Public Abstract

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Title:DLC1 AS A COMPARATIVE EPIGENETIC BIOMARKER FOR RADIOTHERAPY OF NON-HODGKIN'S LYMPHOMA

The American Cancer Society estimates that 58,870 people were diagnosed with non-Hodgkin's lymphoma (NHL) in 2006, and 18,840 people died of the disease. Recent advances in chemotherapy, monoclonal antibody (mAb) therapy, and radioimmunotherapy (RIT) have improved the manageability, but not the curability of indolent forms of NHL in humans. In the search for understanding of the root mechanisms of this disease, covalent DNA modification patterns have been identified that result in epigenetic gene silencing, yet leave the sequence of the genetic code intact. Termed DNA methylation, the addition of a methyl group to cytosine bases in dinucleotides of cytosine followed by guanine persists from generation to generation of cell, often silencing the expression of the gene. However, this addition is also chemically reversible, allowing the silenced gene to be re-expressed. Such hypermethylated genes may serve as markers of disease, markers of prognostic groups, or targets for therapy. The causes of the observed patterns of methylation are not yet clear, and models are necessary for preclinical evaluation of diagnostic and therapeutic strategies. In this series of experiments, evidence of DNA hypermethylation was identified in the gene Deleted in Liver Cancer 1 (DLC1), a tumor suppressor gene, in canine NHL as it is in humans. The structure of the canine form of this gene was further characterized in silico and biologically, and the methylation patterns surrounding its promoter region were defined in 21 cases of naturally occurring NHL. The comparative evaluation of the human and canine promoter regions revealed similarity between Sp1 transcription factor binding sites that are known to be modulated by hypermethylation. Although the presence of hypermethylation did not result in silencing of the gene in the majority of the dogs, methylation patterns were statistically associated with NHL compared to normal lymphoid tissue. Further experiments discovered a significant synergistic interaction between external irradiation or 177Lu-labeled 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA)-tyrosine3-octreotate (TATE) treatment and zebularine, a demethylating agent. Finally, 111In-DOTA-TATE was used to successfully image somatostatin receptors of NHL lesions in three dogs with naturally occurring disease. The comparative evaluation of the DLC1 gene identified important similarities in methylation boundaries between humans and dogs. The presence of hypermethylation and somatostatin receptors in canine NHL, both characteristics of human NHL, suggest that dogs may serve as a pre-clinical model for evaluation of epigenetic modification therapy and targeted imaging and radiotherapy designed for eventual human use. The results of these studies will form the underpinnings of future canine clinical trials, modeling markers for diagnosis, prognosis, and therapy of NHL.