Review Article

The Implication and Significance of Beta 2 Microglobulin: A Conservative Multifunctional Regulator

Ling Li[1,2], Mei Dong[3], Xiao-Guang Wang[4]

[1]Department of Food Quality and Safety, College of Food Science and Biotechnology, Tianjin Agricultural University, Tianjin 300384, China
[2]Tianjin Engineering Research Center of Agricultural Products Processing, Tianjin 300384, China
[3]Department of Clinical Laboratory, Wangdu Hospital of Traditional Chinese Medicine, Baoding, Hebei 072450, China
[4]Department of Immunology and Microbiology, Anschutz Medical Campus, University of Colorado Denver, Aurora 80045, Colorado, USA

Abstract

Objective: This review focuses on the current knowledge on the implication and significance of beta 2 microglobulin (β2M), a conservative immune molecule in vertebrate.
Data Sources: The data used in this review were obtained from PubMed up to October 2015. Terms of β2M, immune response, and infection were used in the search.
Study Selections: Articles related to β2M were retrieved and reviewed. Articles focusing on the characteristic and function of β2M were selected. The exclusion criteria of articles were that the studies on β2M-related molecules.
Results: β2M is critical for the immune surveillance and modulation in vertebrate animals. The dysregulation of β2M is associated with multiple diseases, including endogenous and infectious diseases. β2M could directly participate in the development of cancer cells, and the level of β2M is deemed as a prognostic marker for several malignancies. It also involves in forming major histocompatibility complex (MHC class I or MHC I) or like heterodimers, covering from antigen presentation to immune homeostasis.
Conclusions: Based on the characteristic of β2M, it or its signaling pathway has been targeted as biomedical or therapeutic tools. Moreover, β2M is highly conserved among different species, and overall structures are virtually identical, implying the versatility of β2M on applications.

Key words: Beta 2 Microglobulin; Immune Dysregulation; Major Histocompatibility Complex Class I or Like Molecules

Introduction

Beta 2 microglobulin (β2M) is a small protein (11,800 Dalton), presenting in nearly all nucleated cells and most biological fluids, including serum, urine, and synovial fluid.[1,2] No genetic variant of β2M is known in human.[3] The human β2M shows 70% amino acid sequence similarity to the murine protein and both of them locate on the syntenic chromosomes.[1,4] The secondary structure of β2M consists of seven β-strands which are organized into two β-sheets linked by a single disulfide bridge, presenting a classical β-sandwich typical of the immunoglobulin (Ig) domain.[5-7] β2M has no transmembrane region and contains a distinctive molecular structure called a constant-1 Ig superfamily domain, sharing with other adaptive immune molecules including major histocompatibility complex (MHC) class I and class II.[8] Two evolutionary conserved tryptophan (Trp) residues are important for correct structural fold and function of β2M.[3,9] Trp60 is exposed to the solvent at the apex of a protein loop and is critical for promoting the association of β2M in MHC I. The mutation of Trp60 increases the stabilization of β2M, inhibits β2 amyloidogenic propensity, and weakens the interaction with the heavy chain of MHC I. Trp95 is buried in the β2M core, and the mutation of Trp95 destabilizes the protein, yielding nonfibrillar β2M aggregates. Both Trp residues play differential and complementary roles

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Address for correspondence: Dr. Xiao-Guang Wang, Department of Immunology and Microbiology, University of Colorado Denver, Anschutz Medical Campus, Aurora 80045, Colorado, USA
E-Mail: wxg402@hotmail.com

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in the structure of β2M, distinctly affecting β2M toward self-aggregation into amyloid fibrils. Once the aspartate residue is replaced by asparagine residue at position 76, β2M becomes thermodynamically unstable and remarkably fibrillogenic *in vitro* under physiological conditions.[10]

