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β2-Microglobulin: emerging as a promising cancer therapeutic target

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β2-Microglobulin, a MHC class I subunit, is found to act similarly to a prototypical oncogenic factor capable of stimulating growth and progression of various cancers and plays a key regulatory role in stimulating cancer bone metastasis. Free β2M in serum or urine has been regarded as an independent biomarker in several cancers. Specific antibodies to β2M have remarkable tumoricidal activity for both solid tumors and blood malignancies and are shown to be selective to tumor cells, but caused no toxicity in normal cells. These surprising data strongly suggest that β2M is a promising new therapeutic target for human cancers.

Introduction

β2-Microglobulin (β2M) is a nonglycosylated protein with a molecular mass of 11,800 Da that is synthesized by all nucleated cells and forms a small invariable light chain subunit of major histocompatibility complex (MHC) class I antigen (also known as human leukocyte antigens (HLAs) in humans) through noncovalent linkage on cell surfaces. Because it is noncovalently associated with the α-chain of MHC class I molecules and has no direct attachment to the cell membrane, β2M on the cell surface can exchange with free soluble β2M. Free β2M is found in body fluids as a result of shedding from cell surfaces or intracellular release [1,2]. The best-characterized function of β2M is to interact with and stabilize the tertiary structure of the MHC class I a-chain to present antigenic peptides to cytotoxic (CD8+) T lymphocytes. On recognition of foreign peptide antigens on cell surfaces, T cells actively bind and lyse the antigen-presenting cancer cells. In β2M-deficient mice, antibody responses are shown to be defective because of increased IgG catabolism and natural killer cells are shown with increased sensitivity to MHC class I heavy chain-mediated inhibition [3,4]. In addition to the roles in immunity, recent studies demonstrate that β2M is extensively involved in the functional regulation of survival, proliferation, apoptosis and even metastasis in cancer cells [5–12]. Figure 1 illustrates the complicated effects of β2-microglobulin in cancer. Targeting β2M signaling pathways has shown remarkable tumoricidal activity in various cancers and provides a new strategy for cancer therapeutics [13–17]. Here, we describe these surprising findings of β2M in human malignancies and discuss the potential application of β2M as a promising new cancer target.

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β2M as a cancer prognostic marker

β2M protein is present at low levels in serum, urine and other body fluids under normal physiological conditions and is almost exclusively catabolized within the kidney. Many studies have demonstrated that serum or urine β2M concentration is increased in a variety of abnormal growth diseases, including breast cancer, prostate cancer, lung cancer, renal cancer, gastrointestinal and nasopharyngeal cancers, multiple myeloma and, especially, lymphocytic malignancies, such as non-Hodgkin's lymphoma and multiple myeloma [18–24]. In these malignancies, the β2M level serves as an independent and significant prognostic factor. Moreover, both serum and urine β2M level have also been shown to be significantly elevated in patients with advanced prostate cancer (metastatic and androgen-independent prostate cancer) and correlate negatively with patient survival [20]. Because serum prostate-specific antigen (PSA) elevation, the most widely used marker for prostate cancer diagnosis and treatment, is highly expressed in both benign and malignant prostate epithelium, β2M may be

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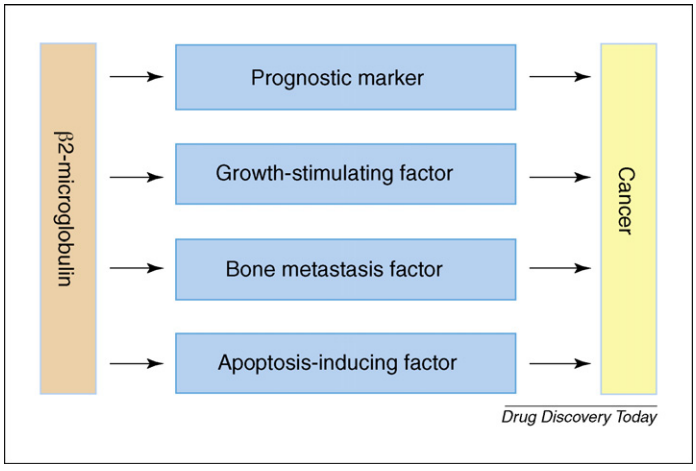

