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RESEARCH ARTICLE

IN-SILICO ANALYSIS OF RECEPTORS INVOLVED IN DOWN REGULATION OF BETA 2 MICROGLOBULIN (B2M): A POTENTIAL DRUG TARGET

Sanjana S., Uday, J. and *Hariprasad, T. P. N.

Department of Life Science, J B Campus, Bangalore University, Bangalore -560056

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ABSTRACT

Beta 2 microglobulin (B2M) is a small ~11KD protein. Increased level of Beta-2-microglobulin (B2M) leads to several diseases like amyloidosis, peripheral arterial disease, coronary heart disease, cancer and inflammatory diseases. B2M downstream signalling is mediated by activation of the protein kinase A/cyclic AMP (cAMP) mediated by potential interaction with Phosphatidylinositol 3-kinase and Mitogen-activated protein kinase signalling in humans. In this study an insilico approach was carried out to identify the possible receptors which interact with this protein and induce the downstream signalling which may be a further used to explore therapeutic target for treating cancer.

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INTRODUCTION

Beta 2microglobulin is a small 11,800 da water soluble protein which is non-covalently associated with class 1 MHC molecules (Krangel, 1979). Association of alpha chain of MHC molecules with B 2 M is required for their expression on cell membranes. It is present in all nucleated cells, biological fluids, including serum, urine, and synovial fluid (Gussow *et al*., 1987; Drueke and Massy, 2009). 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‑s and wich typical of the immunoglobulin (Ig) domain (Krieghoff, 2006). It is critical for the immune surveillance and modulation in vertebrate animals. The dysregulation of beta2M is associated with multiple diseases, including endogenous and infectious diseases (Li, 2016). High B 2 M serum levels have been seen in Renal dysfunction, infections and in several malignancies (Krieghoff, 2006). Impaired renal function and hyperproduction of beta 2-microglobulin are both associated with increased serum levels (Bernier, 1980; Momoi, 1995). It is an amyloidogenic protein responsible for dialysis-related amyloidosis (Colombo*et, al.,* 2012).

Corresponding author: **Hariprasad, T. P. N.,**
Department of Life Science, J B Campus, Bangalore University, Bangalore -560056

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Beta2M is seen to directly participate in the development of cancer cells. Increased serum levels of B2M has been seen in Renal, prostatic, ovarian and breast cancers (Krieghoff, 2006). It has been showed for the first time that the Beta2M-protein kinase A-CREB-VEGF signaling axis plays a crucial role in support of renal cell carcinoma growth and progression (Huang, 2006; Moscatelli, 1992). An insilico study has been done in this paper to identify the receptors involved in this pathway. CREB ('cyclic AMP response element-binding protein) is a transcriptional factor is phosphorylated in response to cAMP to promote cellular gene expression in response to growth factor signals. The accumulation of cAMP in response to activation of guanine-nucleotide-binding (G)-protein-coupled receptors induces most cellular responses through the cAMP-dependent protein kinase. In the basal state PKA resides in the cytoplasm as an inactive heterotetramer of paired regulatory (R) and catalytic (C) subunits. Induction of cAMP liberates the C subunits, which passively diffuse into the nucleus and induce cellular gene expression by phosphorylating CREB at serine residue 133 (Mayr, 2001: Gonzalez, 1989). Many GPCRs like FGF receptors (Moscatelli, 1992), Somatostatin receptor (Nomura, 2006), GPR55 (Pende, 1997), have been shown to induce cAMP-PKA-CREB signalling pathways. An *in silico* analysis was done to identify other proteins similar to B2M in different organisms to characterise the particular Mitogenicfunction of B2M.

Also, a comparative study of the receptors of B2M like FcRn, LIR 1, HFE (Josson, 2011; Wieczorek, 2017) and the GPCRs involved in CREB pathway was done to identify the probable GPCRs to which B2M can bind.

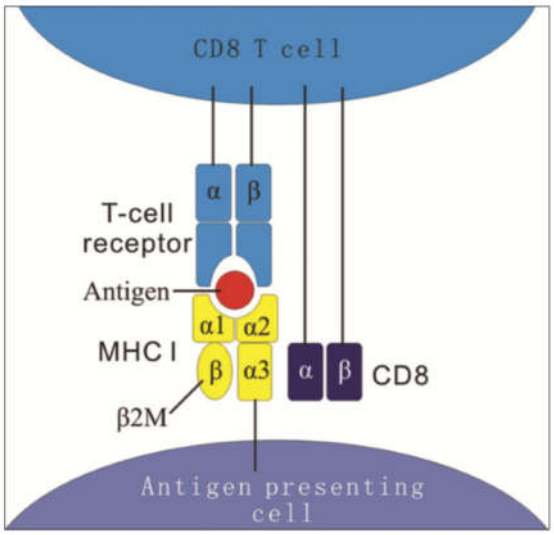

Fig. 1. Schematic representation of MHC I antigen presentation to CD8+ cells (Source : Li *et. al.*, 2016)