Normally, β2M is noncovalently linked with the other polypeptide chain (α chain) to form MHC I or like structures, including MHC I, neonatal Fc receptor (FcRn), a cluster of differentiation 1 (CD1), human hemochromatosis protein (HFE), Qa, and so on. β2M makes extensive contacts with all three domains of the α chain.[11] Thus, the conformation of α chain is highly dependent on the presence of β2M. Although α1 and α2 domains differ among molecules, α3 domain and β2M are relatively conserved, where the intermolecular interaction occurs.[12] A number of residues at the points of contact with β2M are shared among MHC I or like molecules.[13] Furthermore, interactions with α1 and α2 domains are important for the paired association of α3 domain and β2M in the presence of native antigens.[14] β2M could dissociate from such molecules and shed into the serum, where it is transported to the kidneys to be degraded and excreted. An 88-kD protein (calnexin) associates rapidly and quantitatively with newly synthesized murine MHC I molecules within the endoplasmic reticulum.[15] Both β2M and peptide are required for efficient calnexin dissociation and subsequent MHC I transport.[16]

Not only β2M is to interact with and stabilize the tertiary structure of the MHC I or like molecules, but also it is extensively involved in the functional regulation of survival, proliferation, apoptosis, and even metastasis in cancer cells.[17] As well as a cancer prognostic marker, β2M is also a promising cancer therapeutic target. Although β2M acts as both a positive and negative growth factor in different cancer cells, the application of anti-β2M antibodies induces cancer cell apoptosis and do not block the down-regulation effect of β2M in myeloma cells.[18] Moreover, systemic β2M accumulation in aging blood promoted age-related cognitive dysfunction and impairs neurogenesis, suggesting that β2M may be targeted therapeutically in old age.[19] Thus, targeting β2M will shed light on the modulatory activity in the immune system and provide new pathways on cancer or aging-related therapeutics. This review will only focus on the characteristic and function of β2M under present knowledge. For MHC I or like molecules, they have been well reviewed previously and are not the scope of this study.

Regulation and Modulation of Beta 2 Microglobulin

β2M expresses at a constant level in many cells, however, the formation of β2M would be enhanced in the presence of IFN-α.[17] β2M could induce the expression of interleukin 6 (IL-6), 8 and 10 in several cell types, regulate the expression of hormone/growth factor, and coordinate the interaction between cytokines and their receptors.[20-22]

Like a prototypical oncogenic factor, β2M is able to stimulate growth and progression of various cancers.[23-25] In cancer bone metastasis, β2M allows cancer cells to continue to synthesize and deposit bone-like proteins. The growth and migration of mesenchymal stem cells would be promoted by exogenous overexpression of β2M through enhanced phosphorylation of cAMP response element-binding protein and upregulation of IL-6 and vascular endothelial growth factor.[26,27] β2M could support lethal bone and soft tissue metastasis via activating epithelial to mesenchymal transition.[28,29] β2M also acts as an apoptosis-inducing factor in several leukemic, lymphoma, and myeloma cell lines.[18,30,31] Inhibition of β2M enhanced the radiation sensitivity by induction of iron overload in prostate cancer cells.[32]

In patients suffering from long-term hemodialysis, a high concentration of serum β2M leads that β2M deposits in skeletal joints and forms amyloid plaques. Among the fibrils, full-length β2M is the major component, although other derivatives of β2M are also present.[33] Furthermore, the H51A point mutation of β2M exhibits a 2-fold increase in the lag-time of fibril formation.[34]

β2M also induces a dose- and time-dependent, cell-mediated calcium efflux from neonatal mouse calvariae that involves osteoclast stimulation, which is mediated by IL-1β partly.[35] The expression and covalent association of tapasin, assisting MHC I to load antigenic peptides, were enhanced by the presence of β2M.[36]

Indications from the Level of Free Beta 2 Microglobulin

The abnormal level of β2M in blood or urea is associated with multiple diseases, such as some acute and chronic inflammations, liver or renal dysfunctions, some viral infections, and several malignancies.[2,17] Furthermore, amyloidosis associated to hemodialysis is related with persistently high β2M serum levels.[37-39] In rare cases, a cerebrospinal fluid β2M level is used to assess a disease involved with the central nervous system.[40,41]

