Biological and genetic factors associated to treatment resistance in lymphoma

Ken H Young
The University of Texas, USA

Diffuse large B cell lymphoma (DLBCL) is the most common type of lymphoma and accounts for 30% - 40% of all non-Hodgkin lymphomas. In the past two decades, results from several phase 3 studies have established the rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) as the standard therapy for patients with DLBCL with 50-70% of patients being cured. The remaining patients are refractory to R-CHOP or relapse after complete response (CR). Understanding the biology of DLBCL is essential for identifying patients who are not cured by R-CHOP and uncovering potential pathways that could be targeted. A milestone in the research of DLBCL biology is the identification of two different subtypes of DLBCL, germinal center B-like (GCB) and activated B-like (ABC). These two types of DLBCL show distinct gene expression profiles and different clinical outcomes. With the advent of high-throughput sequencing platforms, an increasing number of driver genes in the pathogenesis of DLBCL have been unveiled. Recently, three studies comprising over 1800 DLBCL cases were assessed using whole-exome sequencing with other high-throughput techniques to comprehensively define the genomic landscape of DLBCL, providing more insights into DLBCL development and potential therapeutic targets. I will present the prevalence, functional roles, and clinical implications of genetic events including somatic mutations, copy number alterations (CNVs), and chromosomal translocations in DLBCL.

Clinical heterogeneity is a major challenge for the treatment of DLBCL. Different cell-of-origin may contribute to the distinct biology of DLBCL as suggested by the germinal center-like and activated B cell (ABC)-like DLBCL classification system. Characterization of biological and genetic parameters underlying the molecular mechanisms help to identify critical targets responsible for drug resistance, treatment failure and recurrence, and it is helpful for better understanding the pathogenesis of DLBCL. In this presentation, the important molecular and biological events are systemically analyzed in a large cohort of de novo DLBCL patients to evaluate for the correlation of biological and genetic parameters with clinical outcome using high-throughput next generation sequencing (NGS). Gene expression and epigenetic miRNA profiling have also been explored for particular signature from each of the patients based on B-cell differentiation. Combined genetic, clinical and pathologic dissections provide insight in better understanding of the cell-of-origin, drug resistance, and recurrence in DLBCL patients.

The elaboration of the genetics of DLBCL not only improves our understanding of disease pathogenesis, but also provides us with insights about disease classification, prognostication and therapeutic targets.

e: khyoung@mdanderson.org

Notes: