Journal of Clinical & Cellular Immunology

Nakase et al., J Clin Cell Immunol 2016, 7:4
DOI: 10.4172/2155-9899.1000444

Commentary Open Access

Interleukin-2 Receptor α-chain (CD25) Expression in Acute Myeloid Leukemia

Kazunori Nakase[1,3*], **Kenkichi Kita**[2] **and Naoyuki Katayama**[3]

[1]*Cancer Center, Mie University Hospital, Tsu, Japan*

[2]*Department of Internal Medicine, Japan Baptist Hospital, Kyoto, Japan*

[3]*Department of Hematology and Oncology, Mie University Graduate School of Medicine, Tsu, Japan*

[*]**Corresponding author:** Kazunori Nakase, Cancer Center, Mie University Hospital, 2-174 Edobashi, Tsu, Mie 514-8507, Japan, Tel: 81592315296; Fax: 81592315348; E-mail: k2nakase@clin.medic.mie-u.ac.jp

Received date: May 26, 2016; **Accepted date:** August 05, 2016; **Published date:** August 09, 2016

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 α-chain (IL-2Rα, CD25) expression predicts a poor prognosis of patients (≤ 60 years old) with acute myeloid leukemia (AML). Even in prognostic analyses including unfavorable surface markers and cytogenetics, IL-2Rα is recognized to be an independent adverse indicator in such patients. Assessment of the presence of IL-2Rα 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-2Rα(+) AML patients have a dismal clinical outcome.

Keywords: Interleukin-2 receptor α-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-2Rα 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 α-chain (IL-2Rα, also known as CD25), IL-2Rβ, IL-3Rα, IL-4Rα, IL-5Rα, IL-6Rα, IL-7Rα, the common β-chain (βc), γc, granulocyte-macrophage (GM)-CSFRα, G-CSFR, c-fms, c-mpl, c-kit, FLT3, and GP130, only IL-2Rα expression was significantly associated with a shorter overall survival in younger adult patients (≤ 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-2Rα correlates with adverse outcome in patients with AML [4-6], this is the first report describing that IL-2Rα is the strongest prognostic indicator among those cytokine receptors. Elevated levels of IL-3Rα 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-2Rα(+) AML was poorer than AMLs with known other unfavorable factors such as a white blood cell count ≥ 3×10^4/μl, 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-2Rα 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-2Rα expression. Therefore, we recommend that IL-2Rα 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-2Rα(+) AML so poor?

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

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

considerable portion of the source of sIL-2R [17]. Like cell surface IL-2Rα, 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-2Rα(+) 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-2Rα and that of adhesion related molecules such as CD4, CD11b, CD11c, and HLA-DR, as well as IL-3Rα [3]. As the presence of IL-3Rα shows a typical feature of leukemia stem cells (LSCs), IL-2Rα 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-2Rα may serve a certain role in the control of cell-to-cell interaction [14]. IL-15Rα forms a high-affinity receptor with IL-2Rβ/γc, and IL-15Rα present IL-15 in an intercellular fashion to the IL-2Rβ/γc expressed on neighboring cells [24]. Similarly, it is reported that IL-2Rα on one cell can present IL-2 in trans to IL-2Rβ/γc expressed on another cell to augment IL-2 signaling [25,26]. Thus, IL-2Rα 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-2Rβ/γc 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-2Rα(+) AML cells. So, minimal residual disease (MRD) after chemotherapy, which leads to disease relapse [28],

