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CD38 in Chronic Lymphocytic Leukemia (CLL) – From a Diagnostic Tool to a Therapeutic Target?

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Chronic lymphocytic leukemia (CLL) is a malignancy of mature clonal B cells derived from proliferation in pseudofollicles in the bone marrow and secondary lymphoid tissue, where they receive support from stromal cells as well as immune cells, such as follicular dendritic cells and mature T helper cells [1,2]. CLL is highly heterogeneous in terms of progression, response to treatment and survival. Thus, design of appropriate therapeutic strategy requires a good prediction of the course of the disease. Since Rai and Binet staging systems are not well suited to predict the clinical course at an early stage, molecular and cellular features are analyzed to determine whether a patient has a favorable or unfavorable prognosis. One of the most widely used marker in diagnosis and prognosis of chronic lymphocytic leukemia is CD38.

CD38 as Marker for Poor Prognosis in CLL

In human immune cells, CD38 is expressed by T cells, monocytes and activated dendritic cells as well as natural killer (NK) cells and granulocytes. In B lymphocytes, CD38 expression greatly varies during ontogenesis (reviewed in [3]). Given its ubiquitous expressionon normal immune cells, it is not surprising that CD38 is also found in many B cell malignancies such as plasmacytoma [4], myeloid leukemia [5], hairy cell leukemia [6], multiple myeloma (MM) [7] as well as CLL. Within a patient, CLL cells often display a bimodal CD38 distribution with a $CD38^-$ and a $CD38^+$ CLL cell population, and the ratio between these subsets varies greatly between patients. The distinction of high risk versus low risk disease is based on the percentage of $CD38^+$ CLL cells, with cut-off level between 20% and 30%. CD38 positivity has been associated with poor response to treatment, fast disease progression, short time to first treatment, extent of adenopathy, and low overall survival [8-15]. Furthermore, CD38 expression correlates with other diagnostic markers such as high CD23 and beta2-microglobulinserum levels [13,14,16-18] and absence of mutations in the of *IGVH* locus [11,19,20]. As a consequence, the combined assessment of CD38 expression and other independent risk markers like CD49d, ZAP-70, or IGVH mutation status has become state of the art in CLL diagnosis.

Contribution of CD38 to CLL Pathogenesis

While the importance of CD38 for CLL prognosis is widely accepted, its direct contribution to the disease pathogenesis is still poorly understood. CD38 has a dual function and acts both as a receptor/adhesion molecule as well as an ectoenzyme. The downstream signaling and the biological consequences of CD38 activation depend on the cell type as well as its maturation state. This can be attributed to the fact that CD38 often associates and acts in synergy with, other, cell type specific surface receptors. In CLL cells, CD38 collaborates with the BCR/CD19 complex for signal transduction [21,22] and it can integrate into the CD49a/CD29 integrin complex, thereby enhancing CLL cell adhesion to cells expressing the corresponding ligands [23].

$CD38^+$ cells are characterized by a higher activation state and increased proliferation rates [24] and display enhanced engraftment in xenograft models. Moreover, CLL cells in lymph nodes express higher CD38 levels than CLL cells in peripheral blood [25]. While these observations provide indications for a biological contribution of CD38 to the disease, the first mechanistic evidence for a direct role of CD38 in CLL trafficking is provided by a recent study, where the authors use inhibitors and an enzymatically inactive CD38 molecule to show that CD38 is functionally involved in migration and homing of CLL cells [26]. Given the fact that CLL cells depend on the micro environment in the lymph nodes to survive and proliferate, CD38 expression may enhance CLL cell expansion by supporting their migration from the blood stream into proliferation sites. These niches not only provide anti-apoptotic and proliferative signals, they also offer a certain degree of protection from drugs, which may explain the fact that $CD38^+$ CLL patients show a higher resistance to therapy [10]. Additional support for CD38 being more then a mere risk marker for in CLL comes from the observation that the well characterized C>G SNP (rs6449182) in a regulatory region of the *CD38* gene is associated with poor prognosis and transformation to Richter Syndrome [27-29].

CD38 as Therapeutic Target?

Monoclonal antibodies have become indispensible therapeutic tools in many malignancies. The relatively high expression on many malignant B cells makes CD38 a well-suited target for monoclonal antibody therapies and adoptive transfer of CAR T cells. A major caveat for therapies directed towards CD38 is its expression on other lymphocytes such as precursor B cells and activated T cells, but also cells from brain and retina. In addition, ligation of CD38 by therapeutic antibodies may induce activation of CD38 signaling, thereby leading to undesirable effects such as enhanced migration and proliferation. As an alternative, therapeutic approaches could inhibit the enzymatic activity of CD38 rather than using CD38 antibodies. Several nucleotide-analogues and flavonoids have been shown to block the enzymatic function of CD38 at low micromolar concentrations, some of them with promising results in cell-based *in vitro* experiments as well as in mouse models [30-39].

MM is a malignancy of monoclonally expanding plasma cells. Since MM cells express high levels of CD38, recent efforts have focused on the development of CD38 antibodies for MM therapy. Anti-CD38 antibodies with strong cytolytic activities have been developed by three companies: Daratumumab (GenMab, former Johnson & Johnson), SAR650984 (Sanofi) and MOR03087 (MorphoSys). Daratumumab was first tested as single agent in a dose escalation study to establish its safety profile,and

subsequently moved into phase III clinical trials [40]. While daratumumab proved to be successful as monotherapy in refractory myeloma [41], it has also been found to augment the effect of lenalidomide even in patients that are refractory to lenalidomide [42,43]. From what has been reported to date,side-effects of anti-CD38 antibodies-mediated therapies seem to be rather low.

The fact that CD38 is highly expressed in an aggressive, fast proliferating CLL population makes it a potentially attractive therapeutic target - at least for high-risk patients with a major $CD38^+$ CLL population. Kuromanin, a potent CD38 inhibitor, was shown to block CLL homing to the spleen and lymph nodein a xenograft model [26]. These findings suggest that CD38 inhibitors could be used to shift the localization of CLL cells from their proliferation niches where they get support from the tumor microenvironment, into the blood stream where the cells are resting and more accessible to drugs. Similarly, CLL patients are currently recruited for a trial with CD38 antibodies (study identifier: NCT01084252, expected to be completed in the beginning of 2018).

CD38 has been used as a diagnostic marker in CLLfor over two decades, and its association with clinical parameters has been documented profoundly. In contrast, there is a considerable lack of information regarding its functions and its direct contribution to CLL pathogenesis. In light of a possible application of CD38-directed drugs, functional studies are of great importance in order to gain detailed information about the mechanisms by which CD38 contributes to the disease pathogenesis. Profound knowledge about cell-type specific regulation of CD38 expression and/or activity may allow a development of novel therapeutic strategies with the goal to specifically inhibit CD38 expression and/or function on malignant cells without affecting its physiological functions in healthy cells.

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