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Identification of the CD16^{low} CD56^{low} CD38^{pos} Natural Killer Cell as a Key Subset in Patients with Multiple Myeloma

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ABSTRACT

Background: Natural killer (NK) cells are classified as innate immune cells which can directly recognize and kill tumor cells without antigen sensitization. NK cell-based adoptive immunotherapy for blood malignancies has attracted more attention in recent years.

Objective: To analyze different NK cell subsets in the peripheral blood and bone marrow (BM) of patients with multiple myeloma (MM).

Methods: Using flow cytometry we analyzed: (i) the distribution of distinct NK cell subpopulations (i.e. CD16low CD56low, CD16pos CD56^{high}, CD16^{neg} CD56^{high}, CD16^{high} CD56^{low}, CD16^{neg} CD56^{low}, CD16^{low} CD56^{low} CD38^{pos}) in the BM from MM patients at distinct disease stages. (ii) the expression of NKG2D, DNAM-1 and NKp30, and (iii) the expression of CD107a in CD16^{low} CD56^{low} CD38^{pos} and CD16^{low} CD56^{low} CD38^{neg} NK cells subsets.

Results: CD16^{low} CD56^{low} CD38^{pos} was the dominant subset in BM from patients with MM at the CR stage with a decreased expression of NKp30. CD16^{low} CD56^{low} CD38^{pos} subset showed a higher proportion of CD107a expression compared to CD16^{low} CD56^{low} CD38^{neg} cells. In vitro experiments indicated that the CD16^{low} CD56^{low} CD38^{pos} NK cell subset possesses more cytotoxicity than CD16^{low} CD56^{low} CD38^{neg} NK cells.

Conclusion: Our data suggest that CD16^{low} CD56^{low} CD38^{pos} NK cells may reflect as an effector population with the potential therapeutic target in patients with MM. This group of cells may be useful for adoptive immunotherapy in MM in the future.

Keywords: Cell Immunology, Multiple Myeloma, Natural Killer (NK) Cells

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INTRODUCTION

Multiple myeloma (MM) is a neoplasia characterized by the accumulation of malignant plasma cells (PC) in the bone marrow [1]. Although the prognosis of patients with multiple myeloma (MM) significantly improved in recent years, MM remains an incurable hematological malignancy. A high proportion of patients still relapse and become refractory due to the limited benefits obtained from the newly developed treatment combinations [2, 3]. Natural killer (NK) cells are innate effector cells potentially targeting cancer cells through the immune response. Consequently, adoptive immunotherapy based on NK cells may provide a potential treatment for patients with myeloma [4].

The lack of CD3 human NK cells is recognized by surface expression of CD56, the level of which is utilized to divide NK cells into 2 developmentally related, but functionally distinct subsets: CD56 bright and CD56dim [5, 6]. NK cells also express the CD16 (FcyRIIIa) phenotype, which mainly recognizes the Fc region of human IgG1 antibodies [7]. Different NK cell populations possess different functional characteristics in immune protection [5]. Yet the functional differences between these populations are still unclear. Recently, a subgroup of NK cells with a low level of both CD56 and CD16 (CD56lowCD16low) in the BM and PB in the pediatric healthy donors and the transplantation patients with leukemia has been observed. The $CD56^{low}CD16^{low}$ cells have powerful killing and interferon-gamma (IFNγ) production ability and show higher levels of both CXCR4 and CXCR3 compared with the $CD56^{low}CD16^{high}$ and the $CD56^{high}CD16^{+/-}$ populations [8, 9]. To better understand the properties of NK cell subpopulations during the development of multiple myeloma, we analyzed the distribution of different NK cell subgroups (i.e.$CD16^{low}CD56^{low}$, $CD16^{positive}CD56^{high}$, $CD56^{high}CD16^{negtive}$, $CD56^{low}CD16^{high}$, $CD56^{low}CD16^{negtive}$) in BM and PB of MM stroked patients with different clinical staging followed by the assessment of the expression levels of NKG2D, DNAM-1 and NKp30 in these subpopulations.