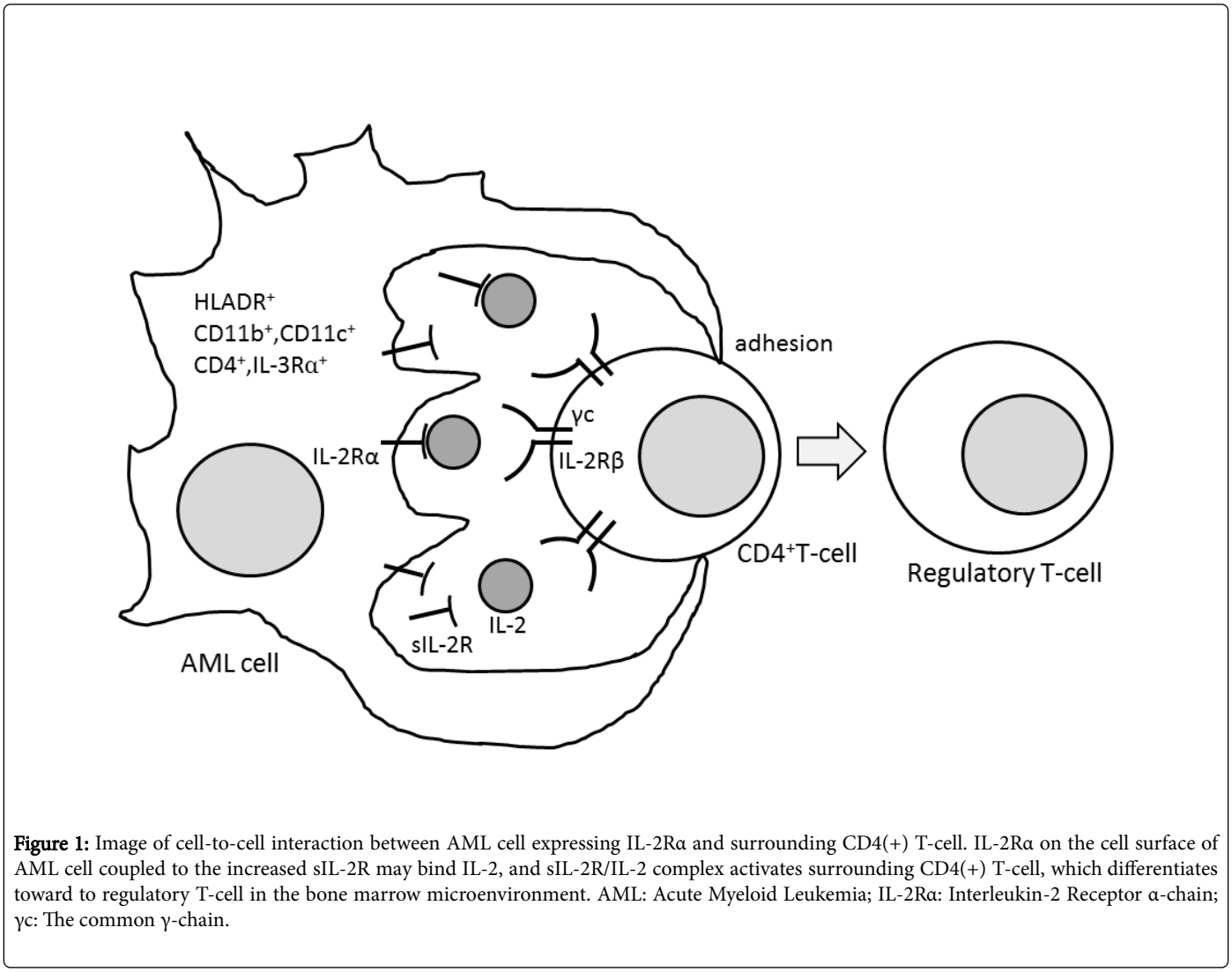

Figure 1: Image of cell-to-cell interaction between AML cell expressing IL-2Rα and surrounding CD4(+) T-cell. IL-2Rα on the cell surface of AML cell coupled to the increased sIL-2R may bind IL-2, and sIL-2R/IL-2 complex activates surrounding CD4(+) T-cell, which differentiates toward to regulatory T-cell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

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

Final Remarks

Among various cytokine receptors, only IL-2Rα had prognostic value which provides an additional marker for better risk stratification of AML patients ≤ 60 years old. IL-2Rα 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-2Rα(+) AML [32]. Accordingly, establishment of newer therapeutic strategies targeting IL-2Rα are strongly expected to overcome this type of AML by possibly eliminating MRD and/or LSCs.

