Vulnerabilities of Indolent Lymphomas: The Tumor and the Microenvironment

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Take-home messages:

- Indolent lymphomas share the dependency on B-cell receptor (BCR) activation for survival and proliferation.
- In early stages of lymphomagenesis the interactions between the microenvironment and the tumor cells play an important role.
- BCR inhibitors directly target the malignant B cells and might disrupt the bi-directional dialogue of the tumor cells with the microenvironment.

“Indolent lymphomas” include different disorders with unique genetic and epigenetic alterations that translate in their different biological and clinical behavior. Recent studies have shown that indolent lymphomas share the dependency on B-cell receptor (BCR) activation for survival and proliferation.\(^1,2\) In the early stages of lymphomagenesis the complex interaction of tumor cells with activated BCR and the microenvironment seems to play an important role (Fig. 1A).\(^3,4\) CLL, MZL and MCL have been shown to have antigen driven skewed immunoglobulin (Ig) repertoire.\(^5,6\) In contrast, in FL the activation of the BCR is secondary to N-glycosylation motifs in the IgV regions accumulated during the process of somatic hypermutation (SHM).\(^7,8\)

CLL is the most frequent adult leukemia in the Western world. CLL is a malignancy of mature B-lymphocytes, which are highly dependent on interactions with the microenvironment for their survival and proliferation.\(^9\) Although CLL has a very homogeneous phenotype (CD19+, CD20dim, CD23+, CD5+, LEF1+), the clinical course is rather heterogeneous. The earliest form of the disease, monoclonal B-cell lymphocytosis (MBL), is defined as the presence of <5000/µl B-lymphocytes in peripheral blood (PB) with a CLL phenotype. CLL is always preceded by MBL, with a progression rate to CLL of 1% to 2% per year. Molecularly, 2 types of CLL are recognized, one with unmutated immunoglobulin heavy-chain variable region (IGHV)/U-CLL, which originates from B cells that have not passed through the germinal center (GC); and the second type with mutated IGVH (M-CLL), which is derived from post-GC B-cells.\(^9\) U-CLL cells express high levels of CD38 and ZAP70 and are more responsive to IGM stimulation. In contrast, M-CLL cells show constitutive phosphorylation of signaling proteins, including ERK kinase, and reduced levels of responsiveness to BCR stimulation, referred as “anergy” and a worse prognosis than patients with M-CLL. The mechanism triggering clonal expansion of CLL cells is not well understood but the analysis of the BCR strongly indicates that antigen selection plays a crucial role. CLL cells recirculate between PB and secondary lymphoid organs. Homing to tissues is dependent on tightly regulated chemokine expression. In lymph nodes (LN), CLL cells proliferate in the so-called “proliferation centers”, where they get in contact with follicular dendritic cells (FDC’s), T-cells, stromal cells and nurse-like cells. As a consequence of these interactions, CLL cells organize their own immune protective microenvironment and impair the antitumor response. Genetically, CLL is a heterogeneous disease with low burden of somatic mutations.\(^10\) However, secondary mutations, like TP53, NOTCH1 and SF3B1 are regarded as important prognostic factors.\(^8\)

FL is characterized by the t(14;18) translocation with subsequent expression of the anti-apoptotic BCL2 protein.\(^11\) This translocation occurs in a pre-B cell in the bone marrow (BM). The t(14;18), although necessary, it is not sufficient for malignant transformation. B-cells carrying the t(14;18) are detected in PB of healthy individuals in low numbers but tend to increase with age.\(^12\) The t(14;18)-carrying cells are memory B-cells with somatically mutated IGV genes that undergo several GC passages. Because these cells have all the characteristics of FL cells, they are referred as FL like-cells (FLLC). FLLC in contrast to CLL, activate the BCR by antigen stimulation but by introduction in the IGV gene of at least one motif characteristic of an N-glycosylation site and addition of mannosylated glycan in the antigen-binding
These highly mannosylated glycans are able to interact with lectins (DC-SIGN) expressed by M2 macrophages, which retain the FL cells in the GC, initially as “in situ follicular neoplasia” (ISFN). FL cells interact not only with macrophages but also with T follicular helper cells (TFH) and FDCs (Fig. 1B). ISFN is the earliest morphological manifestation of FL. ISFN cells show low genetic complexity but carry frequently mutations identified in manifest FL (mFL), predominantly CREBBP mutations, and have glycan modification of surface Ig in the majority of the cases, as the result of SHM. mFL carries frequently mutations in genes involved in epigenetic (CREBBP, KMT2D, EP300, EZH2) and transcriptional regulation (MEF2B, FOXO1, STAT6) that help sustaining the GC B-cell program. FL is also an example of B-cell lymphoma that depends on BCR activation and microenvironment interactions, in addition to the genetic lesions.

MCL is characterized by the t(11;14) translocation with subsequent overexpression of cyclin D1. This translocation occurs in a pre-B cell in the BM. Two molecular pathways are recognized; the most common subtype derives from mature B cells that have bypassed the GC, have unmutated IGH genes, a gene signature of a naïve B cell and express the transcription factor SOX11. In the second subtype the cells have experienced the GC, carry IGHV mutations and have the gene signature of a memory B cell and lack SOX11 expression. This latter subtype is known as “leukemic nonnodal MCL.” The clinical presentation mainly involving the PB and spleen but not LN, at least in early stages. This subtype has an indolent, stable clinical course for a long time but appearance of TP53 mutations heralds the progression to a more aggressive disease. The BCR in MCL, similar to CLL, has a markedly biased usage of IGHV genes, highlighting the influence of antigen selection in the clonal expansion of the tumor cells. Likewise, the tissue microenvironment provides survival and proliferation signals to the tumor cells, and confers drug resistance.

The dependency on BCR activation of the tumor cells and the interaction with the microenvironment reveals vulnerabilities in the lymphoma cells that could be exploited for the design of more effective, targeted therapeutic approaches. Indeed, novel drugs including small molecule inhibitors of EZH2 and BCL2, as well as inhibitors of BCR associated kinases (BAKs), NF-κB pathway plays a key role for the initiation and progression of B-cell lymphomas. BAKs and NF-κB activity inhibitors have the potential not only to directly target the malignant B cell population but also to disrupt the bi-directional dialogue of the tumor cells with the TME. TFH = T follicular helper cell; FDC = follicular dendritic cell; TAM = tissue-associated macrophage.

Figure 1. Pathogenesis of indolent lymphomas and the influence of the tumor microenvironment (TME). (A) The pathogenesis of indolent lymphomas is a multistep process that includes a primary genetic alteration in an early precursor cell usually in the bone marrow. The activation of the B-cell receptor (BCR) mainly by antigen stimulation and microenvironment interactions are important in early stages of lymphomagenesis. As the disease progresses the acquisition of additional genetic alterations determines progression and transformation (modify from Puente et al, ref 9). (B) The activation of BCR associated kinases (BAKs) LYN, SYK, BTK, and PI3K is crucial for the dialogue between lymphoma B cells and TME. The activation of BCR associated kinases: when the B cell is not the target. Biophys Acta. 2016;1863:471–482.

References

This study demonstrated in a large cohort of CCL patients the importance of stereotyped BCR for molecular classification and targeted therapy.


This study was the first and the largest study demonstrating the mutational landscape of CLL.


This study was the first to demonstrate that follicular lymphoma like B-cells in healthy individuals is a premalignant stage important for the development of follicular lymphoma.


This study demonstrated the presence of two distinct molecular subsets in mantle cell lymphoma.