Unlocking the therapeutic potential of targeting MALT1 in B-cell acute lymphoblastic leukemia

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Despite recent advances in treatments, the development of drug resistance and relapse, particularly among adults remain major challenges in B-cell acute lymphoblastic leukemia (B-ALL). The survival rates of relapsed B-ALL in children and adults are low, with over 50% of patients succumbing to the disease.[1,2] Therefore, there is a pressing need to identify new therapeutic opportunities to improve clinical outcomes and reduce disease recurrence. In this issue of *Haematologica*, Safa *et al.* identified a non-canonical function of the para-caspase mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) which has the potential to be leveraged for therapeutic intervention in B-ALL.[3]

MALT1 is a protease and scaffold protein. Upon activation of the B-cell receptor (BCR), MALT1 and B-cell lymphoma-10 (BCL10) are recruited to caspase recruitment domain family member 11 (CARD11) to form the CARD11-BCL10-MALT1 (CBM) complex. Through proteolytic cleavage, MALT1 mediates the inactivation of inhibitors of NF-kB, including TNFAIP3/A20, and the activation of proteins that promote NF-kB activity, including BCL10, CYLD, RelB. Pre-clinical studies have demonstrated the efficacy and feasibility of inhibiting BCR-driven MALT1 activity in multiple B-cell malignancies. For instance, MALT1 is constitutively active in chronic lymphocytic leukemia, and treatment with an irreversible MALT1 protease inhibitor (MI-2) inhibited the proteolytic activity of MALT1 and consequently abrogated BCR and NF-κB signaling, inducing apoptosis in chronic lymphocytic leukemia cells.[4] Reflecting a role of MALT1 protease activity and subsequent NF-κB activation in the pathogenesis of activated B-cell-like diffuse large B-cell lymphoma (ABC-DLBCL), MALT1 inhibitors selectively killed ABC-DLBCL cells *in vitro* and induced tumor suppression of xeno-transplanted ABC-DLBCL i*n vivo*.[5] Additionally, MALT1 is constitutively activated in subsets of mantle cell lymphoma which depend on MALT1 activity for survival.[6] While *MALT1* expression was previously found to be upregulated in primary B-ALL cells,[7] its role in B-ALL biology and the therapeutic potential of targeting MALT1 in B-ALL have not been established.

In this issue of *Haematologica*, we read how Safa *et al.* sought to address the role of MALT1 in B-ALL and investigate the consequences of its inhibition. Using MI-2 and the MALT1 blocking peptide Z-VRPR-fmk, the authors show that MALT1 plays a crucial role in the survival of B-ALL cells, independent of their cell of origin or the presence or absence of the Philadelphia chromosome. Furthermore, treatment of MALT1-dependent B-ALL cells with MI-2 induced apoptosis, mainly in cycling cells. The authors also assessed the proteolytic activity of MALT1 by measuring its ability to cleave its substrates. Contrary to expectation, low or no MALT1 activity was detected in pro and pre B-ALL cell lines sensitive to MALT1 inhibition. Altogether, these findings revealed an unexpected, protease-independent role for MALT1 in pro and pre B-ALL.

To further elucidate the mechanistic contribution of MALT1 independent of BCR signaling in B-ALL, the authors performed gene expression profiling of B-ALL cells following treatment with MI-2 and identified a significant inhibitory effect on MYC-regulated gene signatures. Importantly, MI-2 treatment reduced protein levels of MYC in multiple MALT1-dependent B-ALL cell lines. Previous studies showed that phosphorylation of MYC at threonine-58 and serine-62 is required for its ubiquitination mediated by FBXW7, resulting in its proteasomal degradation.[8,9] Notably, Safa *et al.* demonstrated the upregulation of FBXW7 in B-ALL cells following MI-2 treatment. In addition, increases in FBXW7 expression were associated with concomitant MYC downregulation. Taken together, this study demonstrates that MYC stabilization through MALT1 is independent of its protease activity in pro and pre B-ALL and is likely achieved through a negative impact on FBXW7 (Figure 1).