References

1. Löwenberg B, Touw IP (1993) Hematopoietic growth factors and their receptors in acute leukemia. Blood 81: 281-292.
2. Lotem J, Sachs L (2002) Cytokine control of developmental programs in normal hematopoiesis and leukemia. Oncogene 21: 3284-3294.
3. Nakase K, Kita K, Kyo T, Ueda T, Tanaka I, et al. (2015) Prognostic relevance of cytokine receptor expression in acute myeloid leukemia: Interleukin-2 receptor a-chain (CD25) expression predicts a poor prognosis. PLoS One 10:e0128998.
4. Terwijn M, Feller N, van Rhenen A, Kelder A, Westra G, et al. (2009) Interleukin-2 receptor alpha-chain (CD25) expression on leukaemic blasts is predictive for outcome and level of residual disease in AML. Eur J Cancer 45: 1692-1699.
5. Gonen Mithat, Sun Z, Figueroa ME, Patel JP, Abdel-Wahab O, et al. (2012) CD25 expression status improves prognostic risk classification in AML independent of established biomarkers: ECOG phase 3 trial, E1900. Blood 120: 2297-2306.
6. Cerny J, Yu H, Ramanathan M, Raffel GD, Walsh WV, et al. (2013) Expression of CD25 independently predics early treatment failure of acute myeloid leukaemia (AML). Br J Haematol 160: 262-266.
7. Testa U, Riccioni R, Militi S, Coccia E, Stellacci E, et al. (2002) Elevated expression of IL-3Ra in acute myelogenous leukemia is associated with enhanced blast proliferation, increased cellularity, and prognosis. Blood 100: 2980-2988.
8. Miwa H, Mizutani M, Mahmud N, Yamaguchi M, Takahashi T, et al. (1998) Biphasic expression of CD4 in acute myelocytic leukemia (AML) cells: AML of monocyte origin and hematopoietic precursor cell origin. Leukemia 12: 44-51.
9. Kita K, Miwa H, Nakase K, Kawakami K, Kobayashi T, et al. (1993) Clinical importance of CD7 expression in acute myelocytic leukemia. The Japan Cooperative Group of Leukemia/Lymphoma. Blood 81: 2399-2405.
10. Bradstock K, Matthews J, Benson E, Page F, Bishop J (1994) Prognostic value of immunophenotyping in acute myeloid leukemia. Australian Leukaemia Study Group. Blood 84: 1220-1225.
11. Djunic I, Virijevic M, Djurasinovic V, Novkovic A, Colovic N, et al. (2012) Prognostic significance of CD56 antigen expression in patients with acute myeloid leukemia. Med Oncol 29: 2077-2082.
12. Grimwade D, Hillis RK, Moorman AV, Walker H, Chatters S, et al. (2010) Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. Blood 116: 354-365.
13. Hoshino S, Oshimi K, Tsudo M, Miyasaka M, Teramura M, et al. (1990) Flow cytometric analysis of expression of interleukin-2 receptor ß chain (p70-75) on various leukemic cells. Blood 76: 767-774.
14. Nakase K, Kita K, Otsuji A, Anazawa H, Shirakawa S, et al. (1993) Interleukin-2 receptor alpha chain on acute myelocytic leukemia cells is involved in cell-to-cell interactions. Leuk Res 17: 17-21.
15. Rubin LA, Galli F, Greene WC, Nelson DL, Jay G (1990) The molecular basis for the generation of the human soluble interleukin-2 receptor. Cytokine 2: 330-336.
16. Nakase K, Kita K, Otsuji A, Anazawa H, Hoshino K, et al. (1992) Diagnostic and clinical importance of interleukin-2 receptor alpha chain expression on non-T-cell acute leukaemia cells. Br J Haematol 80: 317-326.