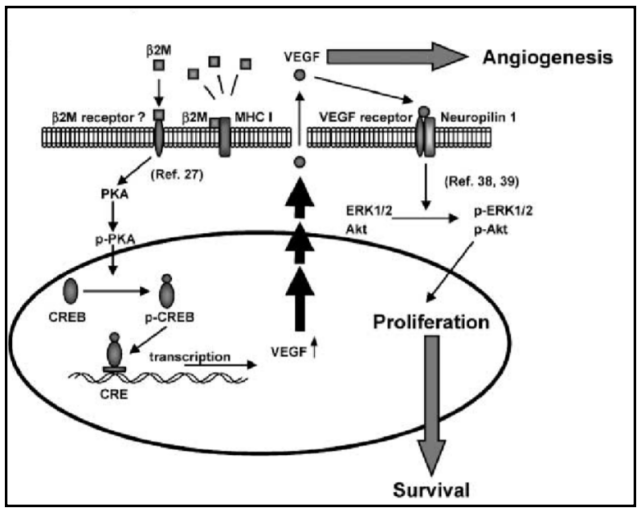

Fig. 2. Molecular mechanism of activation of CREB signalling by B2M (Source : Nomura *et. al.*, 2006)

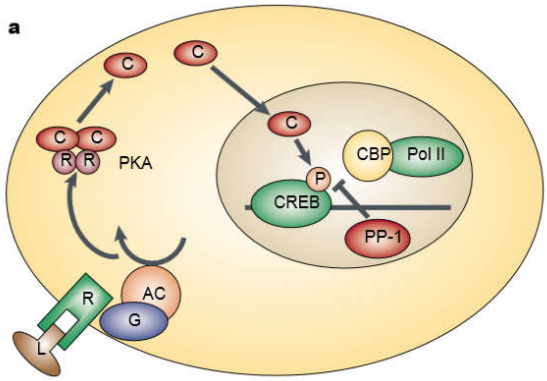

Fig. 3. cAMP-CREB signalling pathway (Source : Mayr and

MATERIALS AND METHODS

1. Domain Homology Study of B2M

- The B2M gene sequence of Human was obtained from NCBI gen bank.
- The obtained Sequence was submitted to ORF finder to obtain the longest Open reading Frame.
- The ORF sequence was submitted to SMART database to analysehomologus domains.
- The interactions of the homolog domain containing protein was analysed using Expasy STRING.
- Pathways involving the homolog domain proteins were analysed in KEGG

2. Pathway identification

- The osteoclast differentiation pathway involving TGFBR 1 receptor and Ig like receptors were analysed in KEGG.

3. Domain Homology Study of receptors

- GPCRs regulating cAMP-pKA-CREB signalling were analysed and compared to receptors of B2M to identify similar domains.

RESULTS AND DISCUSSION

- From SMART analysis ZP domain of Endoglin was near homolog to the ORF of the B2M. Endoglin interacts with TGFBR 1 receptor which in turn activates CREB pathway. Increased serum level pf B2M has been seen in many malignancies. Hence targeting the TGFBR1 receptor may down regulate B2M activated CREB-angiogenesis pathway.
- Further the CREB pathway was known to be activated by Ig like receptors (eg LIRB1, LIRB 2, OSCAR etc.,). It is known that there is an interaction between B2M and LIRB 1 [26]. Thus targeting this receptor might also help to regulate CREB-angiogenesis pathway.
- It is already known that B2M activates CREB induced angiogenesis through cAMP-pKAsignalling which is known to be a GPCR mediated signalling pathway. The GPCRs Fibroblast growth factor receptor 1 (FGFR 1), FGFR2 and FGFR 3, were identified to have similar domains as that of receptors of B2M i.e., LIR 1, HFE and FcRn which is Immunoglobulin like domain. Thus the FGF R class of receptors may be the target receptor for inactivating B2M mediated cAMP-pKA-CREB signalling.

Summary

The receptors TGFBR 1, Ig like receptors in osteoclast differentiation and GPCRs lile FGFR1, FGFR2 and FGFR3 were identified as the probable receptors through which B2M is expressing its mitogenic activity through CREB signalling leading to angiogenesis and cell growth.

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