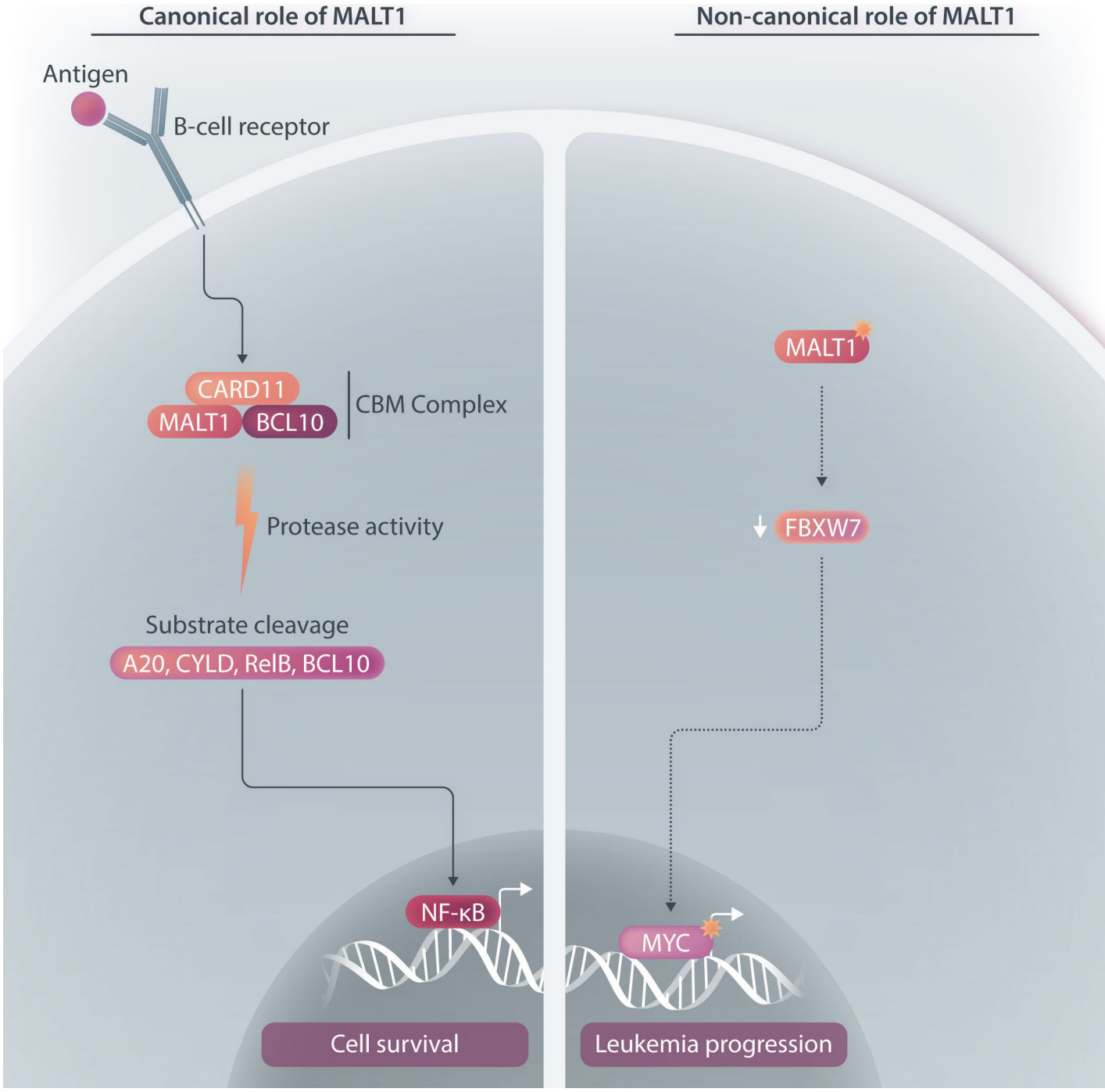

Figure 1. The canonical and non-canonical functions of MALT1 in B-cell malignancies. (Left) Canonical role of MALT1. Upon stimulation of the B-cell receptor (BCR), MALT1, a protease and scaffold protein, and BCL10 are recruited to CARD11 to form the CARD11-BCL10-MALT1 (CBM) complex. Through its protease activity, MALT1 mediates the inactivation of inhibitors of NF-κB, including A20, and the activation of positive regulators of NF-κB activity, including BCL10, CYLD, RelB. Consequently, the NF-κB signaling pathway is activated. BCR-driven MALT1 protease activity has been shown to be essential for the pathogenesis of chronic lymphocytic leukemia, activated B-cell-like diffuse large B-cell lymphoma, and subsets of mantle cell lymphoma. (Right) Non-canonical role of MALT1. Previous studies have shown that *MALT1* expression was upregulated in primary B-cell acute lymphoblastic leukemia (B-ALL) cells. Pro and pre B-ALL cells have low or undetectable MALT1 protease activity but depend on MALT1 survival. Mechanistic studies revealed that MALT1 mediates survival of B-ALL cells through stabilization of MYC, and this is likely dependent on the downregulation of FBXW7 which mediates MYC degradation.

In summary, this study revealed a distinct function of MALT1 in pro and pre B-ALL compared to B-cell malignancies arising from later stages of B-cell development. Specifically, it shows that MALT1 plays a non-canonical, protease-independent role in B-ALL biology. The shift from this non-canonical role of MALT1 in B-ALL to its canonical, protease-dependent role of MALT1 in mature B-cell malignancies suggests that activation of the protease activity of MALT1 requires a fully developed BCR. MALT1 inhibitors are currently under evaluation in several clinical trials (clinicaltrials.gov identifiers: NCT04876092, NCT03900598, NCT05144347) for treating non-Hodgkin's lymphoma. The insights gained from this study provide a strong rationale for pursuing MALT1 as a therapeutic target in B-ALL and supporting the clinical development of MALT1 inhibitors in treating this disease.

Disclosures

No conflicts of interest to disclose.

Contributions

Both authors contributed equally.

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