FIGURE 1
Schematic diagram showing the complicated effects of β2-microglobulin in cancer.

explored as a useful progression marker in prostate cancer, which is more specific for androgen stimulation than PSA [25]. Increased β2M levels in blood specimens are also correlated with a poor prognosis and the failure of multiple myeloma patients to respond to therapy [19]. It is showed that IFN-alpha could cause a rise in the formation of β2M, which helps to present MHC molecules onto cell membranes, decrease tumor evasiveness and thus enhance host defence mechanisms against tumor growth [26]. β2M is known as a classic IFN-responsive gene in multiple myeloma and serum β2M measurement can assess tumor burden [19]. By contrast, although β2M expresses at a constant level, with respect to its mRNA, in many cells and has been used as an internal reference control in studies, a recent study demonstrates a prognostic role of β2M at the mRNA level in colorectal cancer and suggests that low β2M expression levels may be useful for identifying patients with lymph node metastasis and/or poor survival [27]. In summary, β2M may be useful as a prognostic and therapeutic response indicator for cancer patients and additional studies are warranted to explore the potential significance of β2M as a useful marker for more cancers.

β2M as a cancer growth-stimulating factor

The functional roles of β2M in cancers are attractive, but still not fully identified. Previous studies have shown that MHC class I assembly with β2M is important in regulating tumor immunity and progression. There is an increased susceptibility to tumor formation in β2M gene knockout mice, which suggests a potential regulation of cancer growth by β2M. In the late 1980s, β2M was also proposed to be mitogenic for osteoblasts, but this effect observed in early studies has been hotly debated owing to methodological issues [28,29]. Recent studies using a wide range of new experimental approaches to assess the mitogenic role of β2M in malignancy have provided strong evidence to show that β2M acts similarly to a prototypical oncogenic factor capable of stimulating growth and progression of various cancers. β2M has been identified with growth stimulatory activity to human prostatic carcinoma PC-3 cells and shows antagonistic activity to TGF-β-growth-induced inhibition [5]. Recently, the growth stimulation effect of β2M was further identified in a wide series of human prostate cancer cells and also in other cancers, including human breast, lung and kidney [6,7]. Overexpression of β2M promotes rapid growth and inhibition of β2M promotes regression of various cancer xenografts. The mechanisms underlying the growth-promoting effect of β2M are not fully defined. It is reported that β2M could increase the expression of IL-6, 8 and 10 by several cell types, regulate the expression of hormone/growth factor receptors (epidermal growth factor receptor, insulin receptor and IGF-I and IGF-II receptors) and the interaction with their ligands that may enhance tumor growth [14,29,30]. Recently, β2M has been found to activate cAMP-dependent protein kinase A (PKA) activity and phosphorylated cyclic AMP-responsive element binding protein (p-CREB) with increased expression of its target genes, through binding to, and activation of, a seven-transmembrane G-protein-coupled receptor (GPCR) or a yet-to-be-identified β2M receptor [6]. This activation could enhance tumor survival and growth through elevated levels of cyclin A, cyclin D1 and the potent angiogenic factor, vascular endothelial growth factor (VEGF). In convergence with this PKA–CREB–VEGF signal axis, β2M also activates the cell survival pathways phosphatidylinositol 3-kinase (PI3K)/Akt, Raf/mitogen-activated protein kinase (MAPK) and JAK/STAT3 in human renal cell carcinoma cells and prostate cancer cells [7,11,31]. The proposed molecular signaling pathways of β2M in human cancer growth and progression are summarized in Fig. 2.

