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# IL-2/CD25 axis mediates cellular networks promoting the growth of CD25$^+$ acute myeloid leukemia cells

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ABSTRACT

Although the expression of interleukin-2 receptor α-chain (IL-2Rα, CD25) has been provided prognostic significance independent of known biomarkers in acute myeloid leukemia (AML), the functional role of CD25 molecule remains unknown. Since IL-2 can be trans-presented via CD25 to another cell, CD25$^+$AML cells may deliver environmental IL-2 to surrounding immune cells to produce myeloid growth factors for their proliferation. We hypothesize that cellular interactions via IL-2/CD25 axis in the bone marrow microenvironment contributes to the growth advantage of these AML cells and affects the clinical outcome of those AML patients.

Cytokines exert significant effects on the proliferation, differentiation and apoptosis of leukemia cells. As cytokines bind to their respective receptors to send their signals, the dysregulation of the receptor expression tends to affect the biological activities of leukemia cells and clinical behavior of those patients. Although interleukin-2 receptor α-chain (IL-2Rα, CD25) is generally expressed on activated T-cells and on regulatory T-cells, it is also aberrantly expressed on leukemic cells from a part of acute myeloid leukemia (AML), and we and others have demonstrated its prognostic relevance independent of both cytogenetics and molecular genetics in AML [1,2]. However, little is known about the biological function of CD25 in AML and the pathological basis of the inferior outcome of CD25$^+$AML. We speculate that IL-2/CD25 axis can build certain cellular networks in the bone marrow (BM) microenvironment and this situation promotes the proliferation of these AML cells.

The IL-2R consists of three subunits: CD25; β-chain; and common γ-chain (γc), which is also a receptor for IL-4, IL-7, IL-9, IL-15, and IL-21. Generally, CD25 catches free IL-2 and delivers it to dimeric β/γc of IL-2R, resulting in the cytoplasmic signaling. In AML case, the expression pattern of individual chain of IL-2R is peculiar: any case displays γc, whereas most cases lack β chain, and only 10–20 % cases express CD25 [1,2]. It has been reported that CD25$^+$AML cells do not respond to IL-2 because of the lack of functional IL-2R [1,2].

On the other hand, the proliferation of many AML cells requires myeloid growth factors, or colony-stimulating factors (CSFs) such as granulocyte-macrophage CSF (GM-CSF), G-CSF, and M-CSF. Following IL-2 mediated stimulation, these CSFs can be produced by immune cells including T-cells, natural killer (NK) cells, and monocytes/macrophages [3,4], all of which reside in a substantial number in the BM. Moreover, the BM fibroblasts do not produce GM-CSF in response to IL-2, but produce it by stimulation with tumor necrosis factor derived from IL-2 activated T-cells [3]. CD25/IL-2 complex usually presents in *cis* IL-2 to the dimeric β/γc of IL-2R on the same cell surface, but the structural topography of this complex can be permissive for one cell to trans-present IL-2 to the dimeric β/γc of IL-2R on another cell [5]. For example, CD25$^+$ dendritic cells (DCs) were observed to be able to capture IL-2 for its trans-presentation to T-cells for activation [5]. Although IL-2 trans-presentation may induce cytotoxic T-cells and/or NK-cells, and activate regulatory T-cells, predominant growth patterns of CD25$^+$AML cells favor our hypothesis. Further verifications are required *in-vivo* studies.

As the BM is a part of the lymphocyte recirculation network and is a priming site for T-cell responses [6], there are many immune cells bearing the dimeric β/γc of IL-2R, and substantial amount of IL-2 that is released as a result of an immune response in the BM. Such environmental IL-2 is readily taken up by heparin sulfate glycosaminoglycan (HSG), a component of extracellular matrix, in blood vessels [7]. Since vascular density is known to be increased in the BM in AML [8], IL-2 seems to be accumulated on the vascular systems in the BM. This HSG-bound IL-2 on vascular endothelium can be cleaved by endogenous heparanase derived from various immune cells [9]. Notably, as

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heparanase activity was also detected in AML cells [10], HSG-bound IL-2 located in the vicinity of $CD25^+$AML cells could be released by their heparanase, and be entrapped by CD25 on these AML cells. Consequently, such IL-2 may be presented in trans to surrounding immune cells with the dimeric β/γc of IL-2R, leading to their activation to produce CSFs.

Interestingly, $CD25^+$AML cells, compared to the other AML cells, more frequently express adhesion related molecules such as CD4, CD11b, CD11c, and HLA-DR., which are DC like phenotypes suitable for cell-to-cell interaction [2], indicating that those AML cells are likely to have symbiotic relationships with various cells around them. In $CD25^+$AML, as serum soluble IL-2R (sIL-2R) is increased [2], such sIL-2R combined with IL-2 might also contribute to the IL-2 trans-presentation in the BM microenvironment. Therefore, IL-2/CD25 axis could mediate cellular networks with adjacent immune cells, and this situation may facilitate the proliferation of $CD25^+$AML cells.

Although the mechanisms underlying the disease aggressiveness of $CD25^+$AML appears rather complicated, our speculation may explain at least in part the proliferation property of this type of AML associated with adverse prognosis. There are no studies as far as we know that investigate the critical roles of CD25/IL-2 axis in the BM microenvironment in $CD25^+$AML. Our hypothesis will stimulate further research and may pave the way to develop effective treatment strategies for this vicious disease.

## CRediT authorship contribution statement

**Kazunori Nakase:** Writing – original draft. **Kenkichi Kita:** Funding acquisition, Supervision.

## Declaration of competing interest

The authors have declared that no competing interests exist.

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