

## Interleukin-2 Receptor $\alpha$ -chain (CD25) Expression in Acute Myeloid Leukemia

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### Abstract

Recent studies have shown that cytokine/cytokine receptor systems affect leukemic cell biology and clinical behavior of leukemic patients. Among various cytokine receptors, only interleukin-2 receptor  $\alpha$ -chain (IL-2R $\alpha$ , CD25) expression predicts a poor prognosis of patients ( $\leq 60$  years old) with acute myeloid leukemia (AML). Even in prognostic analyses including unfavorable surface markers and cytogenetics, IL-2R $\alpha$  is recognized to be an independent adverse indicator in such patients. Assessment of the presence of IL-2R $\alpha$  should be essential to make therapeutic risk classification of AML patients in a future. However, as the lack of IL-2 responsiveness is observed in AML cells, further investigations are required to clarify the mechanism why IL-2R $\alpha$ (+) AML patients have a dismal clinical outcome.

**Keywords:** Interleukin-2 receptor  $\alpha$ -chain; CD25; Acute myeloid leukemia

### Introduction

Numerous cytokines, including colony stimulating factors (CSF) and interleukins (IL), affect the biological properties of acute leukemia cells [1]. As cytokines bind to their respective receptors on the cell surface to exert their effect [2], aberrant or excessive expression of cytokine receptors may be closely associated with the pathological status of patients with acute leukemia. However, the expression of various cytokine receptors on acute myeloid leukemia (AML) cells has not yet been extensively evaluated, and the detailed clinical significance of their expression remains to be determined. Investigations into cytokine/cytokine receptor system in AML might provide us clues lead to develop a new therapeutic approach.

### Prognostic significance of IL-2R $\alpha$ expression in AML

Recently, we published a paper regarding prognostic relevance of cytokine receptor expression in AML [3]. Among the cytokine receptors we examined by flow cytometric analysis: interleukin-2 receptor  $\alpha$ -chain (IL-2R $\alpha$ , also known as CD25), IL-2R $\beta$ , IL-3R $\alpha$ , IL-4R $\alpha$ , IL-5R $\alpha$ , IL-6R $\alpha$ , IL-7R $\alpha$ , the common  $\beta$ -chain ( $\beta$ c),  $\gamma$ c, granulocyte-macrophage (GM)-CSFR $\alpha$ , G-CSFR, c-fms, c-mpl, c-kit, FLT3, and GP130, only IL-2R $\alpha$  expression was significantly associated with a shorter overall survival in younger adult patients ( $\leq 60$  years old) with AML. These findings were not observed in older patients  $>60$  years old. Although several reports from western countries have also shown that the expression of IL-2R $\alpha$  correlates with adverse outcome in patients with AML [4-6], this is the first report describing that IL-2R $\alpha$  is the strongest prognostic indicator among those cytokine receptors. Elevated levels of IL-3R $\alpha$  correlated with a poor response to conventional chemotherapy, as previously described [7], but, its high expression did not affect the overall survival in patients with AML.

In addition, the prognosis of IL-2R $\alpha$ (+) AML was poorer than AMLs with known other unfavorable factors such as a white blood cell count  $\geq 3 \times 10^4/\mu\text{l}$ , and the expression of CD4 [8], CD7 [9], CD11b [10], and CD56 [11]. The cytogenetic risk classification currently provides the most powerful prognostic information in AML [12]. This method is used to stratify AML patients into three discrete categories such as the favorable-, intermediate-, and adverse-prognosis groups. However, more than half of AML patients are allocated to the intermediate-risk category, and this group is considered to be biologically heterogeneous and prognostically further distinguishable. By incorporating the IL-2R $\alpha$  status in this risk classification, a significantly high-risk cohort equivalent to the adverse-risk category was sorted out from the subset with intermediate-risk cytogenetics [3]. These Japanese data are consistent with that demonstrated in western studies [4,5], suggesting no ethnic difference in the prognostic impact of IL-2R $\alpha$  expression. Therefore, we recommend that IL-2R $\alpha$  assessment, which is cost-effective and less time-consuming, should be incorporated into current prognostic schema in order to improve AML prognostication.