β2M in cancer bone metastasis

Bone is one of the most common sites of cancer metastasis; osteoblastic response and osteoclastic bone resorption are two predominant mechanisms for cancer bone metastasis. Cancer cell plasticity could fuel tumor growth through the production of angiogenic factors and mimicking the normal physiological process [32]. One of the unique features of bone metastatic cancer cells is their ability to mimic gene expression and behaviors of bone cells by synthesizing and depositing bone-like proteins, such as osteocalcin, osteopontin (OPN), receptor activator of NF-κB ligand (RANKL) and bone sialoprotein (BSP), in a process known as osteomimicry [33,34]. β2M has been recently identified as a crucial autocrine and paracrine growth factor allowing cancer cells to continue to synthesize and deposit bone-like proteins. It stimulates the growth and survival of prostate cancer cells by activating VEGF and androgen receptor signaling that eventually enables cancer cells to resist hormone withdrawal, exposure to chemotherapy and radiation therapy [33]. It is reported that osteomimicry in prostate cancer cells is maintained by the activation of PKA signaling, mediated by CREB [6,7]. β2M also regulates cancer bone metastasis through the regulation of epithelial–mesenchymal transition (EMT), a crucial step for cancer metastasis [11]. In androgen refractory cancer of the prostate (ARCaP) cells and human renal carcinoma cells, β2M was shown to be crucial in facilitating EMT by downregulation of E-cadherin expression and upregulation of N-cadherin, vimentin and RANKL, which subsequently promote prostate cancer cell migration, invasion and metastasis to the skeleton [11,35].

Cancer is not a disease of a single cell type. Laboratory and clinical data show that tumor–stroma interactions contribute to the development and progression of solid tumors. Cancer bone metastasis requires an intimate and aggressive interaction between