Serum and plasma β2M values reflect the activation of the cellular immune system, as well as a tumor marker in certain hematologic malignancies.[42-47] For the inflammatory bowel disease, β2M was suggested to be used as an activity parameter.[48] β2M levels also rise during infection with some viruses, including cytomegalovirus and human immunodeficiency virus (HIV).[49] Strong evidence showed cytomegalovirus could directly bind β2M via two envelope proteins.[50] Recently, soluble β2M was proposed as a possible serologic marker of neurologic disease during the infection of human T-cell leukemia virus.[51] On the other hand, abnormality of urine β2M values indicates renal filtration or reabsorption disorders. The small size of β2M allows it pass through the glomerular membrane, however, it can be reabsorbed in the proximal tubules by specific receptors. The disorder of kidney's glomeruli would cause increased β2M in blood and decreased β2M in urea, in contrast, the disorder of kidney's tubules would cause increased β2M in

urea and decreased β2M in blood.[2] In lupus nephritis and neonates, the index of serum β2M/cystatin C is suggested to indicate the renal function.[52,53] Moreover, serum β2M levels at discharge would predict the long-term mortality and graft loss in kidney transplantation recipients.[54] A large nationally representative cohort exhibited serum β2M concentration was associated with a significantly increased risk of cardiovascular and all-cause mortality.[55] Recently, the concentration of β2M was also deemed as a marker of frailty in older people.[56] Thus, the β2M test could indicate how advanced the disease is and the likely prognosis for the patient at the time of diagnosis.

Outcomes Due to Beta 2 Microglobulin Deficiency

β2M deficient mutant has been derived in different models and changes of cellular and humoral responses are evaluated in these β2M deficient animals.[57] The mechanism of MHC I presenting peptides to $CD8^+$ T-cell was shown in Figure 1. Due to the lack of β2M determined MHC I molecules, the number of $CD8^+$ T-cells significantly decreases in β2M deficient mice.[58-62] Therefore, the deficient mice are susceptible to intracellular pathogens, including *Listeria monocytogenes*, *Mycobacterium tuberculosis*, influenza virus, and so on. However, β2M deficient mice could generate $CD4^+$ MHC II-restricted cytotoxic T-cells (CTL) following infection with *Sendai virus* or lymphocytic choriomeningitis virus.[63,64] Furthermore, MHC I-restricted CTL activity could be activated during infections by some specific pathogens even in β2M deficient mice.[65] In β2M deficient mice, natural killer cells are shown with increased sensitivity to MHC I heavy chain mediated inhibition.[66] Other cellular responses are relatively stable, including gamma delta+ T-cells and $CD4^+$ T-cells.[67] Hemochromatosis is evident in β2M deficient mice, presenting iron overload.[62] The iron overload increases the sensitivity to the infection of *M. tuberculosis*.[61] The catabolism of IgG and albumin increased in β2M deficient mice due to low expression of FcRn.[68,69] However, the level of mucosal IgA was significantly increased during enteric infection of β2M deficient mice, indicating different roles of β2M in Ig catabolism. On the other hand, autoantibody-mediated inflammations or immune diseases are prevented or relieved in β2M deficient mice.[70,71] The disruption of β2M significantly reduced the expression of MHC I in human embryonic stem cells, presenting hypoimmunogenic and favoring transplantation therapies.[72] Furthermore, the loss of β2M contributes the immune evasion in cancer cells.[73]

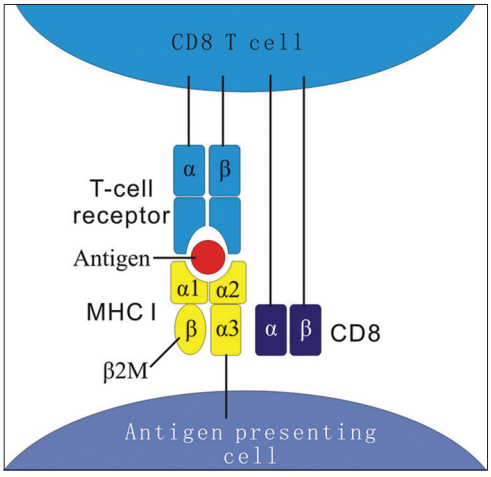

Figure 1: Schematic representation of MHC I antigen presentation to CD8 T-cell. MHC I consists of two polypeptide chains, α (α1, α2, α3) and β2M, which are noncovalently linked between α3 and β2M. The peptides (antigens) generated from cytosolic proteins bind the polymorphic groove between α1 and α2 and are displayed to CD8 T-cell receptors. Meanwhile, the CD8 co-receptor of CD8 T-cell would interact with α3. β2M: Beta 2 microglobulin; MHC I: Major histocompatibility complex class I; CD8: Cluster of differentiation 8.