CD38 was originally found on the surface of thymocytes and T lymphocytes, and today we know this molecule is ubiquitous throughout the immune system, although its expression levels vary [10]. CD38 is a related tumor antigen for immunotargeting therapy. Nowadays, humanized CD38-monoclonal antibody (daratumumab) is proven to be effective in the clinical therapeutics of pretherapy or relapsed and refractory multiple myeloma (RRMM) patients [11-13], A previous study has reported that the $CD38^{positive}$ NK cell population is activated by the internalization of CD38 upon binding to Dara. This step is critical for triggering an immune response against malignant plasma cells [14]. However, the function of the $CD38^{positive}CD56^{low}CD16^{low}$ NK cells in the immune response has not been clarified. Here, we analyzed the distribution of the $CD38^{positive}CD56^{low}CD16^{low}$ NK cells in the bone marrow of MM patients at different stages. The killing abilities of both the $CD38^{positive}$ and the $CD38^{negtive}CD56^{low}CD16^{low}$NK cells were evaluated by *in vitro* experiments. Our results conclude that the $CD38^{positive}CD56^{low}CD16^{low}$ NK cells may reflect the immunological condition of MM patients to a certain extent.

MATERIALS AND METHODS

Clinical Samples

Clinical PBMCs and BM samples were from MM patients registered in the Department of Hematology (Jiangsu Province Hospital). The onset patients refer to newly diagnosed symptomatic patients with multiple myeloma. The diagnostic criteria refer to the Chinese guidelines for the diagnosis and treatment of multiple myeloma [15]. Relapse and complete remission (CR) are defined according to the efficacy criteria developed by the International Myeloma Working Group (IMWG) [16]. Patients were typed according to their disease status (Table 1).

Table 1. Baseline clinical and laboratory characteristics of the MM patients in this study

Characteristics	Onset(n=17)	Relapse (n=6)	CR (n=13)	P value
Age (years)				0.803
Median	62.06	59.50	59.83	
Sex				0.918
Female: Male	7:10	3:3	6:7	
Myeloma type				0.201
IgG	7	2	7	
IgA	5	3	5	
Light chain type	5	1	1	
Kappa	2	1		
Lambda	3	0		
Albumin				0.107
Median	32.26	37.38	36.64	
³35g/l	6	3	8	
£30g/l	11	3	4	
Unknown	1	0	0	
Beta-2-microglobulin (mg/L)				0.018
Median	7.16	2.50	2.32	
ISS Stage				0.006
ISS1	6	2	10	
ISS2	3	4	2	
ISS3	8	0	0	
High-risk FISH				0.646
1q21	9	4	4	
P53	1	0	1	
t(4;14)	1	0	1	
IgH gene rearrangement	4	2	5	
Unknown	2	0	2	
Hemoglobin (g/L)				0.069
Median	92.58	97.66	113.50	
Unknown	1	0		
Calcium(mmol/L)				0.333
Median	2.28	2.30	2.15	
Unknown		0	1	
BMPC(%)				0.02
Median	15.7	19.53	1.5	
Unknown	0	0	`1	
Creatinine (mmol/l)				0.07
Median	188.06	67.78	66.60	
Ferritin (mg/l)				0.088
Median	379.54	196.33	159.88	
Unknown	4	0	0	
Free light chain ratio				0.302
Median	136.94	205.90	12.18	
Range	0.001-1067	0.0009-1213	0.03-67.6	
Lactate dehydrogenase (mmol/l)				0.815
Median	199.66	188.83	174.83	
Unknown	1	0	0	

BMPC: Bone marrow plasma cell; ISS: International Staging System; CR: Complete remission

Ethics Statement

An ethics statement was obtained from the patients engaged by written consent and confirmed by the Ethics Committee of the Jiangsu Province Hospital.

Immunofluorescence and FACS Analysis

Samples were fixed with anti-CD38/PB, anti-CD45/KO, anti-NKp30/PE, anti-CD56/ECD, anti-DNAM-1/PC5.5, anti-NKG2A/PC7, anti-NKG2D/APC, anti-CD16/APC-AF700, anti-CD3/APC-AF750, and anti-CD107a/APC, anti-CD56/ECD at 4 °C for 20 min. All antibodies were purchased from the Beckman Company. All samples were assessed using a Navios flow cytometry (BECKMAN COULTER) and the data were analyzed using the TreeStar FlowJo_ 10.8.1.

Degranulation Test in Vitro

All cells of PBMCs and BM from newly diagnosed or RRMM patients and bone marrow mononuclear cells (BMNCs of MM patients at CR stage) were used as the source of effector cells. K562 was used for objective cells and incubated with effector cells at a 2.5:1 effector/target (E/T) ratio in RPMI-1640 medium with 10% fetal bovine serum (FBS) at 37 °C in a fully humidified atmosphere at 5% CO2 for 2 hrs.

Then, the cells were washed twice and stained with the lysosomal marker CD107a/PB and anti-CD3/APC-AF750, anti-CD38/PE, anti-CD45/KO, anti-CD16/APC-AF700, anti-CD56/ECD, anti-DNAM-1/PC5.5, and anti-NKG2D/APC at 4 °C for 45 min. All antibodies were purchased from the Beckman Company. All the samples were acquired using a Navios flow cytometry (BECKMAN COULTER) and the data were analyzed using the TreeStar FlowJo_ 10.8.1.