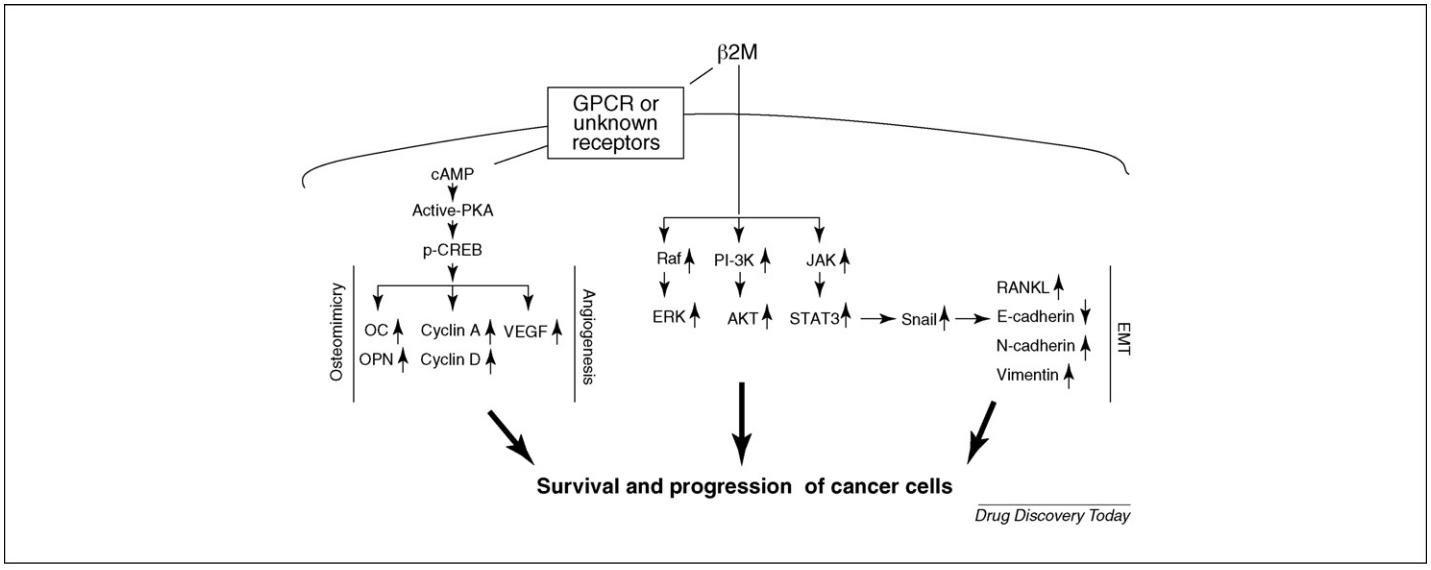

FIGURE 2
Proposed molecular signaling pathways of β2M in human cancer growth and progression. β2M can activate cAMP/PKA/p-CREB signaling and increases cell proliferation, angiogenesis and osteomimicry; β2M also can activate cell survival pathways PI3K/Akt, Raf/MAPK and JAK/STAT3, which has a direct growth-promoting and antiapoptotic action in cancer cell survival and growth through the induction of EMT.

cancer cells and bone microenvironment, which provides a fertile soil for the growth of cancer cells [33]. It has been well documented that β2M is a key regulator for bone metabolism [29]. Subcutaneous injection of β2M induces bone resorption in neonatal mice, which can be demonstrated histologically, and purified human β2M protein induces a dose- and time-dependent calcium efflux in cultured murine calvariae, which is mediated, in part, by IL-1β [36]. β2M also stimulates the synthesis of IL-6, a potent bone-resorbing cytokine, in osteoblasts [37]. Moreover, recent studies have shown that β2M can directly stimulate osteoclast activity and large numbers of osteoclasts are found in prostate tumors over-expressing β2M in bone, which confirms that β2M can stimulate osteoclastogenesis [7,36,38]. It has also been reported that the expression of a key regulator of osteoclastogenesis, RANKL, was increased by the activation of the Stat3–Snail–LIV-1 pathway in metastatic prostate cancer cells [11]. In addition to bone metabolism, β2M has also been proposed to be a potential initiator of inflammatory responses, which have been shown to be involved in cancer development and progression [39]. β2M can also stimulate synovial fibroblasts to produce stromelysin, a neutral matrix metalloproteinase, which is believed to be a key enzyme in inflammatory joint diseases [40].

Mesenchymal stem cells (MSCs) in bone marrow have been proposed to play a role in carcinogenesis because MSCs could undergo spontaneous transformation and may be involved in cancer progression [41–43]. The concept that bone marrow MSCs are stimulated by cancer cells now attracts much attention because bone matastatic cancer cells make close contact with bone marrow stromal cells. Recent evidence suggests that MSCs could migrate toward primary tumors and metastatic sites [41]. Our work shows that MSCs could interact with human prostate cancer cells and promote their growth, migration and invasion through the induction of osteomimicry and EMT [44]. By contrast, β2M secreted by cancer cells is a regulator of the growth and migration of MSCs. Physiological concentrations of β2M could stimulate a dose-dependent mitogenic response in MSCs from various sources. Exogenous overexpression of β2M induces the growth of MSCs, while specific siRNA and blocking antibodies blocked the proliferation-promoting effect on MSCs by β2M [45]. Furthermore, β2M increases the proliferation of MSCs through enhanced phosphorylation of CREB and upregulation of IL-6 and VEGF [44,45]. The human transcriptional positive coactivator, PC4, has recently been identified from transformed MSCs as a new oncogenic factor that can support the growth of advanced prostate cancer in bone through the activation of osteomimicry [46]. Thus, it is interesting to explore the potential relationship between PC4 and β2M in prostate cancer bone metastasis. These studies indicate that β2M may play an important role in mediating the vicious interaction between MSCs and cancer cells. In addition, a recent report also describes a crucial role of MSCs in osteolytic bone destruction in cancer by regulating the activity of osteoclasts through producing IL-6. In osteolytic metastases, the production of osteoclast-activating factors such as IL-1α, IL-6, IL-11, tumor necrosis factor α and RANKL by tumor cells is the driving mechanism by which they invade the bone. It is reported that human neuroblastoma cells that do not produce osteoclast-activating factors could induce MSCs to express markedly increased levels of IL-6 to stimulate osteoclast activity. This study indicated that the expression of IL-6 by MSCs is an alternate pathway for osteoclast activation by cancer cells [47]. The possible roles of β2M in the regulation of osteoblasts, osteoclasts and MSCs are summarized in Fig. 3.

