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Biological and genetic factors associated to treatment resistance in aggressive B-cell lymphoma

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Clinical heterogeneity is a major challenge for the treatment of diffuse large B cell lymphoma (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.

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Leukemia-associated NPM mutations promote quiescence of hematopoietic stem cells and prevent their functional exhaustion upon oncogene-induced hyper-proliferation

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Current acute myeloid leukemia (AML) chemotherapy allows survival of a small number of quiescent cells called Leukemia initiating cells (LICs) that can recapitulate the tumor after remission. How AML mutations lead to LIC selection still need to be elucidated. Mutated nucleophosmin (NPMc+) represents an ideal candidate to study LIC selection mechanisms since is usually found in primary leukemia and is highly conserved between primary and relapsed AML, establishing it as a founder lesion. Our NPMc+ mouse model develops a long latency/low penetrance AML. The analysis of the pre- leukemic phase showed that the expression of NPMc+ in the bone marrow (BM) leaded to the expansion of the hematopoietic stem cells (HSCs) compartment by the enforcement of a stem-cell transcriptional program that increases HSC self-renewal promoting quiescence. To investigate if this program is instrumental to initiation/progression of leukemogenesis, we next analyzed the HSC compartment of mice expressing both NPMc+ and FLT3-ITD mutations (the most frequent concurrent mutations in AML patients). We showed that the expression of NPMc+ in the FLT3- ITD background prevents the HSCs exhaustion imposed by FLT3-ITD that it is known to prevent AML development in FLT3-ITD mice. In particular, NPMc+ expression reduced the high proliferative rate imposed by FLT3-ITD by enforcing its peculiar HSC transcriptional program. Accordingly, NPMc+/FLT3-ITD mice developed high penetrant AML. Our data indicate that the NPMc+ quiescence program is instrumental to LIC selection and it could be responsible for AML therapy resistance thus suggesting that it represents a critical target for the design of novel anti- leukemic strategies.

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