### Why is the prognosis of IL-2R $\alpha$ (+) AML so poor?

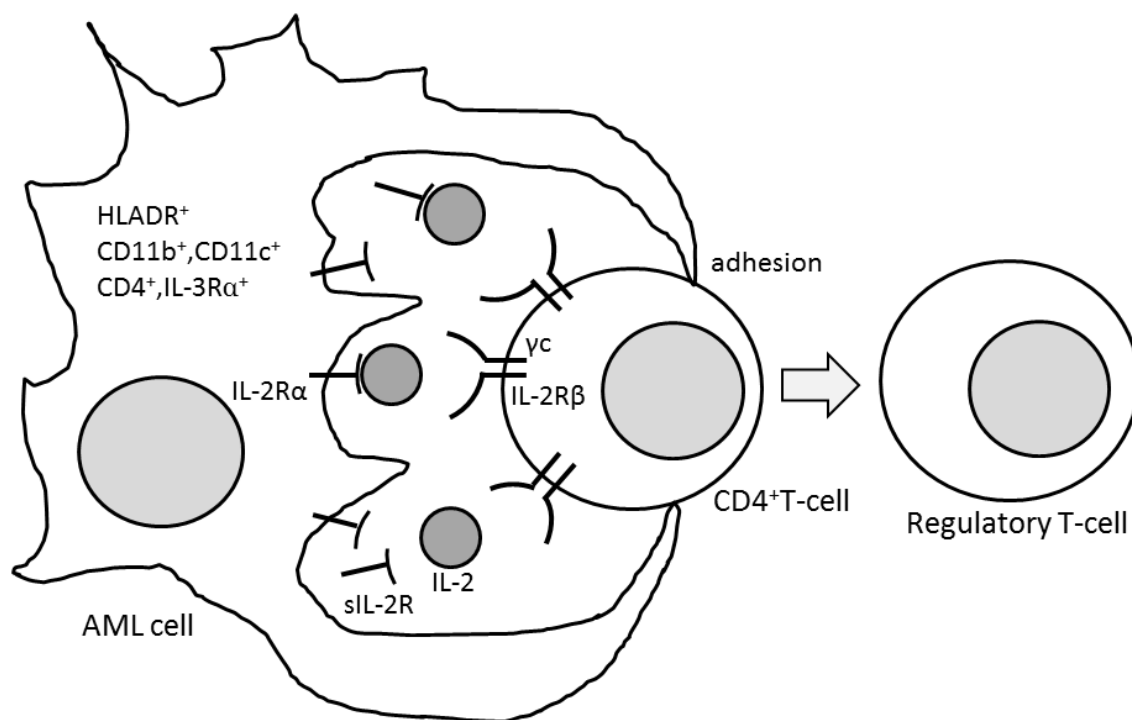
Of note is that leukemia cells from patients with IL-2R $\alpha$ (+) AML did not respond to IL-2 regardless of the expression levels of IL-2R $\alpha$  [1]. The IL-2R consists of IL-2R $\alpha$ , IL-2R $\beta$ , and  $\gamma$ c, and the IL-2R $\beta$ / $\gamma$ c complex is responsible for IL-2 signal transduction. Lack of IL-2 responsiveness of IL-2R $\alpha$ (+) AML cells seemed to be due to the extremely low expression level of IL-2R $\beta$ , as reported previously [13]. Thus, IL-2R $\alpha$  may have a broader function other than originally proposed as one of growth factor receptors [14].

Among three chains of IL-2R, the IL-2R $\alpha$  on the cell surface is cleaved by proteolytic processing, and this cleaved chain is detected as serum soluble IL-2R $\alpha$  (sIL-2R) [15]. Several reports have shown a marked elevation of serum sIL-2R in patients with IL-2R $\alpha$ (+) AML [16,17]. IL-2R $\alpha$  on the cell surface of leukemic cells seems to be a

considerable portion of the source of sIL-2R [17]. Like cell surface IL-2R $\alpha$ , as sIL-2R can also bind to IL-2 [18], this free receptor competes with IL-2R on CD8(+) T-cells and natural killer cells for IL-2. For that reason, IL-2 deprivation by sIL-2R could suppress host antitumor immunity in AML [19].

