A BAFFling ménage à trois in mantle cell lymphoma

by Eric Eldering

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Title: A BAFFling ménage à trois in mantle cell lymphoma

Eric Eldering¹²

1. Dept of Experimental Immunology, Amsterdam University Medical Centers, University of Amsterdam, The Netherlands
2. Lymphoma and myeloma center Amsterdam (LYMMCARE), Cancer Center Amsterdam (CCA) and Amsterdam Infection and Immunity Institute (AIII), The Netherlands

In this issue of Haematologica, Decombis et al. describe a novel tripartite cellular interaction in the tumor microenvironment (TME) surrounding Mantle Cell Lymphoma (MCL)¹. MCL is an aggressive, mostly incurable B cell malignancy, and as many (haematological) cancers, heavily dependent on supportive interactions with the TME. Decombis et al. add a novel layer to this cancer 'ecosystem' by studying interactions between three cell types; MCL, T cells and macrophages. By 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 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 with T cells, suggesting it's the T cells that provide the CD40L. In turn, IL-32β polarizes macrophages in vitro, and induces them to secrete 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 NF-kB signaling via NIK, and can be blocked using inhibitory compounds. An interesting additional aspect is that the induction of the IL-32β 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. In solid cancers, the role of tumor associated macrophages (TAMs) is well established². Our group has described a similar triad in CLL³⁴, where T cells trigger CD40 on CLL cells, that secrete CCL2 that attracts and converts monocytes to the suppressive M2 subtype. In case of CLL,
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 CLL\(^8\). Targeting the TME 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 IL32\(\beta\)-induced secretome in monocytes/macrophages is large and includes many cytokines, chemokines and TNF-family members, yet only BAFF could induce the longterm (measured at 7 days) survival of MCL cells. How BAFF accomplishes this, apart from activating the alternative NF-κB pathway, remains unclear however. Direct pro-survival factors such as Bcl-2 family member Bcl-XL, regulated also via alternative NF-κB signaling\(^10\), or Mcl-1 were excluded, based on qPCR analysis - though 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, apart from the question how to exploit this therapeutically. First, how does BAFF work in MCL, in view of its presumed triggering of non-canonical NF-κB? Perhaps the PI3K-Mcl-1 pathway is also involved, as reported for murine B cell responses\(^12\). Second, the intriguing finding that IL32\(\beta\) is epigenetically dysregulated in MCL leads to the obvious next question; what could be the cause of this. Though mechanistically difficult to address, Decombis et al teach us that apart from intrinsic cancer rewiring, the answer might come from 'affectionate' signals arriving from surrounding cells.
References:


Some general properties between malignant B cells (in particular Mantle Cell Lymphoma), myeloid cells and T cells that can be established from Decombis et al and work in references.

1. T cells engage CD40 on malignant B cells
2. Malignant B cells secrete (a) factor(s) that attract/stimulate monocytes
3. Monocytes differentiate into immune suppressive/cancer supportive M2-like phenotype
4. The differentiated macrophages secrete BAFF which is a survival factor for the malignant cells
5. M2-like macrophages suppress T cell activation (not addressed in Decombis et al but inferred from a large body of work)