

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

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ABSTRACT

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 investigation of epigenetic gene regulation has identified the role of DNA methylation of cytosine followed by guanine in silencing gene expression. Such hypermethylated genes may serve as markers of disease, markers of prognostic groups, or targets for therapy. 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. 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. 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 results of these studies will form the underpinnings of future canine clinical trials, modeling markers for diagnosis, prognosis, and therapy of NHL.