A BAFFling *ménage à trois* in mantle cell lymphoma

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In this issue of *Haematologica*, Decombis *et al.* describe a novel tripartite cellular interaction in the tumor microenvironment surrounding mantle cell lymphoma (MCL).[1] MCL is an aggressive, mostly incurable B-cell malignancy and, like many (hematologic) cancers, heavily dependent on supportive interactions with the tumor microenvironment. Decombis *et al.* add a novel layer to this cancer's 'ecosystem' by studying interactions between three cell types; MCL, T cells and macrophages. Through a combination of techniques and nifty detective work they uncover several key players that act as messengers between these 'guilty' parties.

Based on expression datasets they pinpoint the relatively unknown cytokine interleukin (IL)-32β as a CD40-responsive gene in the MCL microenvironment. Immunohistochemistry made clear that IL-32β expression is enriched in MCL lymphoid tissue infiltrated by T cells, suggesting that it is the T cells that provide the CD40L. In turn, IL-32β polarizes macrophages *in vitro*, and induces them to secrete B-cell activating factor (BAFF) which is a survival factor for the MCL cells. The secretion of IL-32β as well as the BAFF-induced survival of MCL cells depends on alternative nuclear factor kappa B (NF-κB) signaling via NF-κB-inducing kinase (NIK), and can be blocked using inhibitory compounds (Figure 1). An interesting additional aspect is that the induction of the *IL32B* gene in MCL cells as opposed to normal B cells is correlated with epigenetic alterations.

Zooming out to the bigger picture, this type of 'subversive' interaction between multiple cell types, especially the programming of cancer-conducive monocytic cells, may be exemplary.