β2M as an apoptosis-inducing factor

Although extensive studies have demonstrated β2M to be a growth stimulatory factor in the development and progression of various cancers, β2M also seems to play a role as an apoptosis-inducing factor in at least several leukemic cell lines. Mori *et al.* demonstrated, for the first time, the existence of human β2M-induced apoptosis [48] and subsequently it was confirmed that β2M could act as an apoptosis-inducing factor in several leukemic cell lines, in

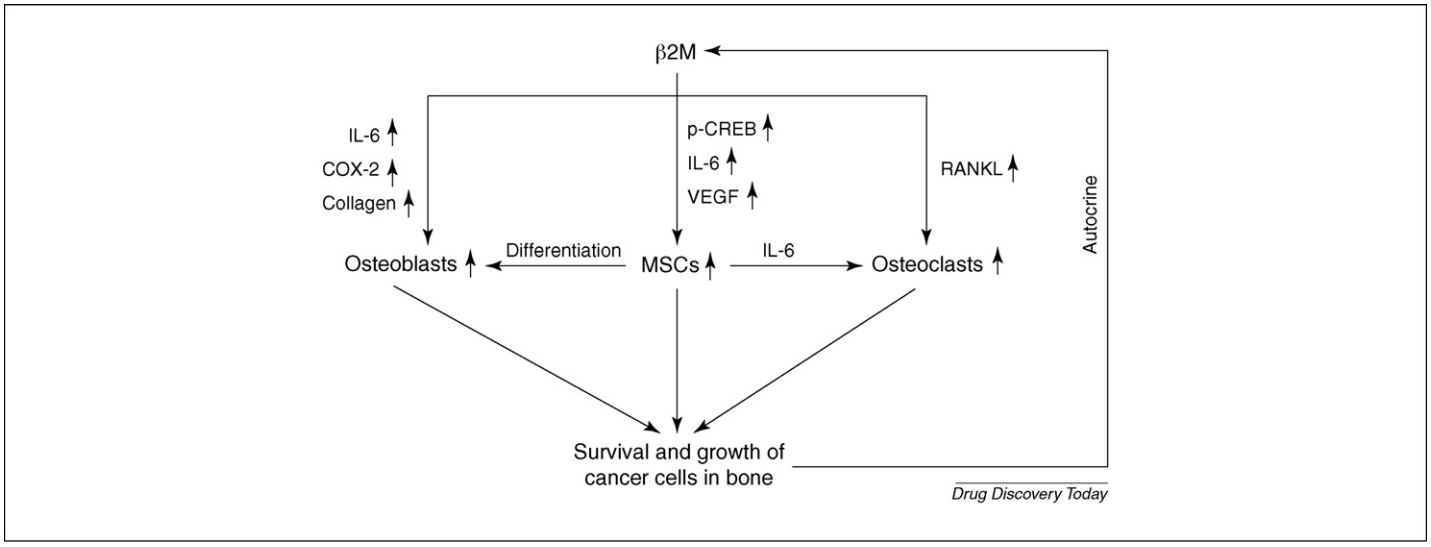

FIGURE 3
β2M mediates the reciprocal communication between cancer cells and bone cells, which supports the survival and growth of metastatic cancer cells in bone microenvironment.

