MEDICAL SCIENCE MONITOR
BASIC RESEARCH

REVIEW ARTICLES

eISSN 2325-4416
© Med Sci Monit Basic Res, 2013; 19: 271-273
DOI: 10.12659/MSMBR.889457

Received: 2013.06.13
Accepted: 2013.06.20
Published: 2013.10.21

Decipher β2-microglobulin: Gain- or loss-of-function (a mini-review)

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

E 1 Shean-Jaw Chiou
F 2 Chang-Han Chen

1 Department of Biochemistry, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Taiwan
2 Center for Translational Research in Biomedical Sciences, Kaohsiung Chang Gung Memorial Hospital-Kaohsiung Medical Center, Kaohsiung, Taiwan

Corresponding Author: Shean-Jaw Chiou, e-mail: sheanjaw@kmu.edu.tw
Source of support: Grant no. M110004 from Kaohsiung Medical University

β2-microglobulin (β2M) functions as a chaperon to maintain structural stability of MHC class I complex that is associated with antigen presentation to cytotoxic (CD8+) T lymphocytes. Cancerous cells in β2M loss-of-function are thought to avoid immune surveillance. As increased level of β2M present in tissue/serum is significantly associated with tumor status in various cancers, β2M may become an important prognostic and survival factor in a range of malignancies. It is believed that β2M acts as hormone-like molecule to trigger a pleiotropic signaling via a ligand-to-receptor binding mechanism. Anti-β2M monoclonal antibodies successfully induce apoptosis in malignant cells, suggesting a surprising therapeutic approach. Of note, β2M is largely localized in the cytoplasm of advanced oral cavity squamous cell carcinoma (OCSCC), in contrast to that in the plasma membrane of normal oral mucosa. This suggests that β2M-derived intracellular signaling might be preceded by its accumulation in the cytoplasm of epithelial cells of tumors. Hence, translocation of β2M from cell surface to cytoplasm in advanced tumors may shed light on the mechanism of β2M-mediated tumorigenesis.

Key words: β2-microglobulin • cytoplasm • translocation • tumorigenesis

Full-text PDF: http://www.basic.medscimonit.com/download/index/idArt/889457

946 — — 14

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Background

β2-Microglobulin (β2M), a structurally light chain of major histocompatibility complex (MHC) class I molecules, is expressed on the surface of all nucleated cells. β2M non-covalently interacts with the heavy chain of MHC class I to function in the presentation of antigenic peptide fragment to cytotoxic (CD8+) T lymphocytes [1]. In the absence of β2M, most MHC class I molecules become less expressed on the surface of cells [2]. Transfection of β2M-deficiency cells with ER-retained β2M restored the function of MHC class I, supporting a role of β2M as chaperone for MHC folding [3]. Nevertheless, β2M is present as a soluble form at low levels in different bodily fluids under physiological conditions. It is increasingly recovered in patients with chronic kidney disease and certain malignancies, including liquid and solid tumors [4,5]. The elevated level of β2M in body fluid is significantly associated with tumor status and poor prognosis. It is believed that cancer cells frequently downregulate the expression of MHC class I to avoid immune surveillance, allowing gain-of-function via the secretion of free β2M. Thus, the free β2M is widely implicated in association with MHC class I-loss tumors.

β2-microglobulin Gain-of-Function in Cancer Cells

There is convincing evidence that β2M acts as a growth-promoting factor and signal molecule in a variety of cancer cells [6–8]. Overexpression of β2M facilitates the invasion and migration of cancer cells of different origin, supporting the increased levels of β2M positively correlated with advanced-stage tumors. β2M gain-of-function is achieved by regulating the androgen receptor and a cyclic AMP-dependent protein kinase A signaling pathway in prostate cancer. A panel of genes related to cell growth, survival, signaling, and angiogenesis is therefore expressed to trigger tumor progression and cause bone metastasis [6]. Similar results were found in human cancer renal cells, showing that β2M promotes tumor growth via the activation of vascular endothelial growth factor axis [7]. Apart from the finding of β2M as an important prognostic and survival factor in a range of malignancies, it also becomes an attractive therapeutic target. Monoclonal antibodies (mAbs) against β2M have a surprising apoptotic effect on prostate cancer, renal cell carcinoma (RCC), myeloma, and other hematological malignancies [9–12]. Yang et al. [12] demonstrated that mAbs induce apoptosis in myeloma cells by recruiting MHC class I molecules to lipid rafts and by excluding growth factor receptors. Similarly, Huang et al. [13] revealed that β2M-specific mAb decreases lipid levels in prostate cancer cells to make a link between β2M-mediated intracellular signaling axis and lipid rafts in the cell membrane. This may explain why β2M mAbs-induced apoptosis in cancers is mediated via quite similar signaling pathways – the inhibition of PI3K/Akt, MAPK, and Bcl-2, and the activation of caspases-dependent cascade – supporting the role of β2M as a mitogenic factor. Of note, β2M-specific mAbs have a higher affinity for surface-bound rather than the soluble β2M and display differential sensitivity to malignant cells but not to normal cells, suggesting that the integrity of lipid rafts is an important factor for both apoptotic and survival signaling [9]. Strikingly, Cao et al. [14] reported the effectiveness of IgM anti-β2M mAbs exhibiting more potent activity than IgG mAbs at inducing tumor cells apoptosis *in vitro* and *in vivo*. The enhanced activity of IgM mAbs in tumor cell apoptosis mainly relies on the pentameric structure of the IgM. Apparently, these studies support that β2M-specific mAb is a promising therapeutic agent for the treatment of several types of malignancies, although further work is needed to evaluate the potential cytotoxicity of the antibody targeting approach. Based on a broad range of evidence, it is believed that β2M acts as a hormone-like molecule to trigger pleiotropic signaling via a ligand-to-receptor binding mechanism. Until recently, a noteworthy aspect to β2M in cancer cell signaling was to identify hemochromatosis (HFE) protein with which β2M induces epithelial-mesenchymal transition (EMT) and confers cancer lethality and bone metastasis in a variety of human cancer cells [8]. On the contrary, inhibition of β2M reverses EMT to mesenchymal-to-epithelial transition (MET). This suggests that β2M binds with HFE protein, namely β2M receptor, in association with transferring receptor to modulate iron homeostasis and activate iron-responsive HIF-1α (hypoxia inducible factor-1α) signaling in cancer cells. Because the HIF signaling cascade is activated by the effects of hypoxia, which keeps cells from differentiating, β2M-derived upregulation of HIF-1α mediates EMT and eventually promotes metastasis for cancer progression. Previously, Chen et al. [5] revealed that overexpression of β2M is associated with poor survival in patients with oral cavity squamous cell carcinoma (OCSCC) and contributes to oral cancer cell migration and invasion. The expression level of β2M in the cytoplasm and cytoplasm membrane of OCSCC epithelial cells at various stages was compared with that in normal oral mucosa, clearly showing that β2M localizes largely in the cytoplasm of tumor samples (~90–92% in a total of 256 cases) rather than in the plasma membrane. This suggests that the increased accumulation of β2M in the cytoplasm of OCSCC is significantly correlated with a relatively advanced tumor stage. This highlights the dramatic changes in β2M localization from cytoplasm membrane to cytoplasm between normal and tumor stages of OCSCC. This feature was also reported by Nomura et al. [7], who found that β2M expression, in a few cases, localized in the cytoplasm of human RCC. Thus, intracellular accumulation of β2M must play a pivotal role in cancer cell signaling and may present a potential target for therapy.