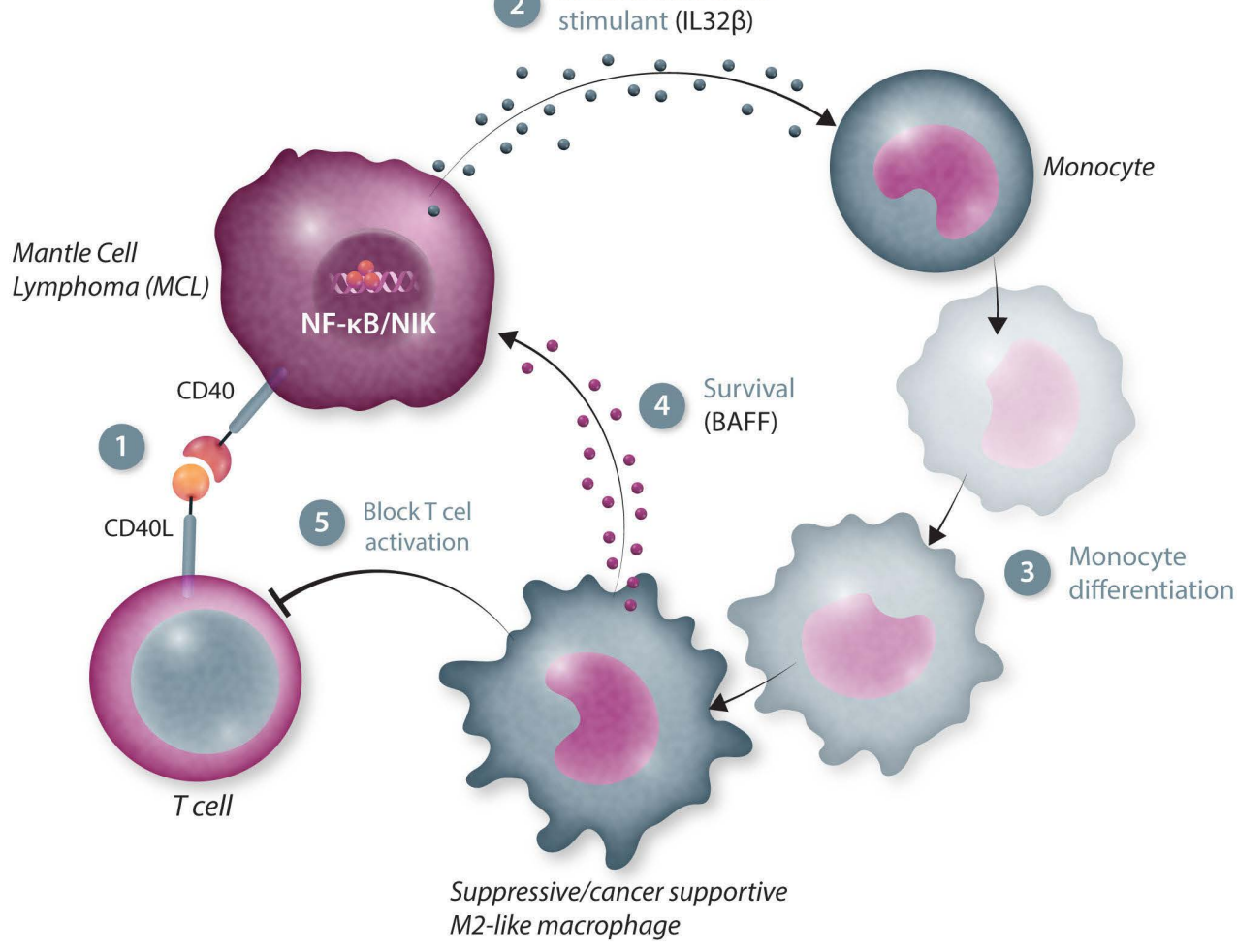

Figure 1. Cross-talk between malignant B cells, myeloid cells and T cells. Some general properties of the interactions between malignant B cells (in particular mantle cell lymphoma), myeloid cells and T cells can be established from the research by Decombis *et al.*[1] and work in the references: (1) T cells engage CD40 on malignant B cells; (2) malignant B cells secrete factors (or a factor) that attract/stimulate monocytes; (3) monocytes differentiate into an immune suppressive/cancer supportive M2-like phenotype; (4) the differentiated macrophages secrete BAFF, which is a survival factor for the malignant cells; and (5) M2-like macrophages suppress T-cell activation (not addressed in the work by Decombis *et al.* but inferred from a large body of work). NF-κB; nuclear factor kappa B; NIK: NF-κB-inducing kinase; BAFF: B-cell activating factor.

In solid cancers, the role of tumor-asociated macrophages is well established.[2] Our group has described a similar triad in chronic lymphocytic leukemia,[3,4] in which T cells trigger CD40 on chronic lymphocytic leukemia cells, which secrete CCL2 that attracts and converts monocytes to the suppressive M2 subtype. In the case of chronic lymphocytic leukemia, inhibitors that block chemokine (receptors) might thus be of therapeutic value. The work of Decombis *et al.* suggests that NIK inhibition,[5,6] or BAFF blockade,[7] both currently studied mainly in inflammatory diseases, might be attempted in MCL, as proposed for chronic lymphocytic leukemia.[8] Targeting the tumor microenvironment supply routes might also reduce the options of cancer cells to escape selective pressure by direct attack on intrinsic cellular targets.

The authors have previously described the role of so-called MΦ-MCL.[9] The IL32β-induced secretome in monocytes/macrophages is large and includes many cytokines, chemokines and tumor necrosis factor-family members, and yet only BAFF was able to induce the long-term (measured at 7 days) survival of MCL cells. How BAFF accomplishes this, apart from activating the alternative NF-κB pathway, remains unclear. Direct prosurvival factors such as the Bcl-2 family member Bcl-XL, also regulated via alternative NF-κB signaling,[10] or Mcl-1 were excluded, based on quantitative polymerase chain reaction analysis - although this may not be enough proof, as Mcl-1 is known to be regulated by various post-transcriptional mechanisms. This aspect is not without importance, as there are now highly specific inhibitory compounds called BH3 mimetics against these prosurvival Bcl-2 members, which could be applied to probe the contribution of their targets *in vitro*.[11]

Two main questions arise from this valuable work by Decombis *et al*., apart from the question of how to exploit the findings therapeutically. First, how does BAFF work in MCL, in view of its presumed triggering of the non-canonical NF-κB pathway? Perhaps the PI3K-Mcl-1 pathway is also involved, as reported for murine B-cell responses.[12] Second, the intriguing finding that IL32β is epigenetically dysregulated in MCL leads to the obvious next question; what could be the cause of this? Decombis *et al.* teach us that apart from intrinsic cancer rewiring, and although mechanistically difficult to address, the answer might come from 'affectionate' signals arriving from surrounding cells.

Disclosures

No conflicts of interest to disclose.

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