Statistical Analysis

Numeric data were analyzed by the Student t-test, and qualitative data used a chi-square analysis, *P<0.05; **P<0.01, ***P<0.001. The statistical analyses were performed using PRISM 7.0a (GraphPad, La Jolla, CA, USA).

RESULTS

Patients' Clinical Information

A group of 36 MM sufferers at various stages of the disease aged between 41 and 75 years were enrolled with the percentage of bone marrow plasmacyte ranging from 0.5% to 67%. Among them, 23 had MM symptoms (17 at the onset and 6 at the relapse) while the rest with complete remission (Table 1).

The $CD16^{low}CD56^{low}$ NK cell subset is enriched in both BM and PB samples of MM patients at different disease staging.

First, we assayed the distribution of the following five distinct NK cell subgroups in the BM and PB MM patients: $CD16^{low}CD56^{low}$, CD16positiveCD56high, $CD56^{high}CD16^{negtive}$, CD56lowCD16high, $CD56^{low}CD16^{negtive}$ (Figure 1A). We observed that the $CD16^{low}CD56^{low}$ was the dominant population in the BM and PB samples, followed by the $CD56^{low}CD16^{negtive}$ and $CD56^{low}CD16^{high}$. We found that the $CD56^{low}CD16^{low}$ subpopulation significantly decreased in the BM cells in patients at CR stage while the $CD56^{high}CD16^{negtive}$ and the $CD56^{low}CD16^{negtive}$ NK cells increased accordingly in the BM and PB (Figure 1B).

The $CD38^{positive}$ $CD56^{low}CD16^{low}$ NK cells showed decreased NKp30 expression in the BM samples from MM cases in remission.

To understand the phenotypic characteristics of the subsets in NK cells in MM patients, we monitored the expression of three important surface-activated receptors in NK cells, namely, NKG2D, DNAM-1, and NKp30, which can partake in the process of recognition and killing of tumor cells. Interestingly, an obvious decrease in NKp30 expression in PB $CD56^{low}CD16^{low}$ subsets from the patients at the CR stages of the disease was observed compared with the onset and the relapse group. The expression of receptors activating NK cells in the $CD56^{low}CD16^{negtive}$ subsets are shown in Figure 2. In addition, the expression of NKp30 decreased in BM $CD38^{positive}CD56^{low}CD16^{low}$ NK cell subsets in CR patients compared with the relapse group.