lymphoma cell lines and in myeloma cells [8–10]. The mechanisms underlying β2M-induced apoptosis appear to be very complex. β2M-induced apoptosis in K562, U937, BALL, CCRF-HSB-2, CCRF-CEM and myeloma cells is mediated through the caspase cascade and not by either the FasL/Fas or the TNF-α/TNFR systems. β2M-induced apoptosis in HL-60 cells, which are sensitive to cancer chemotherapeutic agents and in two MDR variants of this cell line, appears to be mediated through the Fas/Fas-ligand or tumor necrosis factor-α (TNF-α)/TNF-α receptor system. Moreover, exogenous β2M protein treatment or transfection with a full-length cDNA clone expressing human β2M could increase the sensitivity of MCF-7 cells to doxorubicin. Consistent with these results, transfection with an antisense β2M plasmid decreased MCF-7 cell sensitivity to doxorubicin with partial loss of β2M [49]. β2M may, however, use different signaling pathways to induce apoptotic cell death in drug-sensitive and resistant cells with different mechanisms of resistance. It is reported that β2M activates an unknown Z-VAD-fmk-sensitive caspase-dependent cell death pathway in HL-60/VCR cells, which overexpress P-glycoprotein and Bcl-2. This causes the release of cytochrome *c*, but β2M induces apoptosis in HL-60/ADR cells, which overexpress MRP1, but are deficient in Bax expression, by a nonmitochondrial caspase pathway and independently of Bax [50]. Because the apoptosis-inducing effect of β2M is highly variable, the precise action and true clinical relevance of β2M in this issue will need to be studied.

β2M as a promising cancer therapeutic target

Previous studies have indicated that β2M/MHC class I can serve as important signal-transducing molecules. The promising data of β2M as an oncogenic factor in various cancers further support the hypothesis that β2M appears to be an excellent new target for interrupting human cancer growth [16]. Very recently, remarkable antitumoral activity has been observed in a variety of both solid tumors and blood malignancies by targeting β2M signaling pathways using either sequence-specific siRNA or antibodies [6,7,13–19]. Huang *et al*. evaluated the effect of β2M siRNA on various human prostate tumors (including PC-3 and C4-2B) grown both in subcutaneous bone powder xenografts and in mouse skeleton [6]. The results show that β2M siRNA markedly inhibits tumor growth in mouse bone or even eliminated pre-existing tumors in bone powder xenografts. The inhibition of tumor growth by β2M siRNA is mediated by the induction of cancer cell apoptosis through the activation of the initiator, caspase. Furthermore, the treatment of prostate cancer and renal cancer cells with anti-β2M polyclonal or monoclonal antibodies also resulted in significant growth inhibition or apoptosis induction [15,51]. Near-simultaneously, Yang *et al*. described that mAbs against β2M can induce apoptosis in a variety of myeloma and leukemia cell lines and primary tumor cells isolated from patients, both *in vitro* and in xenograft mouse models [13]. The monoclonal antibodies (mAbs) induce apoptosis in a caspase-dependent manner, in the absence of secondary crosslinking and immunological effector mechanisms, such as complement and antibody-dependent cell-mediated cytotoxicity (ADCC). This finding is also supported by siRNA experiments in which knockdown of surface β2M and MHC class I molecules abrogate the induction of apoptosis of tumor cells induced by the mAbs. Yang *et al*. also demonstrated that lipid rafts are involved in anti-β2M mAb-induced apoptosis in tumor cells. Following the treatment of myeloma cells with the β2M mAbs, MHC class I relocated to lipid rafts, where they recruited and activated kinases Lyn and PLCγ2. This led to JNK activation and inhibition of PI3K/Akt and ERK pathways, which in turn induced apoptosis through compromised mitochondrial integrity, cytochrome *c* release and activation of the caspase-9 cascade [14]. Table 1 is presented as showing selected studies of β2-microglobulin on tumor growth.

