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Review

The dual-functional capability of cytokine-induced killer cells and application in tumor immunology

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ABSTRACT

Cytokine-induced killer (CIK) cells represent a heterogeneous cell population, including a large majority of CD3+CD56+ cells, a relatively minor fractions of typical T cells (CD3+CD56−), and natural killer (NK) cells (CD3−CD56+). In order to elucidate the tumor killing mechanism of these three subpopulations of CIK cells, this review summarized the concordances and differences among CD3+CD56+ CIK cells, CD3−CD56+ NK cells and CD3+CD56− T cells to the following aspects: the effects of cell surface molecules, mechanisms of tumor killing, and clinical applications of these cells in immunotherapy. NK cells can be classified into CD56brightCD16− NK cells, which produce cytokines in response to monokine co-stimulation, and the CD56dimCD16+ NK cells, which contribute to lysing susceptible target. Also, the immunity of NK cells is mainly regulated by several immune-receptors, such as ACR, ICR, NCR and KIRs. T cells require TCR and co-stimulatory molecules for initiation of T cell activation. The CD3+CD56+ CIK cells co-express with T-cell marker CD3 and NK cell marker CD56 to appear the most potent cytotoxicity and high impact on adoptive cellular immunotherapy. These CIK subpopulations share some similar tumor killing mechanisms. LFA-1 not only mediates the binding of NK cells to target cells through its ligand ICAM-1 to localize actin accumulation but also acts as a co-stimulatory receptor on NK cells. LFA-1 also functions as co-stimulatory receptor for T cells to transmit intracellular signals from the TCR to LFA-1. Furthermore, cytotoxic effect of CD3+CD56+ CIK cells is blocked by antibodies directly against LFA-1 and its counter receptor, ICAM-1. Clinically, antibody-dependent cell-mediated cytotoxicity (ADCC) is shown in both NK cells and T cells for tumor killing while dendritic cells are another main regulator for the activation of three subpopulations. In summary, CD3+CD56+ CIK cells have dual-functional capability as T-cell subsets which acquire NK cells function and reserve TCR-mediated specific cytotoxicity. Meanwhile, CIK cells play important roles in tumor immunology. It paves the way to more effective immunotherapies for various tumors.

Contents

Abbreviations: CIK, cytokine-induced killer cells; NK, natural killer cells; CTLs, cytotoxic T lymphocytes; LAK, lymphokine activated killer cells; TIL, tumor-infiltrating lymphocytes cells; ADCC, antibody-dependent cellular cytotoxicity; PFS, progression free survival; NCRs, natural cytotoxicity receptors; ITAM, immunoreceptor tyrosine-based activating motif; MHC, major histocompatibility complex; TCR, T-cell receptor; KIR, killer immunoglobulin-like receptors; ITIMs, immunoreceptor tyrosine-based inhibition motifs; APCs, antigen presenting cells; LFA-1, leukocyte integrin leukocyte function associated antigen-l; ICAM-1, intercellular adhesion molecule-1; GVHD, graft-versus-host disease; DLI, donor lymphocyte infusion; HCT, hematopoietic cell transplantation; DC, dendritic cell.

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1. Introduction

Cytokine-induced killer (CIK) cells, which are non-major histocompatibility complex (MHC)-restricted CD3+CD56+ T cells, take advantage of the body's natural ability to eliminate tumor cells by stimulating and restoring the immune system to recognize and kill tumor cells [1]. CIK cells can be expanded from peripheral blood mononuclear cells (PBMC) cultured with the addition of IFN-γ, Ab anti-CD3 [2] and other exogenous cytokines, such as interleukin-2 (IL-2), interleukin-7 (IL-7) or interleukin-12 (IL-12) [3]. CIK cells can lyse a broad array of tumor targets, including acute myeloid leukemia, chronic myelogenous leukemia, and chronic lymphocytic leukemia through a non-MHC-restricted natural killer (NK) – like mechanism to express several chemokine receptors and migrate to the site of tumors after intravenous administration, as shown in in vivo models [4,5]. Phenotypically, CIK cells are a mixture of CD3+CD56+ cells, CD3−CD56+ NK cells and CD3+CD56− T cells. NK cells produce different cytokines that may in turn influence the biology of other cells, especially T cells and potential target cells, such as virally infected cells or tumor cells [6]. NK cells induce target cell death by the release of granules and cytotoxic proteins, Fas ligand and membrane-bound or secreted cytokines (tumor necrosis factor-α (TNF-α)), and TNF-apoptosis-inducing ligand [7]. T cells recognize their targets by binding to antigen associated MHC class I presenting on the surface of all nucleated cells. Through IL-10, adenosine and other molecules secreted by regulatory T cells, the CD8+ cells can be inactivated to an anergic state, which prevent autoimmune diseases, such as experimental autoimmune encephalomyelitis [8]. Distinct from the activated CD3−CD56+ NK cells and CD3+CD56−CD8+ cytotoxic T cells, CD3+CD56+ CIK cells co-express CD3 and CD56 cell surface markers and exert its cytotoxicity in a non-MHC restricted way. Most of the CD3+CD56+ cells co-express CD2, TCRαβ, CD5 and CD8, but are negative for CD4 and CD16. These cells are different from NK cells because they do not mediate antibody-dependent cell-mediated cytotoxicity (ADCC) [9]. CD3+CD56+ CIK cells, as the main effectors, play an important role in the process against various tumor cell targets compared to the others [10], but some reports suggest that CD4+ T cells play an equally important role [11].

