CHAPTER 11

ANIMAL MODELS FOR VACCINE THERAPY

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Abstract: Animal models are important for defining paradigms of tumor immunology and for evaluating therapeutic efficacy of immunotherapy. Many animal models have been used for evaluating in vivo characteristics of malignant gliomas and their responses to therapy. No animal model, however, is perfect because malignant glioma has a very heterogeneous biological behavior. There are so many parallels between mouse and human immunology, but there are significant discrepancies in immune system. Animal models for vaccine therapy can be classified as transplantable tumor models and models of spontaneous tumor in genetically engineered animals. Although transplantable tumor models have been used to test immunotherapeutic efficacy and remain a mainstay in study of brain tumor immunology, a lot of tumor vaccines that look promising in experimental animals have turned out to be ineffective clinically. Recent advances of laboratory techniques and understanding of genetic and molecular characteristics of gliomas allows for animal models of gliomas with similar biologic characteristics. Well-designed glioma models that accurately reflect the biology, pathology and clinical behaviors of human gliomas can provide more useful preclinical informations to predict clinical efficacy of novel immunotherapies and cancer vaccines.

INTRODUCTION

Animal models are important for defining paradigms of tumor immunology and for evaluating therapeutic efficacy of immunotherapy because they provide an in vivo milieu. Many animal models have been used for evaluating in vivo characteristics of malignant gliomas and their responses to therapy. No animal model, however, is perfect because malignant glioma has a very heterogeneous biological behavior. Moreover, there has been
a tendency to ignore differences because there are so many parallels between mouse and human immunology, but there are significant discrepancies in immune system. Those differences should be taken into consideration when using mice models in preclinical testing for therapeutic efficacy of human disease. One of the major limitations to improve the prognosis of malignant gliomas has been the lack of available animal models that accurately reflect the biology, neuropathology and clinical behaviors of these tumors.

Animal models for vaccine therapy can be classified as transplantable tumor models and models of spontaneous tumor in genetically engineered animals. Although transplantable tumor models have been used to test immunotherapeutic efficacy and remain a mainstay in study of brain tumor immunology, many of these tumor models seem to be not good predictors for human clinical trials because a lot of tumor vaccines that look promising in experimental animals turned out to be ineffective clinically. Recent advances of genomics can recapitulate the casual genetic events in mice and consequent molecular evolution of gliomas as they form in situ.

**TRANSPLANTABLE TUMOR MODELS**

Transplantable animal brain tumor models were usually generated by implantation or inoculation of primary animal glioma cells into immunocompetent rats or mice subcutaneously (under the skin) or orthotopically (into native tumor site). Transplantable brain tumor models are characterized by synchrony and reproducibility of tumor formation, rapid tumor development, high penetrance and commercially available immunocompetent syngeneic recipient B6C3F1 mice. Immunotherapy protocols for patients with malignant gliomas should be based on demonstrated efficacy in a syngeneic animal brain tumor model. The first prerequisite of animal models for assessing immunotherapeutic responses is syngeneicity of original glioma cells and animals since immune rejection mechanisms in nonsyngeneic systems can mimic therapeutic efficacy.

Several syngeneic rodent models such as the 9L Fischer model are currently used for studying immunotherapy protocols. The 9L cell line is a gliosarcoma cell line chemically induced in CD Fischer rats. On the other hand, C6 rat glioma cells cloned from an N-nitrosomethylurea transformed rat astrocyte cell line express a MHC which is allogeneic to Wistar rat. So Wistar rats with C6 tumors are not suitable for studying immunotherapy because allogeneicity of tumor cells to animals induce a vigorous immune reaction.

In a murine glioma model, although a primarily cultured cell line derived from an astrocytoma that arose spontaneously in a mouse might have been used in generating animal model to study primary brain tumors including antiglioma immune responses, the GL26 or GL261 murine glioma models have usually been used extensively. The methylcholanthrene-induced murine anaplastic ependymoblastoma, GL26, propagated by serial subcutaneous transplantation in C57BL/6 mice is not immunogenic and is suitable for studying immunotherapy against gliomas.

Transplantable brain tumor models that inbred animals are inoculated with passaged tumor cells derived from the same genetic strain have been used in tumor immunology research for a long time. This approach is convenient and has led to valuable information. They have, however, several limitations in their applicability to human disease and these limitations may lead to different immunological outcomes. First, most transplatable brain tumors that were inoculated by numerous passaged cell lines might have altered genetics according to culture or isolation conditions. As a result, animal models for