Am J Cancer Res 2017;7(8):1637-1641
www.ajcr.us /ISSN:2156-6976/ajcr0061850

Review Article

CS1 (SLAMF7, CD319) is an effective immunotherapeutic target for multiple myeloma

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Received July 19, 2017; Accepted July 27, 2017; Epub August 1, 2017; Published August 15, 2017

Abstract: CS1 (also known as CD319, CRACC and SLAMF7) was identified as an NK cell receptor regulating immune functions. It is also expressed on B cells, T cells, Dendritic cells, NK-T cells, and monocytes. CS1 is overexpressed in multiple myeloma and makes it a target for immunotherapy. A humanized anti-CS1 antibody, Elotuzumab or Empliciti has shown promising results in clinical studies. This review focuses on the biology of CS1 in NK and other hematopoietic cells and multiple myeloma. Anti-CS1 mAb can activate natural cytotoxicity of NK cells as well as enhance ADCC (antibody-dependent cell-mediated cytotoxicity) and thus makes an effective target for immunotherapy of MM.

Keywords: CS1, SLAMF7, CRACC, elotuzumab, antibody-based immunotherapy, multiple myeloma

Introduction

Multiple myeloma (MM) is a hematologic cancer characterized by malignant plasma cells in bone marrow along with monoclonal protein found in the serum and/or urine. MM can cause anemia, renal failure, hypercalcemia, or bone destruction [1]. According to American Cancer Society, it is estimated that in 2017, there will be 30,280 new cases of MM and 12,590 deaths in the United States. Although MM is considered incurable, the 5-year relative survival rate has increased from 29% in 1987-1989 to 49% in 2005-2011, potentially due to recent advances in conventional treatment and the availability of novel therapies [2]. The genetic background of MM is complex and result in the heterogeneous biology and clinical outcome and thus an obstacle to therapies targeting MM signaling pathways [3, 4]. The expression of several surface molecules on MM make it potentially a good target for immunotherapy [5].

Natural killer cell function and role in cancer immunotherapy

Natural killer (NK) cells are bone-marrow derived lymphocytes that play a vital role in the innate immune response against cancer and infection. NK cells recognize and destroy target cells via natural cytotoxicity and antibody-dependent cell-mediated cytotoxicity (ADCC) [6]. NK cells also regulate other immune cells though the secretion of cytokines, such as interferon-γ (IFN-γ) and tumor necrosis factor-a (TNF-α) [7]. NK cell function is regulated through a delicate balance of signals received from activating and inhibitory receptors [8, 9]. Early research was devoted to identifying MHC-recognizing receptors [10]; however, members of the CD2 subset of receptors, such as CS1 and 2B4 (CD244), do not recognize MHC but play a major role in NK cell function [11, 12]. It has been recently show that there is not a singly dominant activating NK cell receptor but rather that activating receptors work in a combinatorial manner to reach the threshold required for cytokine release or natural cytotoxicity. Due to the synergism of activating receptors, there has not been great success in the creation of a single therapeutic agent [13]. Studies over the last decade that revealed molecular mechanisms of NK cell activation and recognition has opened novel strategies for NK cell based immunotherapy [14].

CS1 (CRACC, CD319, SLAMF7)

We have cloned and characterized CS1 (CD2 subset-1) as a human NK cell receptor [15]. CS1

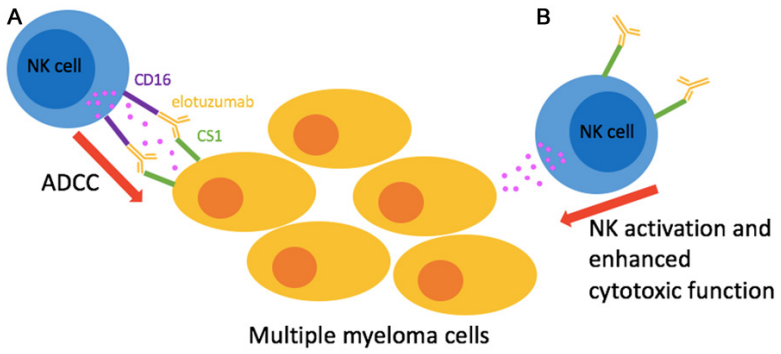

Figure 1. Mechanism of action of anti-CS1 antibody (elotuzumab) against multiple myeloma (MM). A: Activation of antibody-dependent cell-mediated cytotoxicity (ADCC) when NK cell receptor CD16 (FCγRIII) binds to the Fc region of elotuzumab bound to CS1 on MM cells; B: Direct activation of NK cell through CS1-elotuzumab interaction.

is a member of the Signaling Lymphocyte Activation Molecule Family (SLAMF7) and is expressed on NK cells, CD8+ T lymphocytes, B lymphocytes, and mature dendritic cells [15, 16]. CS1 is a homophilic receptor, and the CS1-CS1 interaction leads to activation of NK cell natural cytotoxicity [17]. The human CS1 gene is located on the long arm of chromosome 1 at 1q23-24 between CD48 and CD229 [11]. Human NK cells express two splice variants of CS1; CS1-S which lack the intracellular domain for activation, and the CS1-L which contain the intracellular domain and is thus capable of activating NK cytotoxicity [18]. Both the isoforms of CS1 are membrane bound forms and are expressed in NK cells. However, only the CS1-L isoform is expressed in B cells and signaling through CS1 induce B cell proliferation and autocrine secretion [19].