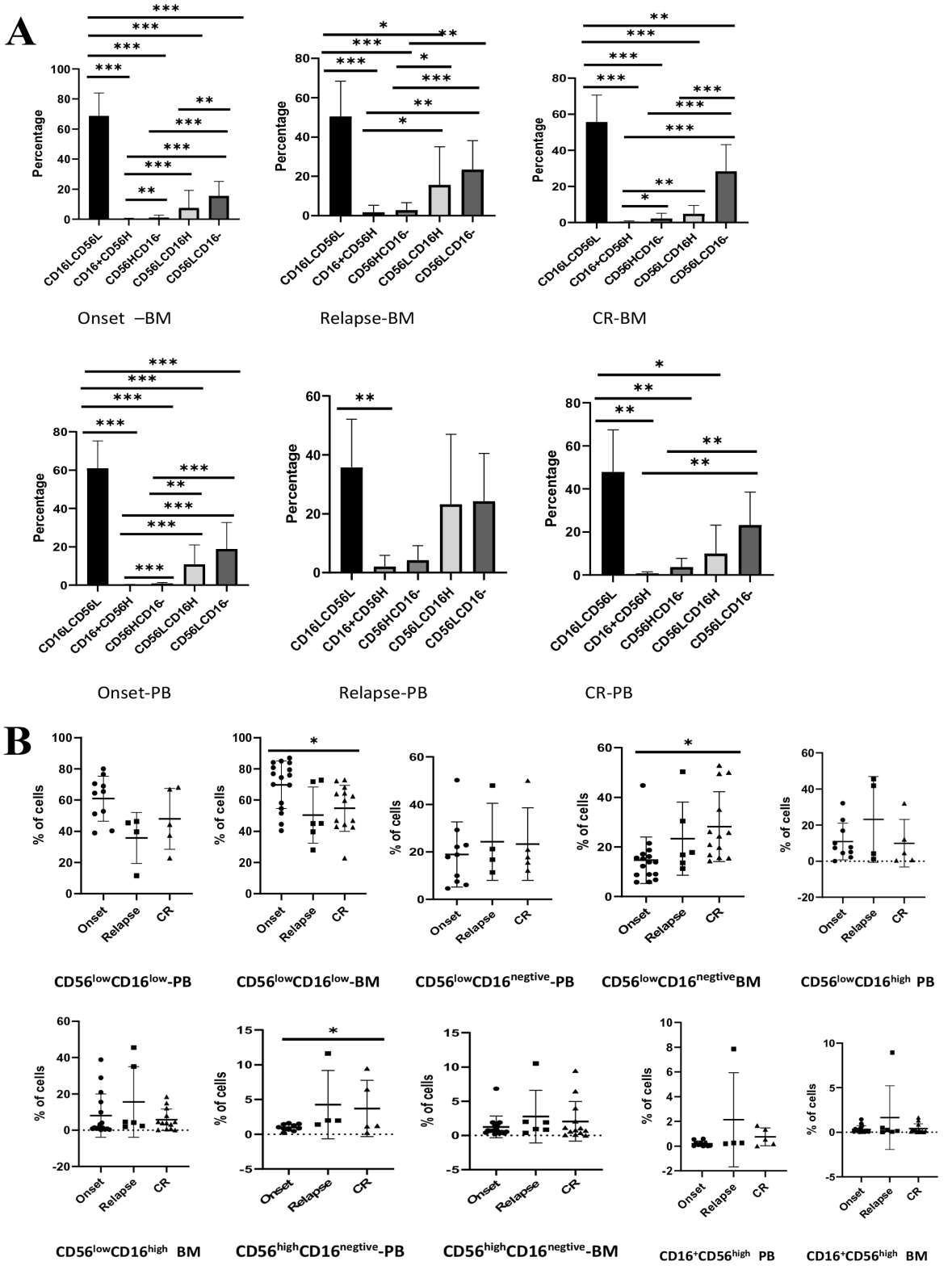

Figure 1. Natural Killer (NK) cell subset distribution in bone marrow (BM) and peripheral blood (PB) of multiple myeloma (MM) patients at different stages of the disease (A). NK cell subset ($CD16^{low}CD56^{low}$, $CD56^{low}CD16^{negtive}$, $CD56^{low}CD16^{high}$, $CD56^{high}CD16^{negtive}$, $CD16^{+}CD56^{high}$) in PB and BM of MM patients at different stages of the disease was shown in (B) (*P<0.05, **P<0.01, ***P<0.001).

