In: Genes, Dogs and Cancer: 2nd Annual Canine Cancer Conference - 2002, J. F. Modiano (Ed.)
Publisher: International Veterinary Information Service (www.ivis.org), Ithaca, New York, USA.

The Canine Hereditary Urothelial Malignancy Study (CHUMS): A Potentially Useful Approach to Understanding Human Urothelial Malignancy

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In the year 2002, urothelial malignancies will be diagnosed in 56,500 American men and women and 12,600 patients will die from advanced disease (1). Low grade tumors limited to the urothelial lining or subepithelial connective tissue are managed conservatively while high grade muscle invasive tumors require aggressive therapy such as radical removal of the bladder, ureter and/or kidney with subsequent urologic reconstruction. Early diagnosis and aggressive treatment of tumors prior to lymph node extension results in long term survival while metastatic disease is usually fatal (2). Our current understanding of the genetic basis for initiation and progression of urothelial malignancies has been limited to evaluation of sporadic tumors and previously characterized oncogenes, growth factors, growth factor receptors and tumor suppressor genes (3). Although hereditary predisposition to urothelial malignancy is implicated by familial clustering (4) and a multi-cancer predisposition syndrome (5-6), genetic analysis or linkage for predominant predisposition to urothelial malignancy has not been established. Identification of families with hereditary predisposition for urothelial malignancy could lead to identification of genes and biochemical pathways involved in carcinogenesis, treatment failure, environmental risk factors and tumor progression. In addition, identification of biochemical pathways could facilitate development of chemopreventive strategies and novel treatment protocols using molecular targeting.

Animal models of urothelial malignancies often rely on artificial production of tumors in rodents using established human carcinoma cell lines or carcinogenic agents (7-8). Although this strategy has utility for investigation of drug efficacy, genetic and molecular analyses of hereditary predisposition require more naturally occurring models of urothelial cancer. Canine models of human diseases have become a useful and important means of investigation of complex genetic traits (9) and genetic mapping of a hereditary canine renal cancer (10). Certain other breeds such as the Scottish Terrier develop naturally occurring urothelial malignancies and may also be useful for genetic analysis (11). A previous report described a 12.9 fold relative risk for bladder and urethral cancer in the Scottish Terrier (11) and limited pedigree analysis (unpublished) demonstrates transmission in successive generations suggesting a possible hereditary predisposition.

We propose to investigate the genetic basis for urothelial malignancy in the Scottish Terrier by extensive and detailed pedigree and molecular analysis of affected dogs. Currently we have identified and collected blood samples from over 40 affected Scottish Terriers, unaffected litter-mates and their relatives on the basis of bladder cancer diagnosis. Breeder, medical and historical information will be used to sort and compile pedigrees from the proband. Potential founder effects may be identified using breeder information alone since Scottish Terriers are highly inbred. The resulting data will be analyzed for genetic indicators of hereditary predisposition such as sex linkage, early age of onset, associated abnormalities, mode of inheritance and penetrance. Analysis of genomic DNA (when available) will establish or confirm relatedness among individual Scottish Terriers and amongst other breeds with less risk for urothelial malignancy. Epidemiologic data will be used to compare disease incidence form independent breeders and geographic locations. Molecular analysis of genomic DNA prepared from affected and unaffected Scottish Terriers will be used to identify the gene(s) predisposing to urothelial malignancy. Once the canine urothelial cancer gene is identified, we hope to identify homologous human genes through comparative analysis.

References


Biographical Profile

Fredrick S. Leach, M.D., Ph.D. completed his B.S. and B.A. degrees with highest honors in biology and chemistry at Southern Methodist University in Dallas Texas. He received M.D. and Ph.D. degrees from Stanford University Medical Center in 1990 after completing the medical scientist-training program (MSTP). He subsequently completed surgical internship and assistant resident positions at the Johns Hopkins Hospital followed by an oncology fellowship in molecular genetics of human malignancies at the Johns Hopkins Oncology Center from 1990-1995. After completing urologic residency including a one-year National Cancer Institute (NCI) Fellowship at the University of Texas-Southwestern Medical School, he joined the Urologic Oncology Branch at the National Institutes of Health as a staff urologist and principal investigator form 1999-2002. Currently, Dr. Leach is an assistant professor in the departments of Urology and Molecular and Human Genetics at Baylor College of Medicine. Dr. Leach is a diplomate of the National Board of Medical Examiners (NMBE) and the American Board of Urology (ABU). His research and clinical interests are development of novel diagnostic and treatment options for urologic malignancies using molecular genetic approaches. Research interests also include hereditary predisposition to urologic diseases and the role of mismatch repair gene expression in the urologic malignancies.

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