TIGIT: an immune checkpoint beyond T cells in chronic lymphocytic leukemia

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Malignant B cells from patients with chronic lymphocytic leukemia (CLL) are known for their expression of genes that are typically found in T cells, the most prominent one being *ZAP70*. In this issue of *Haematologica*, Arruga and colleagues add to the list of these genes another interesting molecule which is TIGIT: T-cell immunoreceptor with Ig and ITIM domains.[1] TIGIT is an inhibitory checkpoint receptor that is up-regulated by T cells and natural killer cells upon antigen recognition and limits their response. Like PD-1, it is associated with dysfunctional or exhausted T cells in cancer and is, therefore, currently being tested as a novel immunotherapy target in several clinical trials where dual blockade of PD-(L)1 and TIGIT shows promising early results in cancer patients.[2]

While TIGIT functions as an inhibitory receptor, it is often co-expressed with the activating co-stimulatory receptor CD226 that works in parallel to CD28.[3] CD226 contributes to the formation of the immune synapse through its interaction with its ligand CD155, which is widely expressed on tumor cells and antigen-presenting cells in the tumor microenvironment. Binding of CD226 to CD155 leads to T-cell activation, which is blocked by the presence of TIGIT via its interaction with CD155 (Figure 1A).[4] Recent studies showed that both PD-1 and TIGIT disrupt activation of the co-stimulatory receptor CD226 through distinct mechanisms.[5] This provides a mechanistic rationale for the dual blockade of PD-(L)1 and TIGIT to reinvigorate anti-tumor activity of $CD8^+$ T cells in cancer immunotherapy.

Besides its abundant expression in activated and exhausted T cells, TIGIT expression was observed in memory B cells where it is essential for effective immune regulation.[6] TIGIT-positive memory B cells also express additional inhibitory molecules, including IL-10, PD-L1, and CD39/CD73, molecules that are expressed also by CLL cells. In line with this, Arruga *et al.* show that TIGIT expression in CLL cells correlates with IL-10 expression. As CLL cells resemble activated, antigen-experienced B cells and share a transcriptional profile with memory B cells,[7] the expression of TIGIT might be part of this signature and, therefore, inherited from the cell-of-origin of CLL. Furthermore, TIGIT expression in memory B cells is induced via B-cell receptor (BCR) or CD40 engagement, and the latter results in the strongest TIGIT upregulation.[8] CD40 stimulation of B cells occurs in secondary lymphoid tissues via CD40-ligand expressed by follicular helper T cells (T_{FH}). Interestingly, TIGIT on B cells limits the proliferation of T_{FH}, likely acting as a negative feedback mechanism to prevent overshooting immune responses (Figure 1B). In agreement with this, mice lacking TIGIT expression in B cells develop severe experimental autoimmune encephalomyelitis, suggesting an important role for TIGIT-expressing B cells in immune tolerance.[9]

Survival and proliferation of CLL cells is driven by stimuli from the microenvironment, with BCR and CD40 stimulation being the most prominent signals.[10] $CD4^+$ T cells, including T_{FH} in lymph nodes expressing CD40-ligand, are important mediators of these stimuli. Considering that TIGIT expression in memory B cells is triggered by such signals, it is likely that the expression of TIGIT in CLL cells is also induced in the lymph node niche via the interaction with T_{FH} and other immune cells. In line with this, Arruga and colleagues observed that blockade of BCR signaling by the Bruton's tyrosine kinase inhibitor ibrutinib leads to a downregulation of TIGIT expression in CLL cells. They further showed that TIGIT expression in CLL cells was inversely correlated with BCR expression and, therefore, associated with non-responsiveness or anergy of CLL cells upon BCR stimulation. Accordingly, CLL cells from patients treated with ibrutinib showed an up-regulated surface IgM expression associated with a loss of TIGIT expression and recovery from anergy. Interestingly, high TIGIT expression in lymph node biopsies of CLL patients was associated with a lower proliferation rate of CLL cells, whereas CD226 expression was linked to greater proliferation, which is in line with the concept that TIGIT induces anergy of CLL cells. In support of this, Arruga *et al.* show that a high TIGIT to CD226 ratio was predictive for good prognosis in CLL,[1] whereas TIGIT expression was low or absent and CD226