17. Nakase K, Kita K, Kyo T, Tsuji K, Katayama N (2012) High serum levels of soluble interleukin-2 receptor in acute myeloid leukemia: Correlation with poor prognosis and CD4 expression on blast cells. Cancer Epidemiol 36: e306-309.
18. Rubin LA, Kurman CC, Fritz ME, Biddison WE, Boutin B, et al. (1985) Soluble interleukin 2 receptors are released from activated human lymphoid cells in vitro. J Immunol 135: 3172-3177.
19. Zoru U, Dallmann I, Grosse J, Kirchner H, Poliwoda H, et al. (1994) Soluble interleukin 2 receptors abrogate IL-2 induced activation of peripheral mononuclear cells. Cytokine 6: 358-364.
20. Yang Z-Z, Grote DM, Ziesmer SC, Manske MK, Witzig TE, et al. (2011) Soluble IL-2Ra facilitates IL-2-mediated immune responses and predicts reduced survival in follicular B-cell non-Hodgkin lymphoma. Blood 118: 2809-2820.
21. Burchill MA, Yang J, Vogtenhuber C, Blazar BR, Farrar MA (2007) IL-2 receptor beta-dependent STAT5 activation is required for the development of Foxp3+ regulatory T cells. J Immunol 178: 280-290.
22. Antignano F, Burrows K, Hughes MR, Han JM, Kron KJ, et al. (2014) Methyltransferase G9A regulates T cell differentiation during murine intestinal inflammation. J Clin Invest 124: 1945-1955.
23. Saito Y, Kitamura H, Hijikata A, Tomizawa-Murasawa M, Tanaka S, et al. (2010) Identification of therapeutic targets for quiescent, chemotherapy-resistant human leukemia stem cells. Sci Transl Med 2: 17ra9.
24. Dubois S, Mariner J, Waldmann TA, Tagaya Y (2002) IL-15Ralpha recycles and presents IL-15 In trans to neighboring cells. Immunity 17: 537-547.
25. Eicher DM, Waldmann TA (1998) IL-2R alpha on one cell can present IL-2 to IL-2R beta/gamma(c) on another cell to augment IL-2 signaling. J Immunol 161: 5430-5437.
26. Wuest SC, Edwan J, Martin JF, Han S, Perry JSA (2011) A vital role for IL-2 trans-presentation in DC-mediated T cell activation in humans as revealed by daclizumab therapy. Nat Med 17: 604-609.
27. Qian BZ1, Pollard JW (2010) Macrophage diversity enhances tumor progression and metastasis. See comment in PubMed Commons below Cell 141: 39-51.
28. Feller N, van der Pol MA, van Stijn A, Weijers GWD, Westra AH, et al. (2004) MRD parameters using immunophenotypic detection methods are highly reliable in predicting survival in acute myeloid leukemia. Leukemia 18: 1380-1390.
29. van Rhenen A, Feller N, Kelder A, Westra AH, Rombouts E, et al. (2005) High stem cell frequency in acute myeloid leukemia at diagnosis predicts high minimal residual disease and poor survival. Clin Cancer Res 11: 6520-6527.
30. Kimby E, Nygren P, Glimelius B, SBU-group Swedish Council of Technology Assessment in Health Care (2001) A systematic overview of chemotherapy effects in acute myeloid leukaemia. Acta Oncol 40: 231-252.
31. Ohtake S, Miyawaki S, Kiyoi H, Miyazaki Y, Okumura H, et al. (2010) Randomized trial of response-oriented individualized versus fixed-schedule induction chemotherapy with idarubicin and cytarabin in adult

acute myeloid leukemia: the JALSG AML 95 study. Int J Hematol 91: 276-283.

32. Ikegawa S, Doki N, Yamamoto K, Shingai N, Takahashi Y, et al. (2014) Clinical impact of CD25 expression on outcome of allogeneic hematopoietic stem cell transplantation for cytogenetically intermediate-risk acute myeloid leukemia. Leuk Lymphoma 56: 1874-1877.