Pathogenesis of Diffuse Large B-Cell Lymphoma

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Diffuse Large B cell Lymphoma (DLBCL) represents the most common form of B cell derived non-Hodgkin Lymphoma (B-NHL), accounting for ~30% of the de-novo diagnoses and also arising as a frequent clinical evolution of Follicular Lymphoma (FL) and Chronic Lymphocytic Leukemia (CLL). DLBCL and FL derive from B cells at different stages of germinal center (GC) development. In order to identify the genetic lesions associated with DLBCL pathogenesis, we have integrated whole-exome sequencing analysis and copy number variation analysis for a comprehensive definition of the DLBCL coding genome. The results have identified a novel set of recurrent genetic lesions, which, in turn, identify mutant genes regulating important pathways involved in GC development, including those involved implicated in chromatin remodeling, transcriptional control of apoptosis and differentiation, NF-kB activation and immune escape. Recent results have identified a pervasive mutational deregulation of a transcription factor network (MEF2B-BCL6-FOXO1) involved in the control of GC development. The normal role of these transcription factors and the consequence of their mutations in DLBCL have been investigated using GC-directed conditional transgenic mice.