On the other hand, Yang et al. has reported an intriguing analysis regarding the mechanism by which sIL-2R may contribute to a reduced survival in follicular B-cell lymphoma [20]. They described that sIL-2R/IL-2 complex facilitates IL-2 mediated STAT5 phosphorylation, thereby up regulating Foxp3 expression in CD4(+) T-cells. Such cells are shown to differentiate toward to regulatory T-cells and to display increased inhibition of CD8(+) T-cell function. Even in IL-2R $\alpha$ (+) AML, a similar situation, which could lead to anti-leukemia immune escape status, may be generated in the bone marrow (BM) microenvironment. In relation to the action of STAT5, however, some researchers have suggested that its activation is not sufficient to induce Foxp3 expression [21]. Wuest et al. have demonstrated that Foxp3 is induced by inhibition of histone methyltransferase G9A and reduction of its mediated heterochromatin H3K9me2 [22]. Hence, IL-2 signaling via sIL2R/IL-2 complex might be also associated with the regulation of G9A expression. Additional studies are needed to clarify this issue.

In our study, a close relationship existed between the expression of IL-2R $\alpha$  and that of adhesion related molecules such as CD4, CD11b, CD11c, and HLA-DR, as well as IL-3R $\alpha$  [3]. As the presence of IL-3R $\alpha$  shows a typical feature of leukemia stem cells (LSCs), IL-2R $\alpha$  appears to be expressed at an immature differentiation level of AML, in agreement with previous observations [5,23]. In addition, we also focus into their phenotypes indicating dendritic cell like characters suitable for cell-adhesion and/or cell-communication. This finding allows us to speculate that IL-2R $\alpha$  may serve a certain role in the control of cell-to-cell interaction [14]. IL-15R $\alpha$  forms a high-affinity receptor with IL-2R $\beta/\gamma$ c, and IL-15R $\alpha$  present IL-15 in an intercellular fashion to the IL-2R $\beta/\gamma$ c expressed on neighboring cells [24]. Similarly, it is reported that IL-2R $\alpha$  on one cell can present IL-2 in trans to IL-2R $\beta/\gamma$ c expressed on another cell to augment IL-2 signaling [25,26]. Thus, IL-2R $\alpha$  on the cell surface of AML cells coupled to the increased sIL-2R bind to IL-2, and their complex may activate surrounding other cells expressing IL-2R $\beta/\gamma$ c such as CD4(+) T-cells, and tumor associated macrophages [27] to promote a tumor-friendly BM microenvironment (Figure 1). This environmental situation could support the survival of IL-2R $\alpha$ (+) AML cells. So, minimal residual disease (MRD) after chemotherapy, which leads to disease relapse [28],



**Figure 1:** Image of cell-to-cell interaction between AML cell expressing IL-2R $\alpha$  and surrounding CD4(+) T-cell. IL-2R $\alpha$  on the cell surface of AML cell coupled to the increased sIL-2R may bind IL-2, and sIL-2R/IL-2 complex activates surrounding CD4(+) T-cell, which differentiates toward to regulatory T-cell in the bone marrow microenvironment. AML: Acute Myeloid Leukemia; IL-2R $\alpha$ : Interleukin-2 Receptor  $\alpha$ -chain;  $\gamma$ c: The common  $\gamma$ -chain.

may be ascribed to these survived IL-2R $\alpha$ (+) cells. In this context, it is quite interesting that the level of MRD has been demonstrated to correlate with the expression of IL-2R $\alpha$  on leukemia cells [4] and the frequency of LSCs [29]. Future investigations are expected to validate our hypothesis regarding some critical role of IL-2R $\alpha$  in the cell-to-cell interaction in the BM microenvironment of AML.

## Final Remarks

Among various cytokine receptors, only IL-2R $\alpha$  had prognostic value which provides an additional marker for better risk stratification of AML patients  $\leq$  60 years old. IL-2R $\alpha$  testing should be added into current AML prognostication system. As therapeutic aspect, although 60-80% of AML patients can achieve complete remission after induction chemotherapy, overall survival at 5 years still remains to be as low as approximately 20-30% [30,31]. This eventually poor outcome is due to the difficulty of eradicating leukemia cells and preventing disease relapse. At present, even allogeneic hematopoietic stem cell transplantation shows a limited effect on IL-2R $\alpha$ (+) AML [32]. Accordingly, establishment of newer therapeutic strategies targeting IL-2R $\alpha$  are strongly expected to overcome this type of AML by possibly eliminating MRD and/or LSCs.

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