CS1 is upregulated in MM and this has been implicated in the uncontrolled proliferation of MM cells [20, 21]. However, the mechanism of CS1 upregulation in MM is not known. We have analyzed the transcriptional regulation of CS1 in NK and B lymphocytes. CS1 transcription is regulated by YY1 (Ying Yang 1) in mice and Blimp-1 (B lymphocyte-induced maturation protein-1) in humans [22, 23]. Blimp-1, encoded by the gene positive regulatory domain zinc finger protein 1 (PRDM1), regulates gene transcription in macrophage, NK cells, B cells, T cells, and skin epithelia [23, 24]. Originally thought to be a transcriptional repressor, Blimp-1/PRDM1 was recently shown to positively regulate the human CS1 (hCS1) gene in NK and B cells. While Blimp-1/PRDM1 is not required for basal level of hCS1 expression, Blimp-1/PRDM1 binding leads to increased transcription and expression of hCS1 [23]. Interestingly, while Blimp-1/PRDM1 is required for the specific stages of B and T cell differentiation, Blimp-1/PRDM1 is induced in immature NK cells and expression is maintained and increased in mature NK subsets [25-27]. Blimp-1/PRDM1 expression and function suggests fundamental differences in transcriptional regulation of CS1 in NK cells compared to other lymphocyte subsets.

CS1 activates NK cell cytotoxicity

CS1 is a self-ligand and homophilic interaction of CS1 activates NK cell function [17]. CS1 contains two signaling motifs called immunoreceptor tyrosine-based switch motif (ITSM) found on the cytoplasmic tail which mediates interaction with Ewing's sarcoma-associated transcript 2 (EAT-2) [18]. Both isoforms of CS1 (CS1-L and CS1-S) are expressed on human NK cells, but only CS1-L mediates signals upon ligation with anti-CS1 mAb [18]. By generating CS1-deficient mice, Cruz-Munoz and colleagues showed that CS1 may function as inhibitory or activating receptor depending on cellular context and availability of effector proteins [28]. Thus, in presence of EAT-2, CS1 acts as an activating receptor and in its absence as an inhibitory receptor for NK cells [28]. The humanized anti-CS1 mAb Elotuzumab (Empliciti) also activates natural cytotoxic function of NK cells against MM cells [29].

Role of CS1 in other immune cells

Naïve B cells only produce the CS1-L variant and expression is upregulated upon activation [18, 19]. In B cells, CS1 signaling leads to proliferation and leads to production of autocrine cytokines such as IL-14 and does not lead to immunoglobulin (Ig) production [19]. Human B cells stimulated with anti-CD40 mAb, and IL-4, crosslinking surface CS1 with anti-CS1 mAb increased proliferation as well as cytokine with

growth promoting activity [19]. These results suggest that CS1 may have growth promoting activity in B cells. In contrast, T cells express CS1 but lack the adaptor protein EAT-2; therefore, CS1 functions as an inhibitory receptor [28]. Our study on the function of CS1 in human monocytes showed an inhibitory role to control proinflammatory immune responses [30]. Crosslinking CS1 in human monocytes cultured in LPS reduced the production of proinflammatory cytokines TNF-alpha and IL-12p70 [30]. CS1 is also expressed in NKT cells and some DCs, but its functional role yet to be investigated.

Targeting multiple myeloma with anti-CS1 mAb

CS1 is highly expressed in MM cell lines and patient MM cells, but not found on healthy tissue, primary tumor tissues, or hematologic and nonhematologic cancer cell lines [21, 31]. Moreover, there was a correlation between soluble CS1 in the patient sera and the disease stage [20]. This indicate that soluble CS1 may be a useful biomarker for MM disease progression. The high expression of CS1 on MM cells make it an attractive target for treatment of this disease. It has been reported that CS1 may contribute to tumor promoting activity of MM cells [21]. A humanized mAb, Elotuzumab or Empliciti was used in preclinical studies and lead to phase 1 and phase 2 studies of MM. In phase 1 studies, treatment with Elotuzumab alone did not show much progress, whereas Elotuzumab in combination with bortezomib or lenalidomide was active against MM [32, 33]. Elotuzumab could activate NK cells in two different ways (**Figure 1**). Elotuzumab binds to CS1 on MM cells and NK cells recognize the Fc region of antibody by CD16 and thus mediate ADCC (Antibody-dependent cell-mediated cytotoxicity) against MM cells. In addition, binding of Elotuzumab on CS1 on the NK cells activate natural cytotoxicity of NK cells [17]. Activation of NK cells induce the secretion of IFN-γ and this could play a role regulating the immune function of other cells. Moreover, CS1 is also expressed on DCs and monocytes. Binding of anti-CS1 to monocytes inhibits the production of proinflammatory cytokines [27]. This could affect the bone marrow microenvironment. Elotuzumab could also prevent the adhesion of MM cells to bone marrow stromal cells. Thus, unlike other mAbs, elotuzumab because of its multiple effects on NK cells and other immune cell function, is more effective in targeting MM cells. Recent study revealed a critical role for CS1 in phagocytosis of hematopoietic tumor cells by macrophages [34]. Phase 3 clinical trial of elotuzumab in combination with lenalidomide/dexamethasone showed clinically relevant improvement in efficacy, with minimal incremental toxicity [35].

The overexpression of CS1 on MM cells makes it an effective immunotherapeutic target. The mechanism by which elotuzumab control MM is not fully understood. Binding of elotuzumab to CS1 can play an inhibitory role on other immune cells, such as macrophages. While, elotuzumab has shown great success in clinical studies in MM patients, its role in normal hematopoietic cells needs to be evaluated more closely.

Disclosure of conflict of interest

None.

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