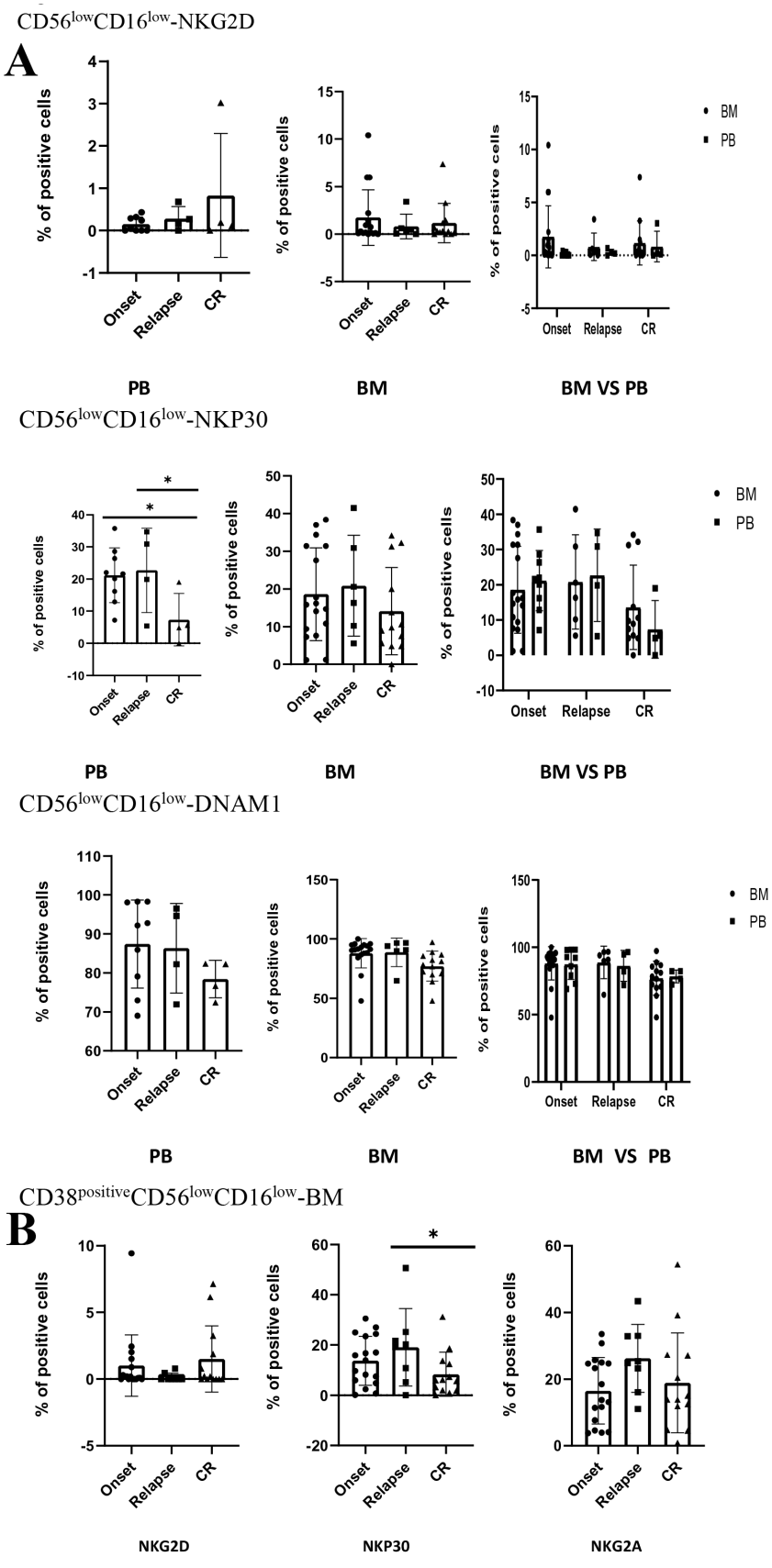

Figure 2. Profile of BM and PB $CD56^{low}CD16^{low}$ NK cell subsets receptor from MM patients during disease progression. FACS analysis of surface expression of NGK2D,NKp30,DNAM-1 (A). The expression of NKG2D,NKp30,NKG2A on $CD38^{positive}CD56^{low}CD16^{low}$ NK cells in BM of MM patients at different stages of the disease (B). (*P<0.05). BM: Bone marrow; PB: Peripheral blood; MM: Multiple myeloma; CR: Complete remission