Specific Roles of Beta 2 Microglobulin Within Heterodimers

The main function of MHC I or MHC I-like molecules is related with molecular presentations or uptakes, depending on the structural-like grooves between α1 and α2 domains. Comparing with MHC I groove, the CD1 groove is relatively narrow, deep, and highly hydrophobic forming two deep binding pockets.[74,75] This hydrophobic channel is specific for binding hydrocarbon alkyl chains. Unlike MHC I, CD1 molecules are targeted to distinct endocytic compartments by cytoplasmic tails. On the other hand, the FcRn groove is collapsed, demonstrating a relatively flat groove. Although these structures are highly similar, different functions are presented with these molecules relating to site mutagenesis on specific binding sites. The most striking difference of FcRn is the closing of the groove that binds peptides in classical MHC I proteins, due to a kink in the α2 helix introduced by proline (Pro)-162.[13] Moreover, the pocket of FcRn is blocked by the positively charged side chain of arginine (Arg)-164. β2M stabilizes the tertiary structure of such heterodimers and also participates in the selections of MHC I-like restricted T-cells. For instance, the selection of invariant $V\alpha19\text{-}J\alpha33^+$ cells is dependent on β2M.[76]

Major histocompatibility complex class I

MHC I molecules are found on nearly every nucleated cell of the body. Their function is to present short endogenous or exogenous peptides from within the cell to CTLs. β2M is crucial to stabilize cell surface MHC I, keep native structure of MHC I heavy chain, facilitate the binding of antigenic peptides, and generate additional high-affinity peptide-bindings.[77] However, some cells express a considerable number of surface MHC I heavy chain molecules not associated with β2M.[14,78,79] The superficial nonpeptide-associated heavy chains can associate with exogenously provided β2M and synthetic peptide antigens.[80] Moreover, normal β2M-sufficient cells grown in serum-free media devoid of β2M also require an exogenous β2M to efficiently bind synthetic peptide. By

using this characteristic, β2M was developed to vaccine adjuvant for CTL activation.[81] Using the immunization protocol with human β2M, CTL responses were strongly primed with peptides from OVA, *S. virus*, and vesicular stomatitis virus in mice. The versatility of β2M in different species confirms the conservative evolutionary lineage of this small protein. ESAT-6, an abundantly secreted protein of *M. tuberculosis*, could directly interact with human β2M to inhibit the expression of MHC I, resulting in down-regulation of class I-mediated antigen presentation.[82]

Neonatal Fc receptor

FcRn is a heterodimer of a nonclassical MHC I alpha chain and β2M. It efficiently binds the two most abundant serum proteins, IgG, and albumin. Both proteins are protected by FcRn from lysosomal degradation and extend the catabolic half-lives.[69] Beside the protection role with FcRn heterodimer, β2M seems to have another way to protect the degradation of IgG and albumin.[83] Furthermore, FcRn is critically involved in the transport of IgG across cells, thus helping antigen delivery via transcytosis.[84]

β2M is critical for surface expression of FcRn, facilitating FcRn to exit the endoplasmic reticulum.[85] Furthermore, β2M is important for efficient pH-dependent binding of IgG by FcRn. Strong evidence show β2M could directly contact IgG ligand.[86] Not only overexpression of FcRn enhances the transcytosis of immune complexes and increases the number of antigen-specific IgM or IgG-producing B cells,[87] but also the expression of β2M increases the transcytosis of IgG between the basolateral and apical directions of epithelial cells.[88] Moreover, the application of β2M as adjuvant requires the temporal proximity with antigens, confirming that β2M facilitates the uptake of antigens.[81]

Cluster of differentiation 1

CD1 is a family of glycoproteins expressed on the surface of various antigen-presenting cells, and CD1-like genes have been found in many vertebrate genomes. They are closely related to the MHC I and are involved in the presentation of lipid antigens to restricted T-cells. According to protein sequence homologies, the members of the CD1 family are mainly divided into two groups.[89] Group 1 CD1 includes CD1a, -b, and -c and human, mouse, rat, and rabbit CD1d form group II. Furthermore, CD1e is proposed to form a third group due to its intracellular chaperone function.[90,91] The size and shape of the antigen-binding groove vary among different CD1 isoforms and decide the nature of the binding lipid molecules.

