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New insights of common gamma chain in hematological malignancies

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ABSTRACT

The common gamma chain (γc) receptor family of cytokines including interleukin-2 (IL-2), IL-4, IL-7, IL-9, IL-15, and IL-21 has the common feature of sharing γc signaling subunit of their receptors. The γc cytokines have unique biological effects that regulate differentiation, survival and activation of multiple lymphocyte lineages and control proliferation of malignant cell by influencing tumor environment. It has been also described that different types of lymphoid leukemia and lymphoma exhibit expression of divergent γc cytokines and their receptors, as they may promote malignant transformation of lymphoid cells or on the contrary lead to tumor regression by inducing cell-cycle arrest. Therefore, cytokine-based or cytokine-directed blockade in cancer immunotherapy has currently revolutionized the development of cancer treatment. In this review, we will discuss about the role of γc cytokines and their signaling pathways in hematological malignancies and also propose a novel alternative approach that regulates γc cytokine responsiveness by γc in hematological malignancies.

1. Introduction

The γc cytokines have the common feature of sharing γc signaling subunit of their receptors and include interleukin-2 (IL-2), IL-4, IL-7, IL-9, IL-15, and IL-21 [1]. Many reports have described that γc cytokines are involved in the pathogenesis of neoplasms [2,3]. There are indeed precedents whereby aberrancies of γc cytokine signaling or abnormal activation of their signaling pathways have been shown to be closely related to leukaemogenesis [4,5]. Recently, soluble form of common gamma chain (sγc) which is generated by alternative splicing is identified as regulator of γc cytokine signaling [6]. This review thus highlight show γc and their family cytokines are linked to tumorigenesis and prospects how newly identified sγc would be applied and approached to anti-tumor therapy in hematological malignancies.

2. γc cytokine signaling pathway and hematological malignancies

γc cytokines are indispensable for the generation of lymphoid cells, and are especially essential for formation, homeostasis and function of T, B and natural killer (NK) cells [1]. The functional γc cytokine receptors consist of cytokine specific receptor α or β chain and the shared γc receptor [1]. Ligand biding leads to heterodimerization or heterotrimerization of these components and induces the trans-phosphorylation of receptor-associated kinases such as Janus-activated kinase1 (JAK1) and JAK3 which finally induce activation of signal transducer and activator of transcription (STAT) family [7]. IL-2 and IL-15 have three receptor chains including γc which contains a second subunit the β-chain IL-2/15-Rβ, and a specific subunit, IL-2Rα or IL-15Rα, respectively [1]. The other cytokines IL-4, IL-7, IL-9 and IL-21 have two chains which consists of γc and cytokine specific IL-4Rα, IL-7Rα, IL-9Rα and IL-21Rα [1]. JAK-STAT5 (STAT5A and STAT5B) pathway is mainly activated by IL-2, IL-7, IL-9 and IL-15, whereas JAK-STAT6 pathway and JAK-STAT3 pathway is generally activated by IL-4 and IL-21, respectively. Phosphorylation of JAK phosphorylates STAT and induces homo-dimerization and translocation to and retention in the

Abbreviations: γc, common gamma chain, CD132; IL, interleukin; sγc, soluble form of common gamma chain; JAK, Janus-activated kinase; STAT, signal transducer and activator of transcription; T-ALL, T-cell acute lymphocytic leukemia; B-ALL, B-cell acute lymphocytic leukemia; AML, acute myeloid leukemia; AMKL, acute megakaryoblastic leukemia; CTCL, cutaneous T-cell lymphoma; Tg, transgenic; HTLV-I, human T-cell lymphotropic virus type I; NHL, non-Hodgkin's lymphoma; CLL, chronic lymphocytic leukemia; ALL, acute lymphocytic leukemia; HL, Hodgkin's lymphoma; PI3 kinase, phosphatidylinositol-3-kinase; SCID, severe combined immunodeficiency; ALCL, anaplastic large cell lymphoma; DLBCL, diffuse large B-cell lymphoma; PBMCs, peripheral blood mononuclear cells; LGL, larger granular lymphocyte; MM, multiple myeloma; FL, follicular lymphoma; NPM-ALK, nucleophosmin-anaplastic lymphoma kinase; SOCS, suppressors of cytokine signaling; PIAS, protein inhibitor of activated STAT; TCR, T-cell receptor.

