

Studies on therapeutic vaccination and immune evasion in chronic lymphocytic leukemia

Katarina Junevik

Department of Clinical Chemistry and Transfusion Medicine, Institute of Biomedicine
Sahlgrenska Academy at University of Gothenburg
Göteborg, Sweden

Chronic lymphocytic leukemia (CLL) is characterized by an accumulation of malignant B cells in blood, bone marrow and secondary lymphoid organs and is considered incurable. Our main aims were to investigate different aspects of the cellular immunology in order to develop immunotherapeutic strategies. First, the function of cytotoxic T cells (CTL) in CLL seems to be negatively related to disease stage. In **paper I**, we investigated if natural killer (NK) cell inhibitory receptors on CTL were differentially expressed and found an increased expression of these receptors on CTL in patients with advanced disease. This dysregulation could potentially contribute to immune evasion and disease progression. In **paper IV**, a co-operative study of global methylation profiles of stereotyped subsets in CLL, it was found that genes involved in immune response had higher methylation levels in the poor-prognostic subset #1 than the good-prognostic subset #4. High methylation status of those genes correlated with low expression of CD80 and CD86, two co-stimulatory receptors important for T cell immune response. We performed co-culture experiments, where CLL cell lines expressing CD80/86 induced T cell activation. Thus, one explanation for the poor prognosis in subset #1, could be that low CD80/86 expression on CLL cells leads to immune evasion.

It is believed that CLL could be a good candidate for dendritic cell (DC) anti-tumor vaccination. Yet, in earlier clinic trials there has been minimal response. Optimal DC activation requires specific cytokine production and expression of co-stimulatory receptors. Apart from CD80/86, another prominent co-stimulatory receptor is CD70, which plays an important role by promoting T cell survival and effector functions. In **paper II and III**, we studied two types of DCs matured with different cocktails, the standard PGE₂DC and the alternative α DC1, to investigate if effective DCs could be generated from CLL patients. We found that α DC1s produced a NK, NKT and CTL-attracting cytokine profile, which may favor priming of CTL. Also, α DC1s expressed CD70 in a time-dependent manner and their IL-12p70 production, with a subsequent desirable T helper cell type 1 response, appeared to be CD70-associated. Together, these data imply that the α DC1-cocktail induce a more efficient DC activation and function.

In conclusion, our findings describe new mechanisms of immune evasion in CLL and also give further support to the idea that an α DC1-based vaccine has higher immunotherapeutic potential in CLL patients.

Keywords: CLL, α DC1, vaccine, CTL, inhibitory receptors, CD70

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Katarina Junevik

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- I. **Junevik K**, Werlenius O, Hasselblom S, Jacobsson S, Nilsson-Ehle H, Andersson PO. The expression of NK cell inhibitory receptors on cytotoxic T cells in B-cell chronic lymphocytic leukaemia (B-CLL)
Annals of Hematology 2007;86(2):89-94
- II. Gustafsson K, **Junevik K**, Werlenius O, Holmgren S, Karlsson-Parra A, Andersson PO. Tumour-loaded α -type 1-polarized dendritic cells from patients with chronic lymphocytic leukaemia produce a superior NK-, NKT- and CD8+ T cell-attracting chemokine profile.
Scandinavian Journal of Immunology 2011;74(3):318-26
- III. **Junevik K**, Werlenius O, Fogelstrand L, Karlsson-Parra A and Andersson PO. High functional CD70 expression on α -type 1-polarized dendritic cells from patients with chronic lymphocytic leukemia.
In manuscript
- IV. Kanduri M, Marincevic M, Halldórsdóttir AM, Mansouri L, **Junevik K**, Ntoufa S, Kultima HG, Isaksson A, Juliusson G, Andersson PO, Ehrencrona H, Stamatopoulos K, Rosenquist R. Distinct transcriptional control in major immunogenetic subsets of chronic lymphocytic leukemia exhibiting subset-biased global DNA methylation profiles.
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