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Decreased CD161 activating and increased CD158a inhibitory receptor expression on NK cells underlies impaired NK cell cytotoxicity in patients with multiple myeloma

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ABSTRACT

Aim As innate immune cells natural killer (NK), NK-like T and CTLγδ are important in antitumour response in multiple myeloma (MM), the aim of this study was to investigate some functional and phenotypical characteristics of these cells in MM.

Methods 29 patients with MM prior to therapy, in clinical stage I–III and 15 healthy controls (HCs) were investigated. Percent of immune cells in peripheral blood, NK cell activity, expression of activating (CD161) and inhibitory (CD158a, CD158b) NK cell receptors on $CD3^{-}CD16^{+}$ NK cells were evaluated using 51-chromium-release assay and by flow cytometry. Production of interleukin (IL) 2 and tumour necrosis factor (TNF)α was analysed in supernatants from in vitro activated peripheral blood mononuclear cells.

Results In patients with MM the percent of NK cells and their two subsets did not differ from controls, while NK-like T and CTLγδ cells were significantly decreased. Significant impairment of NK cell cytotoxicity, CD107a expression and interferon γ intracellular level was also shown. There was a significant decrease in CD161 and an increase in CD158a receptor expression on NK cells in these patients. Also IL-2 production was lowest in clinical stage III. However, TNF-α production did not differ between patients and HCs.

Conclusions Altered expression of CD161 activating and CD158a KIR inhibitory receptor is responsible for impaired antitumour activity of NK cells in MM patients. These new biomarkers may be helpful for patient selection for immunotherapy with cytokines, and novel KIR blocking monoclonal antibodies that enhance NK cell antimyeloma activity and provide clinical benefit.

INTRODUCTION

Natural killer (NK) cells might be involved in the disease process in multiple myeloma (MM) by exerting a regulatory function on the proliferating B cell clone and the inability of the immune system to recognise and kill malignant plasma cells in patients with MM has been attributed in part to the ineffective activation of NK cells.[1]

NK cells are important effectors of innate immune response that were defined by their capacity to kill certain tumour-target cells without prior sensitisation or major histocompatibility (MHC) restriction. In addition to their role in antitumour reactions they also regulate adaptive immune response by producing interferon (IFN)γ, tumour necrosis factor (TNF)α and granulocyte-macrophage colony stimulating factor.[2 3] They are characterised by a $CD3^{-}CD16^{+}$ phenotype, CD16 (FcγRIII) being the low affinity receptor for IgG expressed on the majority of NK cells that is involved in direct and antibody dependent cell-mediated tumour cytotoxicity.[4 5] Based on CD16 cell-surface expression, NK cells are divided into two subsets, the larger $CD16^{bright+}$ NK cell subset has high expression of CD16 and is composed of cytotoxic cells, while the smaller $CD16^{dim+}$ NK cell subset has low expression of CD16 antigen and includes immunoregulatory NK cells that produce different cytokines.[6]

NK cells are equipped with multiple activating and inhibitory cell surface receptors whose engagement by cognate ligands on target cells determines NK cell activation. Activating receptors include C-dependent lectin-like receptors, CD161, Natural-killer group 2, member D (NKG2D), natural cytotoxicity receptors and DNAX accessory molecule-1.[7] Contrary to this, killer cell inhibitory immunoglobulin receptors (KIRs) are type I membrane glycoproteins responsible for the inhibition of NK cell-mediated lysis of normal cells that express MHC class I molecules and thus maintain NK cell tolerance to self.[8] Moreover, in the functional maturation of NK cells ligation of inhibitory KIR receptors with self-MHC molecules in the process of education, also referred to as licensing, enables NK cells to acquire effector' functions.[9] In this sense, activation of NK cells, according to the 'missing-self' hypothesis, occurs in contact with malignantly transformed cells that have lost MHC class I molecules, and have therefore become susceptible to lysis.[10] However, even without loss of MHC class I molecules, NK cells can be activated if target cells abundantly express NK cell-stimulating ligands.[11] In this sense, it has been established that the activity of NK cells is regulated by opposing activating and inhibitory receptor signalling and their balance, influenced by tumour-related immunosuppressive factors, determines NK cell cytotoxicity.[12]

Additionally, NK-like T and γδ cytotoxic T (CTLγδ) effector cells, also constituents of the innate immune system, may express both T cell receptors and some NK cell surface markers.[13 14] Unlike NK cells, NKT and CTLγδ cells are best defined as a minor subset of T cells that mostly recognise tumour antigens in the context of MHC complex-related non-classical CD1d molecules.

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