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nucleus, where they work as transcription factors [7]. JAK-STAT pathway activated by γc cytokines transmits and regulates cell proliferation, survival, differentiation and immune responses. On the other hands, several cancers, including hematological malignancies, have been related to JAK-STAT signaling pathway induced by γc cytokines [7]. Indeed, JAK1 mutations have been defined in 10–20% of T-cell acute lymphocytic leukemia (T-ALL), less extensively in B-cell ALL (B-ALL) [8] and rarely in acute myeloid leukemia (AML) [9]. They are constitutively activated with interacting to γc cytokine specific receptors like α or β chains, indicating that JAK1 may play a critical role in the pathogenesis of T-ALL as IL-7Rα- and JAK3-activating mutations [10]. Mutation of JAK3 gene is less associated with hematological malignancies compared with other JAKs, but recently JAK3 mutations have been defined in rare cases of acute megakaryoblastic leukemia (AMKL) [11], adult T-cell leukemia/lymphoma [12], cutaneous T-cell lymphoma (CTCL) [13] and more recently in T-ALL [10]. As JAK mutants have been more frequently found in lymphoid leukemia rather than in myeloid leukemia, it indicates that they require cytokine receptor complex for constitutive signaling. It remains to be clarified whether mutant JAKs display the same role as normal JAKs for cognate receptors, because mutant JAK3 acquires the ability to bind other receptors as shown in AMKL. Although constitutive STAT activation has been frequently observed in hematological malignancies, mutations in STAT gene have been rarely defined. STAT6 mutations have been reported in primary mediastinal B-cell lymphoma [14], the oncogenic properties of these mutants however have not been clear yet. Mutations in STAT1, STAT3 and STAT5 have not been determined in other human hematological malignancies. The role of STAT5 in neoplasms has been identified in mouse models that overexpress IL-7 [15]. The IL-7 transgenic (Tg) mice show phenotypes ranging from increased number of T and B cells to lymphoproliferation and then lymphoma development, in addition to dermal lymphoid infiltration [16]. The haploinsufficient of STAT5 in IL-7Tg mice showed a dramatic amelioration of overexpressing IL-7-mediated mortality and moderation of lymphoma development compared to STAT5 sufficient IL-7Tg mice [15]. All together, these studies demonstrate that the delicate regulation of γc cytokine signal strength that is affected by JAK and STAT is one of the key mechanisms in the development of hematological malignancies and also indicate that downstream molecules of γc cytokine responsiveness may be important targets to treat hematolymphoid diseases that are sensitive to JAK-STAT pathway.