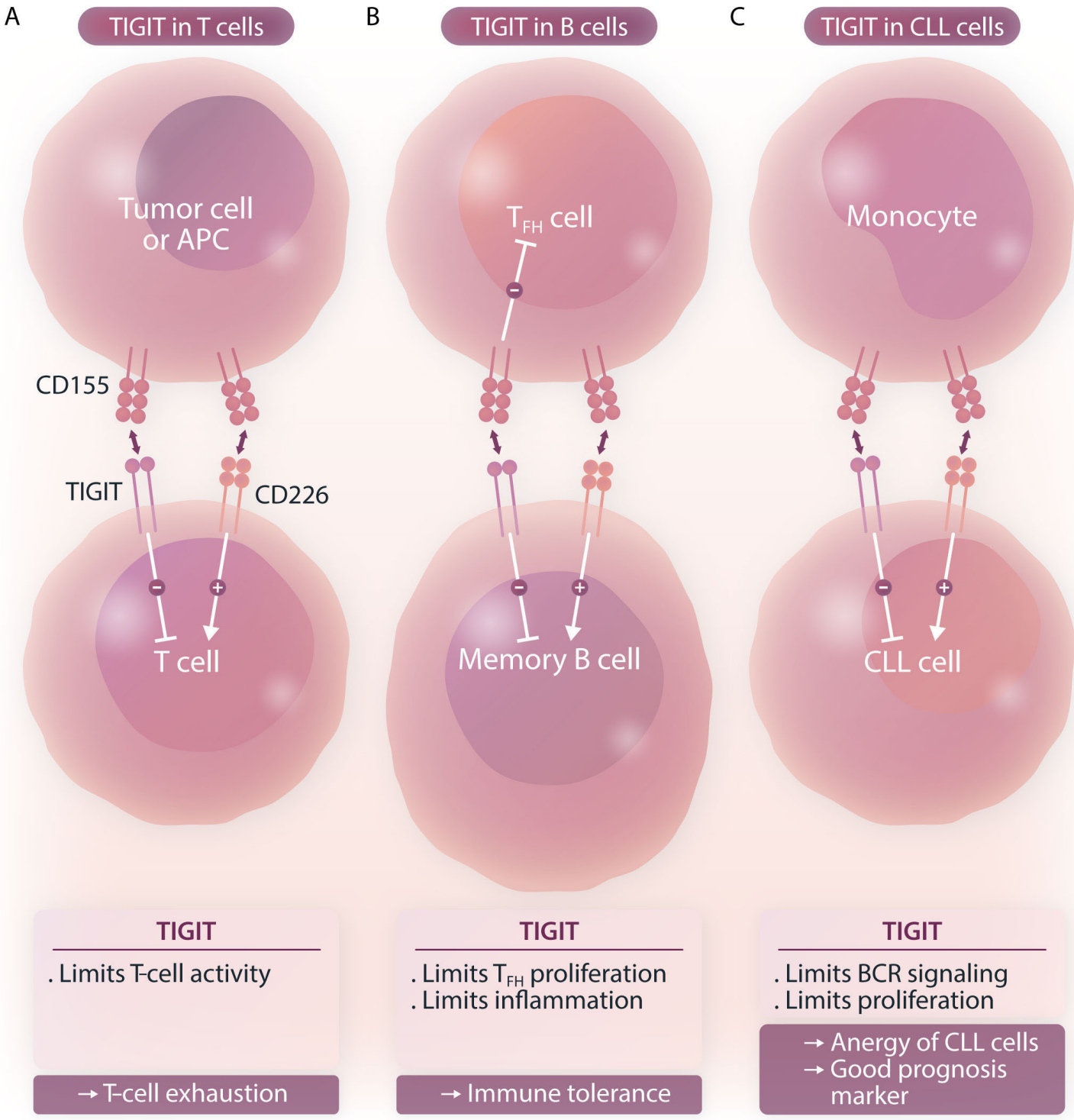

Figure 1. TIGIT has a modulatory role in T cells, memory B cells, and chronic lymphocytic leukemia cells. (A) The interaction of TIGIT expressed on T cells with CD155 expressed on antigen-presenting cells (APC) or tumor cells limits T-cell activity and thereby contributes to T-cell exhaustion. (B) TIGIT is also expressed on a subset of memory B cells where it limits proliferation of CD155-expressing follicular helper T cells (T_{FH}) and tissue inflammation. (C) In patients with chronic lymphocytic leukemia (CLL), expression of TIGIT is observed on malignant B cells and CD155 mainly on monocytes. Here, TIGIT expression is associated with B-cell anergy and better outcome of patients as it limits B-cell receptor (BCR) signaling and proliferation of CLL cells.

expression was high in Richter's syndrome, an aggressive transformation of CLL that is driven by highly proliferative B cells.[11] Altogether, this suggests that TIGIT in CLL cells is linked to anergy and a limited proliferation rate (Figure 1C). However, a causal relationship and the underlying mechanisms of this link remain unresolved.

As in T cells, TIGIT might limit B-cell activation and proliferation as part of an immune shutdown mechanism that is important to limit immune-mediated tissue damage. Exploring the role of TIGIT, and probably also other immune checkpoint molecules in B cells, will be important to better understand their potential role in B-cell transformation. The observations of Arruga *et al.* raise the question as to if and how the expression of TIGIT and other immune checkpoint molecules in malignant B cells influences treatment response to immune checkpoint inhibitors. While blockade of TIGIT might increase T-cell activity, and, therefore, immune control of CLL, it might further release anergy of CLL cells, and increase BCR and other signaling activity. This might lead to an increased proliferation rate and transformation to a more aggressive disease. It is hard to predict what the net outcome of such counteracting activities of TIGIT blockade will be, and future studies are necessary to improve our understanding of the role of immune checkpoints including TIGIT in B-cell malignancies.

Disclosures

No conflicts of interest to disclose.

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