The excretion of different CD1 isoforms differs in the presence of β2M. For instance, heavy chains of CD1b are detained in the ER in β2M-deficient cells,[92] however, a portion of CD1d heavy chains can exit the ER and reach the cell surface independent onβ2M.[93-95] Interestingly, the non-β2M formed CD1d only presents at the apical site of intestinal epithelial cells.[96] Like the adjuvant application of β2M on CTL, β2M seems like a potential adjuvant to prime CD1d specific immune responses.

Human hemochromatosis protein

As an MHC I-like molecule, HFE is a ligand for the transferrin receptor, regulating the uptake of iron-bound transferrin. Hepcidin regulated by HFE degrades the iron transporter ferroportin on the cytoplasmic membrane of enterocytes and macrophages, resulting in decreased iron uptake from food and iron release from recycled red blood cells. Therefore, mutations of HFE or absence of β2M result in iron excess and hemochromatosis.[59-61] The mechanism of iron accumulation in the β2M deficient mouse may be more complex than only involving HFE.[62] In contrast to HFE α chain-deficient mice, β2M-deficient mice display increased levels of iron transporters and iron overload, suggesting that (an) additional β2M interacting protein(s) could be involved in controlling iron homeostasis. The interaction with β2M is crucial for surface expression of HFE.[97,98] Unlike other MHC I-like molecules, HFE does not bind any antigen.[99]

Other Major Histocompatibility Complex I-like Molecules

Qa-1 (HLA-E, human functional counterpart) is designated as nonclassical histocompatibility Ags, eliciting strong CTL responses.[100] β2M is required for an initial folding of Qa-1, however, transporter associated with antigen processing (TAP) is not necessary for processing of Qa-1 molecules. Furthermore, the presence of CD8α/α TCRα/β cells in intestinal intraepithelial lymphocytes is highly restricted by Qa-2 (HLA-G, human functional counterpart).[101]

Histocompatibility 2, M region locus 3 (H2-M3) associates with β2M to form MHC I-like structure. The expression of H2-M3 is confined to murid species, which are highly conserved. H2-M3 mainly presents N-formylated peptides, and its surficial expression is dependent on ligand binding. Once H2-M3 binds peptides in the endoplasmic reticulum, they transit rapidly to the cell surface, where they stimulate $CD8^+$ αβ T-cells in a TAP-dependent manner.[102,103]

Human MR1 encoded on chromosome 1 is highly conserved among mammals and is more closely related to classical class I molecules than are other nonclassical class I family members.[104,105] The MR1 is responsible for activation of mucosal-associated invariant T-cells expressing semi-invariant T-cell receptors in the presence of bacteria. Moreover, the MR1 messenger RNA is ubiquitously expressed in different tissues or cell lines[104], and the surficial expression of MR1 requires the presence of β2M.[106] The lack of β2M or MR1 increases the susceptibility to infection by *Klebsiella pneumoniae*.[107] MR1 is ideally suited to bind ligands originating from vitamin metabolites.[108]

MILL (MHC class I-like located near the leukocyte receptor complex) is a family of MHC I-like molecules, which are glycophosphatidylinositol-anchored glycoproteins associated with β2M. Surface expression of MILL does not require functional TAP molecules and is not related with the presentation of peptides.[109]

Evolutionary Relationship among Major Histocompatibility Complex I or Like Molecules

Given the structural similarities, it is believed that all these MHC I or MHC I-like molecules have evolutionary lineage with a common ancestor.[13] The MHC locus has been found in all jawed vertebrates, however, the proto-MHC could trace back to the cephalochordate (amphioxus) and jawless vertebrate lineages.[110-112] MHC II genes were firstly derived from proto-MHC by exon shuffling, combining an Ig-like C domain with a peptide binding region.[113] Subsequently, another peptide binding region exon was added to MHC II β chain to form the MHC I heavy chain, which happened at approximately 500 million years ago. The emergence of CD1 occurred in the reptile form lineage after the amphibian–reptile split roughly between 365 and 385 million years ago. The MR1 is highly conserved and seems to be unique to mammals.[114] Contrasting to positive selection on the ligand-binding site of MHC I, the conservative ligand-binding site of MR1 evolved under strong negative selection. H2-M3 is also highly conserved, and its expression is confined to murid species. The emergence of H2-M3 occurred 50–65 million years ago.[114] FcRn is supposed to share an ancestor with the MHCs that it does not with the CD1s.[13] Further evidence shows, FcRn diverged from the MHC near the most recent common ancestor of lizards and mammals.

