A Porcine Model of T-cell Lymphoma

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ABSTRACT

Non-Hodgkin’s lymphoma (NHL) is a disease of increasingly serious proportions. The highest incidence rate in the world is seen in the United States and Canada, with forty to fifty thousand new cases per year in the U.S. NHL is the sixth most common cancer and the sixth most common cause of cancer death, accounting for 4% of all cancers and 4% of cancer-related deaths. There is a clear need for relevant animal models of lymphoma that provide preclinical tools. Our objective is to create a porcine model of lymphoma analogous to the human disease. Genetically engineered porcine tumors may prove to be invaluable for: (1) determining the efficacy of anti-cancer drugs; (2) studying the process of tumorigenesis; and (3) producing cancer in a genetically compliant animal model that is physiologically more similar to humans than rodents. We have previously shown that solid tumors could be readily induced in immunosuppressed pigs via the expression of proteins disrupting the p53 tumor suppressor pathway, and activating c-Myc and Ras pathways, all of which are commonly corrupted in human cancers. In an attempt to induce a less immunogenic tumor with a defined phenotype, we constructed retrovirus vectors encoding four genes (Cyclin d1, CDK4, c-Myc, and H-Ras) and injected them into porcine blastocysts to create transgenic pigs. All pigs with transgenes demonstrated visible signs of disease development and were found dead or euthanized prior to the end point of the study. Necropsies showed all pigs had developed aggressive T-cell lymphoma. Remaining pigs euthanized two months after injection were also diagnosed with T-cell lymphoma, albeit a less aggressive form.

MATERIALS AND METHODS

INTRODUCTION

Key Genes in Human & Porcine Tumorigenesis

OBJECTIVES

- Develop methods to induce genetically defined tumor formation by altering pathways commonly disrupted in human cancers.
- Develop a porcine model of lymphoma analogous to the human disease.

RESULTS

Figure 1. (A) Retroviral constructs used to induce cancer in the pig. (B) Lymphomas in mice: a model for human lymphoma. (C) Expression of the indicated transgenes by RT-PCR from RNA isolated from the liver.

Table 1. Mortality rate for pigs injected with retrovirus encoding cyclin D1, CDK4, c-Myc and H-Ras.

Table 2. Tumor progression is independent of viral concentration and injection site.

CONCLUSIONS

- A porcine model of T-cell lymphoma was successfully created by genetically modifying pathways commonly disrupted in human cancers.
- This genetically compliant animal model is physiologically more similar to humans than rodents and supports adjunct therapies.
- The ability to manipulate gene expression in vivo and rapidly generate pathologically accurate tumors makes this model an ideal preclinical system for the generation of novel therapeutics and testing new drugs for the treatment of lymphoma and other types of diseases.
- The rapid development of novel technologies for manipulating the pig genome has allowed and will allow, in the next few years, to recreate in the pig virtually any pathological condition whose molecular basis has been elucidated in humans.

FUTURE DIRECTIONS

- Expand methods to support a preclinical model for testing of novel therapeutics, experimental therapies and imaging.
- Develop cell-based solid tumor models from known tissue of origin and with designated clinical outcomes in the absence of immunosuppression.
- Establish a porcine model for breast cancer using retroviral injection methods.
- Generate a transgenic pig model that will be used to induce tissue-specific, conditionally expressed solid tumors.
- Induce tumors in cloned animals, thus producing tumors that can be transferred to any number of identical animals to study the process of tumorigenesis and cancer phenotypes.

REFERENCES


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