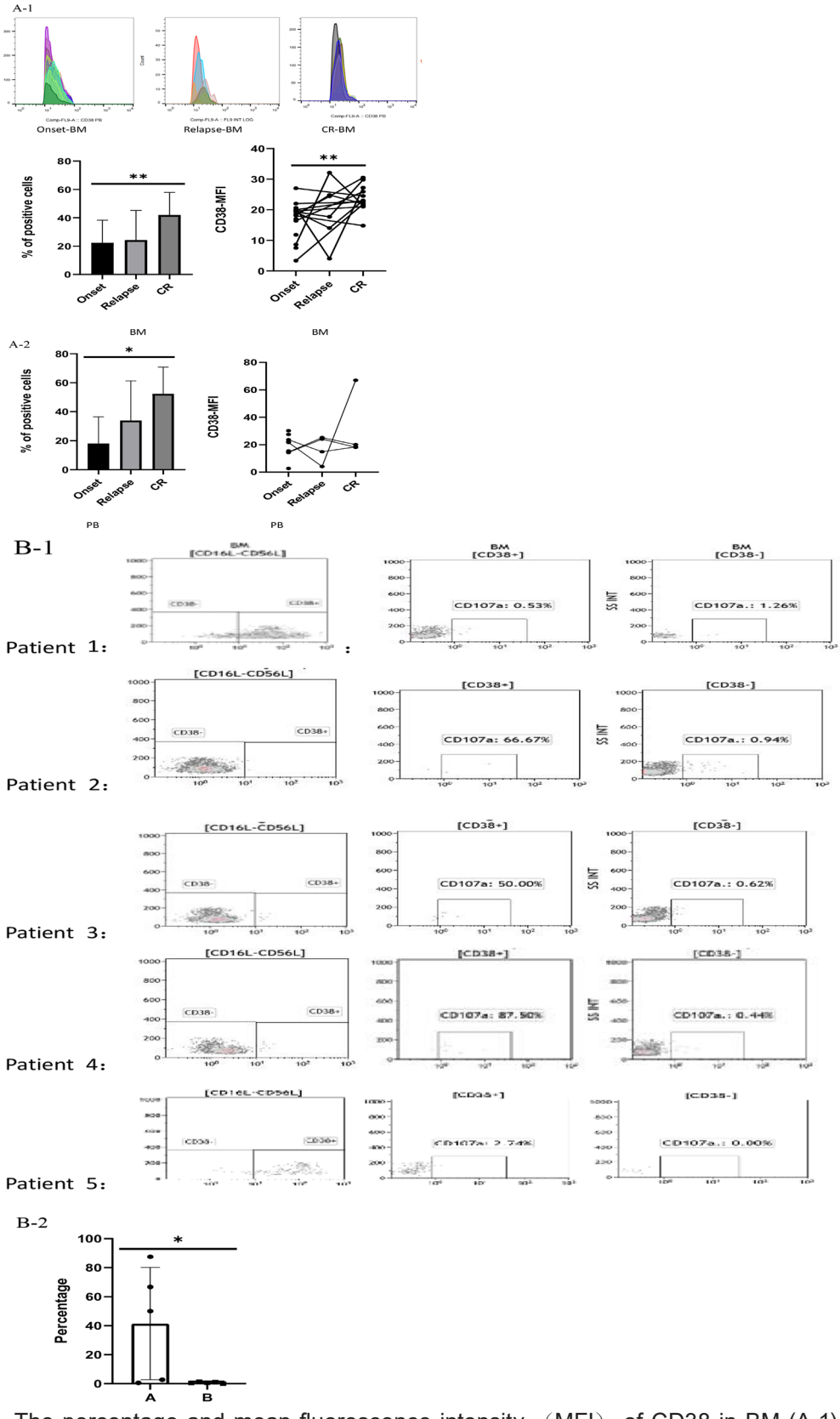

Figure 3. The percentage and mean fluorescence intensity （MFI） of CD38 in BM (A-1). and PB $CD56^{low}CD16^{low}$ NK cell subsets (A-2). of MM patients at different stages The Percentage of CD107a on $CD38^{positive}CD56^{low}CD16^{low}$ and $CD38^{negtive}CD56^{low}CD16^{low}$ in five different MM patients (B-1). Degranulation of $CD38^{positive}CD56^{low}CD16^{low}$ and $CD38^{negtive}CD56^{low}CD16^{low}$ NK cell subset in BM of MM patients(B-2, A=$CD38^{positive}CD56^{low}CD16^{low}$, B=$CD38^{negtive}CD56^{low}CD16^{low}$) (*P<0.05,** P<0.01). BM: Bone marrow; PB: Peripheral blood; CR: Complete remission

