Expression of Surface Molecules in Hematological Malignancies

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ABSTRACT

Hematological malignancies are represented in many cases by very aggressive tumors with poor outcome. For many years, immunophenotyping, that allows to describe specific surface antigens (also termed lineage-defining cell markers) in particular population of malignant cells has been widely used to assist in the diagnosis and monitoring of the broad spectrum of them. One of the greatest interest of both scientists and clinicians has been still multiple myeloma. Multiple myeloma is one the hematological neoplasm that belong to plasma cell dyscrasias. Their diagnosis is strictly associated with the description of specific phenotype on the population of malignant plasma cells. Among cell surface specific markers of these cells CD200, CD27, CD70 and CD40 are particularly significant. It was found that they directly associated with both immune escape and aggressiveness of malignant plasma cells. In these circumstances they may serve as a targets for a further treatment of multiple myeloma.

Keywords: hematological malignancies, phenotype, cell surface molecules, multiple myeloma, monoclonal antibodies

INTRODUCTION

Hematological malignancies are myeloid and lymphatic neoplasms caused by disruption of normal hematopoiesis in different stages. Many of them, despite being forefront of clinical interest, are characterized by poor outcome. Understanding their pathogenesis is still insufficient but discovery of lineage-defining cell surface markers significantly changed the paradigm of diagnosis and treatment. Among numerous hematological neoplasms one of the most curious from both scientific and clinical point of view is multiple myeloma.

Multiple myeloma is a hematological malignancy that is characterized by the clonal proliferation of malignant plasma cells in bone marrow, bone lesions, renal failure and immunodeficiency[1]. Myelomagenesis is a complicated, comprehensive and multistep process that involves MGUS (Monoclonal Gammopathy of Undetermined Significance), SMM (Smoldering multiple myeloma) and symptomatic plasma cell myeloma also known as multiple myeloma[2]. Among many targets in multiple myeloma the point of interest are the cell surface markers that define malignant plasma cell [3,4,5]. Many years of work on the assessment of the phenotype of multiple myeloma cells allowed not only to specify but also to fully describe their characteristic surface markers. Among numerous of them, glycoproteins CD200, CD27, CD70 and CD40 deserve a special attention. Briefly, CD200 initially referred to as OX-2, is a highly conserved, 48 kDa type 1a transmembrane glycoprotein related to the B7 family of costimulatory receptors[6,7]. It is widely expressed by most cells with the exception of skeletal muscle cells[8,9,10,11]. Overexpression of CD200 in malignant plasma cells is associated with poorer outcome. Despite high-dose chemotherapy and ASCT, MM patients with cells overexpressing CD200 have shorter event freesurvival (EFS) when compared with patients whose cells do not (over) express CD200[12]. In separate studies it has been reported that CD200 positive tumor cells can attenuate the ability of PBMCs to eradicate tumor cells[13].

CD27, also termed as S152, is a 120-kDa type I transmembrane glycoprotein belonging to the nerve factor/TNF receptor gene family[14]. CD27 is expressed in normal plasma cells, but not malignant plasma cells, peripheral T cells, and a subset of mature B cells[15]. On binding to its ligand CD70, CD27 induces T dependent B cell immunity[16,17]. As mentioned above, CD27 is expressed by normal plasma cells (CD19+CD38+) but its expression is reduced or absent in malignant plasma cells, a process which might have causal implications in progression of disease in MM[18,19]. Thus low expression of CD27 is associated with clinically aggressive cases of multiple myeloma[20,21], and the lack of CD27 expression in plasmacytomas may be a marker for progression to myeloma (22). CD70, also referred to as CD27L, is a 50 kDa, homodimeric, type II-TNF related transmembrane glycoprotein[23,24,25] which mediates the interaction between B- and T-lymphocytes and enhances the proliferation of activated T lymphocytes. Contrary to CD27, CD70 is overexpressed in malignant plasma cells and this might be associated with the increased proliferation of malignant plasma cells and their shorter overall survival. Interactions between CD27 and CD70 are known to promote the differentiation of peripheral blood memory B cells into plasma cells in association with several cytokines (IL-4, IL-10), CD40:CD40L signalling, and the up-regulation of PRDI-BF1/Blimp-1[26]. Since CD70 is expressed on activated B and T cells it is possible that loss of CD27 during B cell differentiation in germinal centres (GC) contributes to immune escape and development of malignant clone of plasma cells[18, 27]. Restoration of the expression CD27 on malignant plasma cells would results its re-interaction with CD70, what could give a chance to induce apoptosis of these cells[28,29].

CD40L is a 32-33 kDa II type transmembrane protein belonging to the TNF-superfamily. It is expressed on the cell surface as one of three splice variants. Two shorter versions of the protein, 18 and 31 kDa respectively retain the ability to form trimers and bind to CD40 and thus can still apparently mediate biological signaling[30,31,32].

Overexpression of CD40L- CD40 axis in malignant plasma cells induce the cascade of intracellular signaling pathways responsible for its proliferation and survival[33,34,35]. Preliminary studies showed that that targeting of the molecules mentioned above may be associated with significant beneficial effects. Preliminary studies showed that targeting CD200, CD70 and CD40L-CD40 axis may significantly enhance local immune response in tumor microenvironment. Namely, use of human anti-CD200 monoclonal in AML (acute myeloid leukemia) animal models successfully induced immune responses. They recovered the activity of NK (natural killer) cells[36].

Next, blockade of CD70 in variety CD70 positive cancer cell lines (e.g. multiple myeloma, Burkitt lymphoma, mantle cell lymphoma), in animal models, blocked their proliferation and survival and induce ADCC (antibody-dependent cell-mediated cytotoxicity), CDC (complement dependent cytotoxicity), and ADCP (antibody-dependent cell-mediated phagocytosis) mechanisms[37]. Use of humanized anti-CD40 monoclonal antibody (SGN-40) against human MM.1S and MM1R multiple myeloma cell lines significantly inhibited their proliferation and survival, induced apoptosis and enhanced ADCC. SGN-40 both induced activity of FasL, TNF-α, and TRAIL and inhibited both AKT/IκBα and ERK pathways. It is well known that IL-6R: IL-6 interactions promote bone loss, disease progression and drug resistance in multiple myeloma. SGN-40 diminished the expression of IL-6R[38].

OBJECTIVES

The first objective of this study was to present the significance of CD200, CD27, CD70 and CD40 in the development of multiple myeloma. The next purpose was to evaluate whether proper expression of CD200, CD27, CD70 and CD40 can put malignant plasma cells on the path to programmed type II death. The other aim of this study was to show if the above-mentioned molecules may become or direct or indirect therapeutic targets in the further treatment of multiple myeloma.

CONCLUSION/RESULTS

1. Reinstatement of normal CD27-CD70 axis may induce apoptosis of malignant plasma cells
2. Inhibition of CD200 and CD70 in malignant plasma cells may restore local immune response
3. inhibition of CD40 in positive malignant plasma cells both inhibits their proliferation and survival and induce apoptosis
4. CD200, CD27, CD70 and CD40 may serve as a future therapeutic targets.

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