Encouraging studies have suggested that MHC class I and II molecules are unique targets for the induction of cell apoptosis. Both murine and fully human HLA-DR-specific mAbs have been shown to inhibit growth and induce apoptosis of tumor cells [52]. There are still, however, potential safety concerns owing to the expression of HLA-DR on normal hematopoietic cells. A very interesting finding is that β2M antibodies were shown to be selective to tumor cells and failed to damage normal marrow

TABLE 1

Selected studies of β2-microglobulin on tumor growth.

Cancer type	Materials	Results	Refs
Prostate cancer	Purified β2M	Stimulates cell growth *in vitro*	Rowley *et al.* [5]
Prostate cancer	β2M cDNA; recombinant β2M	Stimulates cell growth both *in vitro* and *in vivo*	Huang *et al.* [6]
Renal cell carcinoma	β2M cDNA; recombinant β2M	Stimulates cell growth both *in vitro* and *in vivo*	Nomura *et al.* [7]
Myeloma and other hematological malignancies	Monoclonal β2M antibody; sequence-specific siRNA to β2M	Induce cell apoptosis both *in vitro* and *in vivo*	Yang *et al.* [13,14]
Renal cell carcinoma	Polyclonal β2M antibody	Inhibit cell growth and induce apoptosis *in vitro*	Nomura *et al.* [15]
Prostate cancer	Polyclonal and monoclonal β2M antibodies	Inhibit cell growth and induce apoptosis *in vitro*	Huang *et al.* [51]

hematopoietic cells of implanted human bone or murine organs that express human β2M/HLA molecules. Similar results have also been obtained following treatment with antibodies specific to human leukocyte antigen-DR (HLA-DR). It would appear that the antibodies cause no long-lasting hematological toxicity in primates, *in vivo* [52]. So far, it is unclear why β2M antibodies display different effects on cancer cells and normal cells. It is reported that there was a differential expression of β2M/MHC class I molecules by normal and cancer cells. In normal B cells that Lyn was not associated with lipid rafts and β2M-specific mAbs did not trigger MHC class I relocation to the rafts and that JNK, PI3K/Akt and ERK activities remained unchanged after the mAb treatment [17]. These data provide a plausible explanation for the selectivity and sensitivity of β2M-specific mAb-mediated apoptosis of normal versus malignant cells. In addition, dexamethasone is one commonly used chemotherapy drug for myeloma, but some reports have shown that growth factors, such as IL-6, induce translocation of their receptors to lipid rafts and confer protection against dexamethasone-induced apoptosis [14]. Anti-β2M mAbs induce cell death via recruiting MHC class I molecules to lipid rafts, which not only activate JNK via Lyn and PLCγ2, but also inhibit PI3K/Akt and ERK pathways by excluding IL-6 and IGF-I receptors from lipid rafts and disrupting their signaling pathways. These results may explain why the cytokines protect myeloma cells from dexamethasone-induced apoptosis, but had no effect on cell death induced by the mAbs.

Conclusion

The evaluation of the potential clinical implications of nonimmunological functions of β2M in cancer therapeutics is just starting, but there are several questions that need to be defined. The growth regulatory effects of β2M seems to depend on the nature of the cells, because it can act as both a positive and negative growth factor in different cancer cells. Although β2M is a growth-stimulating factor in various cancers, the mechanisms underlying this activity are not fully understood. In common with other molecules of the MHC complex, β2M may possibly act through a variety of receptors (including GPCR and hormone and/or growth factor receptors) to produce such diverse responses. There is still, however, a lack of an identified receptor specific for β2M and additional studies are clearly needed.

The remarkable tumoricidal activity obtained from targeting β2M signaling is potentially very promising for a variety of cancers and shows great promise. β2M antibodies have also been shown to be selective to tumor cells over normal cells. Surprisingly, anti-β2M antibodies do not block the effect of β2M when β2M serves as a negative growth regulator in myeloma cells and also are synergistic with β2M to induce cancer cell apoptosis [9]. These surprising preclinical data may pave the way for an entirely new class of antibody-based pharmaceuticals for cancer control and eradication.

Conflict of interest

The authors declare no conflict of interest.

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