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POSTER ABSTRACTS

641.CHRONIC LYMPHOCYTIC LEUKEMIAS: BASIC AND TRANSLATIONAL

Skewing Towards Effector Memory Cells in CLL Is Associated with IGHV -Mutation Status and IFNγ and IL-4

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Memory T cells are a small, heterogenous population of T cells that remain following pathogen clearance and provide long-lasting protection. They are generally characterized as either central memory (T_{CM}) or effector memory (T_{EM}) based on differences in their surface and intracellular markers, anatomic location, effector function, and cytokine production. It is well known that patients with chronic lymphocytic leukemia (CLL) display differences in both T cell function and population compared to healthy individuals. Previous studies have shown that CLL patients skew towards the $CD4^+$ memory compartment and among these, a skewing toward T_{EM} is especially associated with unmutated IGHV and more progressive disease. Moreover, T_{EM} cells appear to protect CLL cells, possibly via IFNγ and IL-4 mediated pathways.

To understand this crosstalk between memory T cells and CLL B cells, we co-cultured FACS-purified T_{CM} ($CD3^+CD4^+CD19^-CCR7^+CD45RA^-CD45RO^+CD62L^+$) and T_{EM} ($CD3^+CD4^+CD19^-CCR7^-CD45RA^-CD45RO^+CD62L^-$) cells with CLL B cells and assessed shifts in the memory population as well as cytokines produced. Furthermore, as leukemic B-cell subpopulations differing in time since cell birth/division display distinct functional abilities to present antigen, we also investigated the effect of B-cell activation on this crosstalk.

FACS-purified peripheral blood memory T cells and CLL B cells were obtained from treatment-naïve patient samples and co-cultured for 7 days to determine if the presence of CLL B cells, either resting (B_{rest}) or pre-activated with CpG-ODN2006 and IL-15 (B_{act}), would alter the T-cell population distribution. In the presence of either B_{rest} or unmanipulated PBMC, overall, there were no significant changes in population of T_{EM} or T_{CM}. However, the distribution of T_{EM} with B_{rest} was bimodal and when grouped based on IGHV mutation status, we found significantly reduced counts of T_{EM} in co-cultures with M-CLL (14.50% T_{EM}, 11,019 cells) as compared to U-CLL (26.68% T_{EM}, 20,648 cells) based on relative percentages and absolute cell counts ($P<0.001$). Conversely, we saw an increase of T_{CM} in M-CLL B_{rest} co-cultures that correlated with decrease of T_{EM} ($P<0.01$). We then analyzed supernatants taken at the end of the 7-day co-culture period for IFNγ, IL-4, IL-17A, and IL-17F. We found elevated concentrations of IFNγ in co-cultures with both mutated-CLL and M- CLL, but significantly higher concentrations ($P<0.01$) were found with U-CLL (312pg/ml) than M-CLL (173pg/ml). Similarly, IL-4 was elevated but more so ($p<0.001$) in U-CLL (88pg/ml) than M-CLL (44pg/ml). Of note, IFNγ and IL-4 have been implicated in progression of CLL with literature suggesting their role in prolonging CLL B cell survival. IL-17A and IL-17F were not elevated above baseline and no differences were found. Consistent with literature, the relative fraction of T_{EM} in our patients negatively correlated with TTFT.

We then repeated the experiments with pre-activated CLL B cells. When B_{act} were co-cultured with memory T cells, we found significantly ($P<0.001$) elevated absolute number of T_{EM} and T_{CM}. This indicated heightened proliferation of the memory population, with a greater degree of increase in the T_{EM} population, resulting in a skewing toward T_{EM}. Subsequent experiments found that co-culture with B_{act} led to significantly elevated IL-4 and IFNγ levels. Interestingly, the effects mediated by B_{act}, on both memory cell proliferation and cytokine production were markedly greater than with B_{rest}. Moreover, unlike B_{rest}, the effects of B_{act} did not depend on IGHV mutation status but rather showed uniform increase in both T_{EM} proliferation and IFNγ and IL-4 levels.

Lastly, we analyzed the survival of CLL B cells at the end of the co-cultures. Overall, the addition of memory T cells significantly ($P<0.001$) enhanced survival of CLL B cells and this effect was more prominent in B_{act} (U-CLL: 51.1%, M-CLL: 40.3% survival) than B_{rest} (U-CLL: 34.8%, M-CLL: 23.5% survival).

Together, our *in vitro* results suggest crosstalk between memory T cells and CLL B cells in which CLL B cells, especially U-CLL, promote the expansion of T_{EM} which is associated with shorter TTFT and more progressive disease. T_{EM}, in turn, promote the survival of CLL B cells possibly through increased production of IFNγ and IL-4.

Disclosures No relevant conflicts of interest to declare.

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