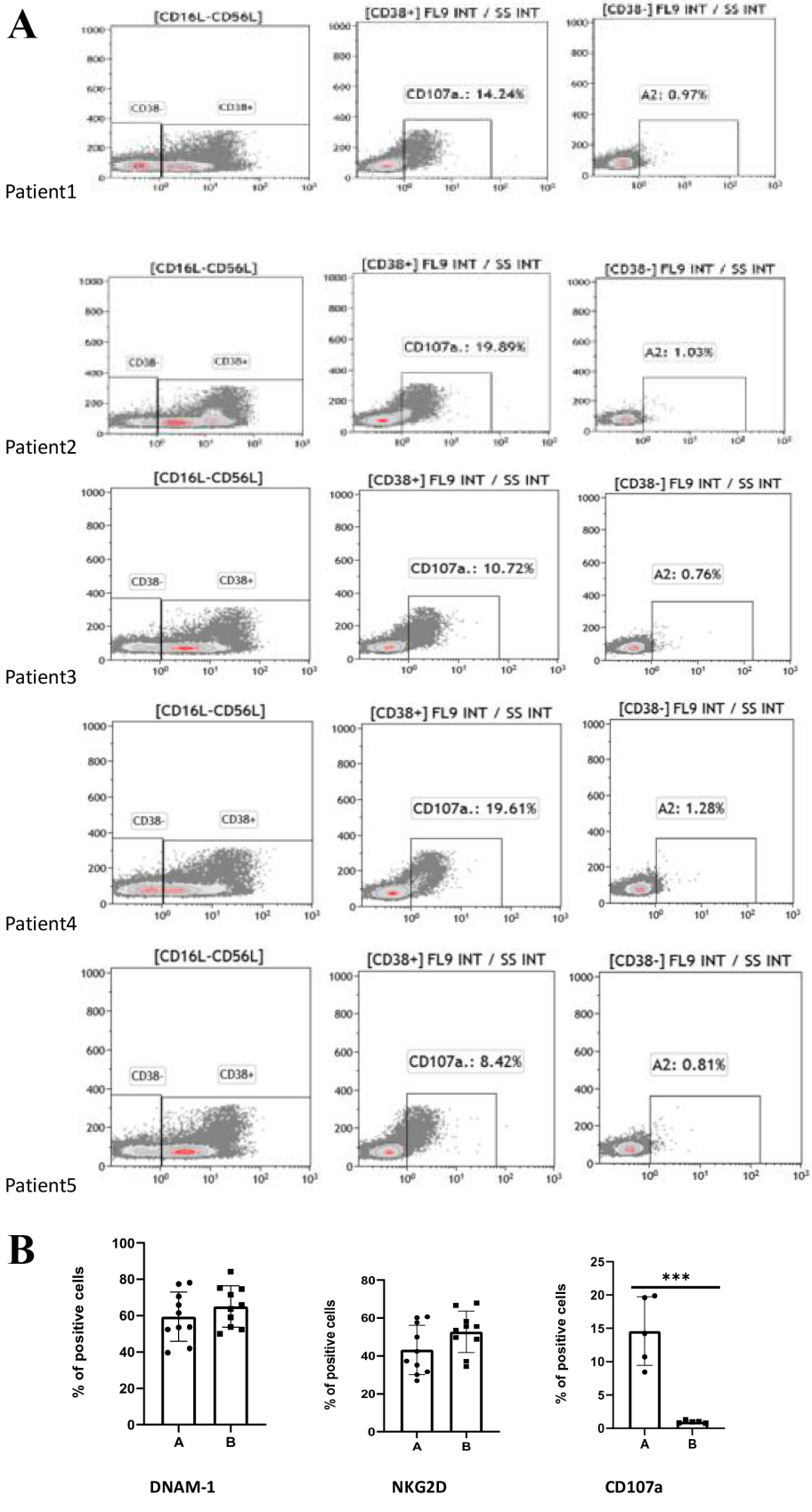

Figure 4. Percentage of CD107a in BM CD38^{positive}CD56^{low}CD16^{low} and CD38^{negtive}CD56^{low}CD16^{low} from five different MM patients in in vitro experiment (A). BM CD38^{positive}CD56^{low}CD16^{low} and CD38^{negtive}CD56^{low}CD16^{low} NK cell subset degranulation in MM patients (B,A=CD38^{positive}CD56^{low}CD16^{low}, B=CD38^{negtive}CD56^{low}CD16^{low}) (***P<0.001) (B).

The proportion of the $CD38^{positive}CD56^{low}CD16^{low}$ NK cell increased in MM patients at the CR stage CD38 in NK cells is important for Dara-triggered immune response, and its expression is limited to NK cells with effector function. Although a study published recently speculated the potential role of daratumumab in killing the $CD38^{positive}$ NK cells and subsequent expansion of a more powerful CD38 (−) NK cell population [17], the characteristics of both CD38 (-) and $CD38^{positive}$NK cell subset have hardly been studied. We observed that the expression level of CD38 significantly increased in the BM and PB CD56lowCD16low NK cell subgroups in the remission phase compared with the onset of the disease (Figures 3 A-1, A-2). In BM, the average fluorescence intensity of CD38 in the CR group was significantly higher than that in the onset group. To further explore the potential cytotoxicity of the $CD38^{positive}CD56^{low}CD16^{low}$NK cells, we aimed to examine the killing ability of immune response against autologous tumor cells in patients. For this purpose, we assessed the CD107a expression in the $CD38^{positive}CD56^{low}CD16^{low}$ subset and the $CD38^{negtive}CD56^{low}CD16^{low}$ NK cells respectively (Figures 3B-1). The result showed that the $CD38^{positive}CD56^{low}CD16^{low}$ subset had more CD107a compared with the $CD38^{negtive}CD56^{low}CD16^{low}$ cells (Figures 3B-2).

In vitro experiment showed the $CD38^{positive}CD56^{low}CD16^{low}$ NK cell subset possesses higher cytotoxicity than the $CD38^{negtive}CD56^{low}CD16^{low}$ NK cell.

In the light of the high percentage of the $CD38^{posive}CD56^{low}CD16^{low}$ NK cell subset in MM patients at CR stage, we hypothesized that this group may represent the major cytotoxic NK cells against tumor cells, which leads us to further investigate the ability of the CD38posiveCD56lowCD16low NK cells to recognize and kill K562 cells. As shown in Figure 4A, the killing ability of the $CD38^{positive}$ $CD56^{low}CD16^{low}$ NK cell subset to kill K562 cells was higher than in the $CD38^{negtive}CD56^{low}CD16^{low}$ NK cell group, suggesting a key role for this subgroup in recognizing and killing tumor cells (Figure 4B). However, there is no difference in the expression of receptors activating NK cell DNAM-1, NKG2D).