In recent years, adoptive immunotherapy has become the most promising novel strategy for the treatment of tumors compared to the traditional cancer vaccine therapy. Two representative cells used in adoptive immunotherapy have been reported: the lymphokine activated killer (LAK) cells and tumor-infiltrating lymphocyte (TIL) cells. LAK cells, first described in 1980s, are essentially activated natural killer (NK) cells capable of recognizing cancer cells in a non-MHC-restricted manner [12]. Furthermore, several NK cells expressing CD16 receptors have been confirmed to have cytotoxic activity through antibody-dependent cellular cytotoxicity (ADCC) [13]. TIL cells are immune cytotoxic T effector cells with more potent antitumor activity and MHC-restricted tumor-specific cytotoxicity compared to LAK cells [14]. The major effectors of TIL cells are phenotypically CD3+CD56−CD8+ cells. The differences between CIK and LAK cells are based on the following aspects [15]: higher proliferation rate of CIK cells, antitumor cytotoxic activity per culture, purging activity against malignant cells derived from patients with chronic myelogenous leukemia [16] and cytotoxic activity of CIK cells in a xeno-transplant model [17]. In addition, differences exist in the phenotype between CIK and LAK cells [18]. The main effector cell in CIK cell culture co-expresses T- and NK-cell markers [19]; also, the co-expression of lymphoid and myeloid markers does exist in CIK cell cultures [20]. Following the above demonstrations, CIK cells may have potential in adoptive immunotherapies because of higher proliferative and cytolytic activities [21]. Importantly, they are easy and inexpensive to be produced via ex-vivo expansion, and have MHC-unrestricted tumor killing ability. This may overcome some crucial problems that have limited the diffusion and clinical application. Several clinical trials have already confirmed the safety and feasibility of the CIK adoptive infusion [22]. Recent clinical research, especially in Asia, has surprisingly found that CIK cells can significantly improve progression free survival (PFS), median survival, and obtain effective clinical response in patients with lung and gastric cancers [23]. However, there are some issues concerning about it: firstly, consistent curative effect of CIK cells for different tumor types are hard to obtain; secondly, there is no dependable way to predict the curative effect; finally, although CIK cells infusion has so much potential for the treatment of tumors, it is only recommended as an adjuvant treatment [24].

CIK cells have been used in clinical care with good prospects for successful treatment, but the molecular structures that account for tumor recognition and killing by CIK cells are not fully understood yet. In this review, we focused on the cytotoxic mechanisms of CIK cells against tumors, and compared the potential in tumor immunology among CD3+CD56+ CIK cells, NK cells and T cells.

2. Cell surface molecules of the three CIK cell subpopulations

2.1. Natural killer (NK) cells

NK cells which are derived from CD34+ cells and represent only 10–20% of total lymphocytes in peripheral blood play an important role in the innate immune system. In addition, NK cells are a subset of large granular lymphocytes. The phenotype of NK cells appears to be CD3−CD56+CD16+. According to the intensity of surface expression of CD56 and CD16, NK cells can be classified into two subsets: the CD56brightCD16− NK cells and the CD56dimCD16+ NK cells. CD56bright NK cells have genetically longer telomeres and greater proliferative ability, implying a more immature nature than CD56dim NK cells. In the meantime, CD56bright cells can be differentiated into cells similar to CD56dim cells which is not only phenotypically but also functionally [25]. CD56bright NK cells,