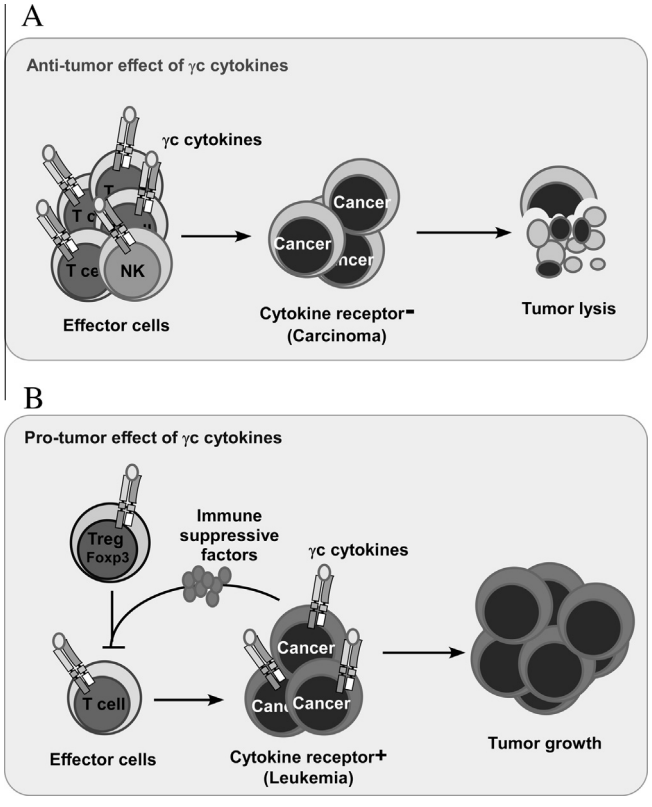

Fig. 1. Schematic action mechanism of γc cytokines in non-hematological and hematological malignancy. (A) γc cytokines induce apoptosis in non-hematological malignancy (carcinoma and sarcoma) via activation of effector cells such as NK and T cells. (B) γc cytokines does not exert their role only as a trophic factor for hematological malignancy (leukemia and lymphoma), but also as stimulator of regulatory T (Treg) cells which suppress effector T cells.

3. γc cytokines in hematological malignancies

3.1. Introduction

As we described above, γc cytokines directly exploit indispensable roles in normal hemato-lymphopoiesis. A major role of γc cytokines in non-hematological tumors has been generally defined in which they activate effector cells, such as NK and cytotoxic T cells, and finally mediate anti-tumor effect (Fig. 1A) [17]. Since malignant lymphoma/leukemia cells have similar phenotype to normal lymphocytes, it is easy to imagine that hematological tumors can vigorously proliferate in response to γc cytokines by outcompeting with remnant normal lymphocytes (Fig. 1B) [17]. Although immunotherapy using γc cytokines has been applied in patient with diverse type of tumors, their roles in hematological malignancies are controversial [18]. Therefore, the divergent impacts of each γc cytokines in hematologic malignancies will be discussed for comprehensive understanding (Table 1).

3.2. IL-2

IL-2 signaling is engaged in cell-mediated immunity via differentiate naïve T cell into effector T cells such as memory T cells or regulatory T cells [44]. In physiologic resting state, IL-2Rα is expressed scarcely on the surface of normal lymphocytes [45]. By contrast, persistent expression of IL-2Rα on the surface of tumor cells and elevated serum levels of soluble IL-2Rα are observed in patients with hematologic malignancies such as human T-cell lymphotropic virus type I (HTLV-I) associated adult T-cell leukemia/-lymphoma [27], cutaneous T-cell lymphoma [29], hairy B-cell leukemia [46] and Hodgkin's lymphoma [19]. Constitutive expression of IL-2Rα on leukemia forms high affinity IL-2R complex and induces survival signal by IL-2, resulting in aggressive malignant transformation of IL-2R complex expressing lymphoma may be enhanced by amplification of IL-2 signaling pathway. Moreover, increased serum levels of soluble IL-2Rα is also found in patients with non-Hodgkin's lymphoma (NHL) [47], chronic lymphocytic leukemia (CLL) [38], AML, acute lymphocytic leukemia (ALL) [35].

3.3. IL-4

IL-4 is an inevitable cytokine that induces differentiation of naïve T cells to Th2 cells differentiates B cells into plasma cells [48]. In normal physiologic state, IL-4 promotes proliferation of T and B cells and elongates their survival [49]. Initially, IL-4, as an anti-tumor cytokine, has been shown in vivo and in vitro animal models [50,51]. Administration of recombinant IL-4 to IL-4R overexpressing Hodgkin's lymphoma (HL) cells shows significant anti-tumor effect [24]. IL-4-secreting tumors are rejected and maintained anti-tumor immune responses in transplanted mice

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