DISCUSSION

In this study, we first examined the proportion of the five NK cell subsets in the BM and PB in patients by the immunofluorescence and cytofluorimetric analysis. The results demonstrated that most NK cells in the bone marrow of MM patients are the $CD16^{low}CD56^{low}$, followed by the $CD56^{low}CD16^{negtive}$and $CD56^{low}CD16^{high}$ subsets. It has been reported that the $CD56^{low}CD16^{low}$ NK cell is a dominant subpopulation in BM of MM patients. Vulpis E et al. also found out that the $CD56^{low}CD16^{low}$ NK cells were the major population in the BM and PB of all MM patients [5], which is consistent with the conclusion from our study.

Some activated cytokines expressed by NK cells such as NKG2D, DNAM-1, and NKp30 were implicated in the inflammatory reaction and immune response. These receptors can bind to the corresponding ligands on the surface of MM cells and trigger NK cell-mediated tumor cell lysis. These activating receptors play a crucial role in improving NK cell recognition and avoiding tumor immune evasion [18, 19]. Researchers have reported a marked decline of NKp30 expression level in BM $CD56^{high}CD16^{+/-}$and $CD56^{low}CD16^{low}$ NK cell subgroups at all phases of MM patients [5], which is consistent with our observations. Given the fact that the $CD16^{low}CD56^{low}$ was the largest subgroup in the BM and PB of MM patients, next we assessed the expression of CD38 in this subgroup. Likewise, the expression of NKp30 decreased in the BM $CD38^{posive}CD56^{low}CD16^{low}$ NK cell subsets in the CR patients.

At present, there are limited studies on the detection of CD38-positive NK cells in MM patients. By characterizing the expression of CD38 on immunocytes from both the healthy

normal donors and MM patients, previously Chen Zhu et al. found that the largest proportion and highest expression levels of the $CD38^{positive}$ cells were observed NK cells and monocytes. By comparing the density of CD38 receptors immunocytes in both the donors and patients with MM, they further detected a trend of raised CD38 receptors on NK cells and B cells from MM patients [20]. However, there is no report regarding the connection between CD38 and disease progress, thus requiring further investigation.

CD38 is present on several nonpathological cell subsets, including NK cells, activated T cells, and B lymphocytes [21, 22]. According to a recent study, CD38 is a multifunctional protein both exoenzymatic activity and adhesion properties mediated through its interaction with CD31 on endothelial cells [20, 23]. Our data show that the BM $CD38^{positive}$ $CD56^{low}CD16^{low}$ effector cells, instead of the BM CD38-negative CD56lowCD16low, can kill K562 cells. We suspected that the $CD38^{positive}CD56^{low}CD16^{low}$ NK cells may activate the immune system of myeloma patients, potentially important for treating cancer patients. Modern medical studies have demonstrated that the surface protein CD38 is an important functional receptor of human NK cell essential for immune synapse formation. NK cells representing high levels of CD38 indicate enhanced killing ability and IFN-γ secretion in response to tumor cells. Suppressing the enzymatic activity of CD38 does not affect NK cell function, but blocking the binding of CD38 with its ligand CD31 abrogates the cancer-fighting ability and IFN-γ expression of NK cells in response to cells infected by the influenza. Blocking CD38 on NK cells is similar to removing the effector cells targeting tumor cells. The CD38 locates and aggregates at the immune synapse between NK cells and their target cells. As a result, blocking the CD38 severely impairs the ability of NK cells to form conjugates and immune synapses with targets. Taken together, the CD38 plays a critical role in the immunological synapse formation of NK cells. These findings provide new avenues in the development of immunotherapy against cancer and infection by revealing a crucial role of the CD38 in NK cell killing activity. Furthermore, the upregulation of the CD38 NK cells has been reported in patients with acute influenza infection; the level of CD38 expressed by NK cells is related to the cytolytic function and the formation of immune synapses in infected cells [24, 25]. Here, we analyzed the distribution of the $CD38^{negtive}$ $CD56^{low}CD16^{low}$ NK cells in the bone marrow of MM patients at different stages, as well as the killing ability of both the $CD38^{positive}$ and $CD38^{negtive}CD56^{low}CD16^{low}$ NK cells by *in vitro* experiments. Our data suggest that the $CD38^{positive}CD56^{low}CD16^{low}$ NK cells may reflect the immune status of patients to some extent, and this group of cells may be useful in approaches of adoptive immunotherapy in the treatment of MM patients in the future.

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Conflicts of Interest: None declared.

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