

Targeting Human β -Microglobulin with Monoclonal Antibodies in Multiple Myeloma - A Potential in Treatment

Mingjun Zhang^{1,2}, Jin He¹ and Jing Yang^{1,3*}

¹Department of Lymphoma/Myeloma, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

²Department of Cancer Biology, Lerner Research Institute, Cleveland Clinic, USA

³Cancer Research Institution, Guangzhou Medical University, Guangzhou, China

*Corresponding author: Jing Yang, Department of Lymphoma/Myeloma, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Texas, USA, Tel: 713-563-0357; Fax: 713-745-1179; E-mail: jiyang@mdanderson.org

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Introduction

Multiple myeloma (MM) is a clonal plasma cell neoplasm that utilizes bone marrow microenvironment for survival and proliferation [1-3]. However, current therapies could rarely cure MM. The relapse or refractory aspect of the disease is commonly seen in MM patients, especially among patients with high-risk MM. In past decades, targeted immunotherapy with monoclonal antibodies (mAbs) emerged as a major new treatment modality that offered great benefits for MM patients [4]. Different approaches, aimed at finding potential mAb-based therapeutics for this disease including identification of alternative, or novel, target antigens [5], conjugation of mAbs with classic or novel drugs [6], and generation of chimeric antigen receptor T cells with specific mAbs [7], have been developed by scientists. Recently, our group has generated the mAbs that work directly against human β 2-microglobulin (β 2M) both in vitro and in the mouse experiments, and has demonstrated that β 2M is a potential target for MM treatment [8].

Human β 2M is part of major histocompatibility complex (MHC) class I molecules [9], that is involved in the presentation of peptide antigens to immune cells. Elevated β 2M levels can be observed in patients with MM or other hematological malignancies, and this molecule has served as one of the key prognosis indicators in MM [10,11]. Using human-like mouse models, our research has demonstrated that anti- β 2M mAbs have strong and direct apoptotic effects on MM (Figure 1A) and other hematological malignancies, with little toxicity towards normal tissues and cells [12]. The anti- β 2M mAbs activate the c-Jun N-terminal kinases and inhibit extracellular-signal-regulated kinases and phosphatidylinositide 3-kinases/Akt (also known as protein kinase B). The mediated signaling pathways, and the mAbs, can recruit MHC class I molecules into and exclude receptors for growth factors, such as IL-6 and IGF-1, from lipid rafts [12,13]. Our results suggest that anti- β 2M mAbs could be a novel therapeutic agent specifically targeting MM in a clinical setting.

In addition, enhancing antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) activities is one of the most promising ways to improve the clinical efficacy of already-approved antibodies. This concept is now actively being examined in the clinic, especially in the field of hematological malignancy treatment [14]. Our recent studies show that anti- β 2M mAbs effectively lysed MM cells via ADCC and CDC (Figure 1B and

1C). We examined the anti-MM activity of anti- β 2M mAbs combined with lenalidomide, an immunomodulatory drug that has been widely used in the treatment of MM [15], and we found that lenalidomide potentiated the mAb-induced ADCC activity both in vitro and in vivo against MM cells by enhancing the killing activity of natural killer cells (Figure 1C) [16]. These findings provide a rationale for combining anti- β 2M mAbs with lenalidomide to improve patient outcomes in MM.

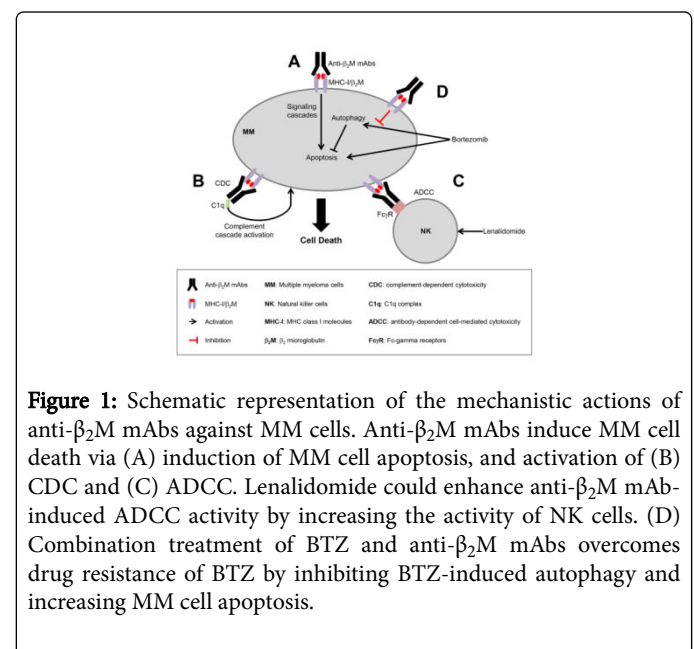


Figure 1: Schematic representation of the mechanistic actions of anti- β 2M mAbs against MM cells. Anti- β 2M mAbs induce MM cell death via (A) induction of MM cell apoptosis, and activation of (B) CDC and (C) ADCC. Lenalidomide could enhance anti- β 2M mAb-induced ADCC activity by increasing the activity of NK cells. (D) Combination treatment of BTZ and anti- β 2M mAbs overcomes drug resistance of BTZ by inhibiting BTZ-induced autophagy and increasing MM cell apoptosis.

Another standard regimen to treat MM patients is proteasome inhibitor-based chemotherapy. As an example, bortezomib (BTZ) is currently being used worldwide to treat MM and mantle cell lymphoma [17]. However, adverse effects and drug resistance are emerging as great challenges for its extended application [18]. We speculated about whether the addition of anti- β 2M mAb treatment would indeed improve the efficacy of BTZ alone. Our investigations showed that the combination treatment offered a much higher anti-MM effects than either agent alone, and anti- β 2M mAbs enhanced BTZ-induced apoptosis in MM cells and in mouse models. Mechanistic studies showed that anti- β 2M mAbs could overcome BTZ resistance by inhibiting BTZ-induced nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) signaling and autophagy

activation (Figure 1D) [19]. Thus, our studies provide a new insight in the development of anti- β 2M mAbs and BTZ combination to overcome chemotherapy resistance in MM patients.

In summary, our results suggest that anti- β 2M mAbs may be a more promising next-generation antibody-based immunotherapeutic agent for the treatment of MM. The clinical development of anti- β 2M mAbs, both as a monotherapy or in combination with existing MM drugs, such as lenalidomide or BTZ, offers MM patients increased treatment options and improves overall patient outcome.

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