak

Glioblastoma multiforme (GBM) is the most common and lethal primary malignant brain tumor. The traditional treatments for GBM, including surgery, radiation, and chemotherapy, only modestly improve patient survival. Therefore, immunotherapy has emerged as a novel therapeutic modality. Immunotherapeutic strategies exploit the immune system’s ability to recognize and mount a specific response against tumor cells, but not normal cells. Current immunotherapeutic approaches for glioma can be divided into 3 categories: immune priming (active immunotherapy), immunomodulation (passive immunotherapy), and adoptive immunotherapy. Immune priming sensitizes the patient’s immune cells to tumor antigens using various vaccination protocols. In the case of immunomodulation, strategies are aimed at reducing suppressive cytokines in the tumor microenvironment or using immune molecules to specifically target tumor cells. Adoptive immunotherapy involves harvesting the patient’s immune cells, followed by ex vivo activation and expansion before reinfusion. This article provides an overview of the interactions between the central nervous system and the immune system, and discusses the challenges facing current immunotherapeutic strategies.

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