β2M is believed to arise in a basal jawed vertebrate (gnathostome).[8] The close proximity of MHC I, MHC II, and β2M implies that they were derived from a common ancestor by tandem (*cis*) duplication.[8] β2M protein sequences are highly conserved among species, and overall structures are virtually identical. Ten residues are identical in all species, including the two characteristically spaced cysteine residues which form the disulfide bridge.[12]

Conclusion and Perspectives

The structure and function are highly conserved not only in β2M but also in its related molecules. It indicates that β2M is irreplaceable in animals, especially in vertebrate. β2M involves in the network of cytokines, modulating the development of several cell lines. Furthermore, hormone, growth factors, and cognate receptors are also regulated by β2M. As a prognostic marker of various diseases, the level of β2M reflects the progress of the disease and the likely prognosis for the patient. The special role of β2M in regulating the survival, proliferation, apoptosis, and even metastasis of cancer cells makes itself being targeted for cancer therapeutics [Table 1].

As a key component of MHC I or like molecules, β2M is critical for CTL response. The CTL immune response is obligatory for prevention against intracellular pathogens. By use of MHC I α chain, β2M has been successfully employed as an adjuvant for augmented CTL immune responses. Due to the surface expression of other MHC I-like α chains (e.g., CD1d α chain), it can be deduced the application of β2M on additive immune responses. Since MHC I and CD1 could present different antigens from *M. tuberculosis* to $CD8^+$ T-cells; the adjuvant effect of β2M may have dual applications on prevention of tuberculosis.

Though several β2M-related molecules have been identified, there are still some unknown β2M-related molecules. Besides FcRn and HFE, other β2M-related molecules involve in the catabolism of IgG and the homeostasis of iron. With the sequences of the whole genomes, more putative β2M-related molecules would be revealed.[115]

Table 1: Examples of multifunction of β2M

Year	Author	Targeting	Mechanism	Application
2007	Yang *et al.*[22]	IL-6 and IGF-I receptors and signaling pathways	Anti-β2M mAbs redistribute or block IL-6 and IGF-I receptors or signaling pathways	Apoptosis of myeloma cells
1995	Rowley *et al.*[25]	Antagonistic activity to transforming growth factor beta 1	Hormone/growth factor receptors	Immune regulation and cell proliferation
2008	Zhu and Shi[27]	Mesenchymal stem cells	Growth stimulator	Prognostic marker and therapeutic target of cancers
1992	Moe and Sprague[35]	Osteoblast	Mitogen	Therapeutic target
2006	Huang *et al.*[23]	Prostate cancer bone metastasis	Signaling and growth promoting factor	Therapeutic target
2006	Nomura *et al.*[24]	Human renal cell carcinoma	Growth stimulator via the β2M-protein kinase A-CREB-VEGF signaling pathway	Therapeutic target
2002	Min *et al.*[18]	Myeloma cells	Negative growth regulator, induce cell apoptosis	Therapeutic strategy
2001	Mori *et al.*[30]	Leukemic cell-bearing mice	Apoptosis-inducing activity via activation of caspase-3 and nuclear factor-kappa B	Therapy for leukemia
2003	Gordon *et al.*[31]	Human lymphoblastic leukemia cell line	Induce apoptosis via increasing reactive oxygen species	Therapy for leukemia
1993	Rock *et al.*[81]	MHC I reconstruction	MHC I or like molecules stabilizer	Vaccine adjuvant

MHC I: Major histocompatibility complex class I; IL: Interleukin; CREB: cAMP response element-binding; VEGF: Vascular endothelial growth factor; β2M: Beta 2 microglobulin; IGF-I: Insulin-like growth factor-I; cAMP: Cyclic adenosine monophosphate.

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Conflicts of interest

There are no conflicts of interest.

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