Chapter 10

ANIMAL MODELS OF LEPTOMENINGEAL CANCER

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Abstract: Animal models are a critical tool for our understanding of pathogenic mechanisms and the development of therapeutic strategies. Since the 1970's, numerous syngeneic and allogeneic rodent models of leptomeningeal cancer have been developed; in this chapter, we present representative models and discuss their clinical and translational implications.

Key words: Syngeneic, allogeneic, xenogenic; animal models; leptomeningeal cancer; translational research

1. INTRODUCTION

Since its initial description in a landmark paper by Eberth\(^1\) in 1870, significant advancements in the understanding and treatment of leptomeningeal cancer (LC) have been made through the use of experimental animal models. These models have provided a useful means for in vivo evaluation of various potential chemotherapeutic agents and other antineoplastic treatment modalities including intrathecal immunotherapy and gene therapy.

In scientific research, modeling provides a practical approach for investigating the normal and abnormal function of living organisms.\(^2\) By constructing a model, the problem being studied is simulated as accurately as possible. Using animal models, experiments can be performed that are not feasible with living human subjects or patients. Unfortunately, despite decades of research in this field, there are few animal models that accurately parallel the clinical condition in humans.\(^3\)

Reports of experimental models for LC were first published in the mid-1970's.\(^4\) Murine animal models have traditionally been used for testing the
chemosensitivity of cancer cells. The models for LC in the literature can be divided into two categories: 1) syngeneic, and 2) allogeneic/xenogeneic. In syngeneic models, animal tumor cell lines are implanted into a genetically identical host. In allogeneic models, genetically dissimilar cells are implanted into an immunocompromised host. If species lines are crossed, the model is actually xenogeneic. The earlier animal models of LC were typically syngeneic using mice, rats, rabbit or guinea pigs. Recently, allogeneic and xenogeneic models using nude mice and nude rats have also been developed. The advantage of using the latter type of models is that human tumor cell lines can be used and tested. Many of the syngeneic and xenogeneic models for LC are listed according to the type of tumor cell line in Tables 1 and 2, respectively.

One potential problem in treating malignant tumors of the central nervous system (CNS) and/or the meninges is inadequate drug delivery across the blood-brain barrier (BBB). Systemically administered hydrophilic (and even lipid soluble) drugs usually penetrate the CNS parenchyma for short distances and thus fail to reach tumor cells in sufficient concentrations. Intrathecal injection of drugs directly into the cerebrospinal fluid (CSF) has been used to circumvent this problem with the rationale that high concentrations of the drug may be achieved in the vicinity of tumor located on the meninges. Most animal models involve the use of the intrathecal drug delivery method for this purpose. Animals are usually prepared by direct inoculation of tumor cells into brain parenchyma or by intracisternal inoculation.