Conclusions

Cancerous cells in β2M loss-of-function are thought to avoid immune surveillance. Although β2M-mediated key molecular

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

events such as tumor growth, cancer cells invasion, and metastasis can be attenuated by β2M-specific mAbs, questions about translocation of β2M from plasma membrane to cytoplasm in advanced-stage tumors remain to be answered.

References:

1. Margalit A, Sheikhet HM, Carmi Y et al: Induction of antitumor immunity by CTL epitopes genetically linked to membrane-anchored beta2-microglobulin. J Immunol, 2006; 176: 217–24
2. Siddle HV, Kreiss A, Tovar C et al: Reversible epigenetic down-regulation of MHC molecules by devil facial tumour disease illustrates immune escape by a contagious cancer. Proc Natl Acad Sci USA, 2013; 110: 5103–8
3. Solheim JC, Johnson NA, Carreno BM et al: Beta 2-microglobulin with an endoplasmic reticulum retention signal increases the surface expression of folded class I major histocompatibility complex molecules. Eur J Immunol, 1995; 25: 3011–16
4. Tsimberidou AM, Kantarjian HM, Wen S et al: The prognostic significance of serum beta2 microglobulin levels in acute myeloid leukemia and prognostic scores predicting survival: analysis of 1,180 patients. Clin Cancer Res, 2008; 14: 721–30
5. Chen CH, Su CY, Chien CY et al: Overexpression of beta2-microglobulin is associated with poor survival in patients with oral cavity squamous cell carcinoma and contributes to oral cancer cell migration and invasion. Br J Cancer, 2008; 99: 1453–61
6. Huang WC, Wu D, Xie Z et al: beta2-microglobulin is a signaling and growth-promoting factor for human prostate cancer bone metastasis. Cancer Res, 2006; 66: 9108–16
7. Nomura T, Huang WC, Zhau HE et al: Beta2-microglobulin promotes the growth of human renal cell carcinoma through the activation of the protein kinase A, cyclic AMP-responsive element-binding protein, and vascular endothelial growth factor axis. Clin Cancer Res, 2006; 12: 7294–305
8. Josson S, Nomura T, Lin JT et al: beta2-microglobulin induces epithelial to mesenchymal transition and confers cancer lethality and bone metastasis in human cancer cells. Cancer Res, 2011; 71: 2600–10
9. Yang J, Qian J, Wezeman M et al: Targeting beta2-microglobulin for induction of tumor apoptosis in human hematological malignancies. Cancer Cell, 2006; 10: 295–307
10. Huang WC, Havel JJ, Zhau HE et al: Beta2-microglobulin signaling blockade inhibited androgen receptor axis and caused apoptosis in human prostate cancer cells. Clin Cancer Res, 2008; 14: 5341–47
11. Nomura T, Huang WC, Seo S et al: Targeting beta2-microglobulin mediated signaling as a novel therapeutic approach for human renal cell carcinoma. J Urol, 2007; 178: 292–300
12. Yang J, Zhang X, Wang J et al: Anti beta2-microglobulin monoclonal antibodies induce apoptosis in myeloma cells by recruiting MHC class I to and excluding growth and survival cytokine receptors from lipid rafts. Blood, 2007; 110: 3028–35
13. Huang WC, Zhau HE, Chung LW: Androgen receptor survival signaling is blocked by anti-beta2-microglobulin monoclonal antibody via a MAPK/lipogenic pathway in human prostate cancer cells. J Biol Chem, 2010; 285: 7947–56
14. Cao Y, Lan Y, Qian J et al: Targeting cell surface beta2 -microglobulin by pentameric IgM antibodies. Br J Haematol, 2011; 154: 111–21

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]