

AGGRESSIVE B-CELL LYMPHOMA: GENOMIC AND EPIGENOMIC PROFILING AND INVESTIGATION OF NOVEL TREATMENTS

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Diffuse large B-cell lymphoma (DLBCL) is the most common and devastating form of non-Hodgkin lymphoma (NHL) in the world. The incidence of NHL and DLBCL, ranked fifth of all cancer types in the United States, has increased by at least 100% over the last twenty years. Majority of patients diagnosed with DLBCL are elderly (65 year old) with poor survival. The objective of this study is to determine the impact of specific p53 genetic aberrations and altered genetic/phenotypic expression patterns in patients with DLBCL. The present project is the initiation of a largescale clinical attempt in our group to identify new molecular links between p53 genetic aberrations and clinical outcome in DLBCL. Specifically, we analyze to address: the distribution profile of p53 genetic aberrations (mutation and deletion) in a large cohort of DLBCL patients; whether any or subsets of p53 aberrations have predictive value for clinical outcome in DLBCL; whether genetic subtypes of DLBCL with different clinical outcome will exhibit unique structural profiles of p53 gene aberrations; the location of critical mutations on the p53 molecule that play significant roles as prognostic indicators in DLBCL by structural analysis and finally the correlation of the gene expression profiling and genetic data with the results obtained from functional study to determine if there are unique gene expression alterations associated with specific candidate genes or unique genetic pathway. The general approaches delineated in this study are used to expand our study for additional molecular targets, including MDM2 and MDM4, in the same signaling pathway that are responsible for lymphoma pathogenesis. We build a prognostic model combining both the genetic information obtained in this study and associated clinical data. The findings provide insight into the functional consequence of the p53 genetic lesions and the genes of significance in the abnormal loci.

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