

Assessment of Programmed Death Receptor Ligand-1 In Chronic Myelogenous Leukemia

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

﴿قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا

عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ﴾

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Dedication

To

My Family

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ABBREVIATIONS

ALL	: Acute lymphoblastic leukemia
AP	: Accelerated phase
AP-1	: Activator protein 1
APCs	: Antigen-presenting cells
Ara-C	: Arabinoside cytosine
ATP	: Adenosine triphosphate
B7-H1	: B7 homolog 1
BC	: Blastic crises
Bcl-2	: B-cell lymphoma-2
Bcl-xL	: B-cell lymphoma-extra large
Bcr-Abl	: Breakpoint cluster region/ Abelson oncogene
BMT	: Bone marrow transplantation
CaLB	: Calcium dependent lipid binding domain
CBC	: Complete blood count
CBL-b	: Cbl (Casitas B-lineage Lymphoma) Proto-Oncogene B
CCA	: Clonal chromosome abnormalities
CCgR	: Complete cytogenetic response
CCL	: Chemokine (C-C motif) ligand
CD	: Cluster of differentiation
CFC	: Colony forming cell
CHR	: Complete haematologic response
CIN	: Cervical intraepithelial neoplasia
c-Kit	: cell tyrosine kinase
CML	: Chronic myeloid leukaemia
CP	: Chronic phase
cpCML	: Chronic phase chronic myeloid leukaemia
CpG	: Cytosine-phosphate-guanine
CrkL	: CT10 Regulator of Kinase homologue-like

CSCs : Cancer stem cells

CTLA-4 : Cytotoxic T-lymphocyte-associated protein 4

CTLs : Cytotoxic T Lymphocytes

DAPk1 : Death-associated protein kinase 1

DCs : Dendritic cells

D-FISH : Double-fusion fluorescent in situ hybridization

DNMT : DNA methyl-transferase DNMTi

: DNA Methylation Inhibitors EDTA :

Ethylene diaminetetra acetic acid

ELISA : Enzyme-linked immunosorbent assay

ELN : European Leukemia Network

FDA : Food and Drug Administration

FGF-b : Fibroblast growth factor-basic

FISH : Fluorescence *in situ* hybridization

Foxp3 : Forkhead box P3

FTI : Farnesyl-transferase Inhibitors

GAP : GTPase activating protein

G-CSF : Granulocyte-colony stimulating factor

GDP : Guanosine-diphosphate

GEF : Guanine nucleotide exchange factor

GM-CSF : Granulocyte-macrophage colony-stimulating factor

Grb2 : Growth factor receptor bound protein 2

Gr-MDSCs : Granulocyte- myeloid derived suppressor cells

GTP : Guanosine triphosphate

GUSB : Glucuronidase beta

HATs : Histone acetyl-transferases

HDAC : Histone deacetylases

HGF : Hepatocyte growth factor

HLA-DR : Human Leukocyte Antigen - antigen D Related

HPV	: Human papilloma virus
HR-HPV	: High-risk human papilloma virus
HRP	: Horseradish peroxidase
HSCs	: Haematopoietic stem cells
IFN- γ	: Interferon gamma
Ig	: Immunoglobulin
IgV	: Immunoglobulin variable region
IL	: Interleukin
ILCs	: Innate lymphoid cells
IM	: Imatinib mesylate
IRF5	: Interferon regulatory factor 5
IRIS	: International Randomized Study of Interferon and STI571
IS	: International Scale
JAK2	: Janus Kinase 2
KD	: kinase domain
kDa	: kilodalton
LCMV	: Lymphocytic choriomeningitis virus
LDLR	: Low density lipoprotein receptor
LPS	: Lipopolysaccharides
LSC	: Leukemic stem cell
LTi	: Lymphoid tissue inducer
M1	: Macrophages type 1
M2	: Macrophage type 2
MAPK	: Mitogen-activated protein kinase
m-bcr	: Minor break point cluster region
M-bcr	: Major break point cluster region
MCA	: Methylcholanthrene
Mcl-1	: Myeloid cell leukaemia-1
mDC	: Myeloid dendritic cells

MDSC	: Myeloid-derived suppressive cells
MHC	: Major histocompatibility
MICA	: MHC class I polypeptide-related sequence A
MNC	: Mononuclear cells
Mo-MDSCs	: Monocyte- Myeloid derived suppressor cells
MPDL3280A	: Monoclonal programmed death ligand 3280 antibody
MPN	: Myeloproliferative neoplasms
MR	: Molecular response
mRNA	: Messenger ribonucleic acid
mTOR	: Mammalian target of rapamycin
NES	: Nuclear export signal
NF-κB	: Nuclear factor kappa-light-chain-enhancer of B cells
NK	: Natural killer
NKG2D	: The Natural Killer Group 2D receptor
NKT	: Natural killer T cells
NLSs	: Nuclear localization signals
NOD	: Non-obese diabetic
NOS2	: Nitricoxide synthase 2
NSCLC	: Non-small cell lung cancer
OSM	: Oncostatin M
p53	: 53- kilodalton (kDa) protein
PBMC	: Peripheral blood mononuclear cell
PCD	: Programmed cell death
PCgR	: Partial cytogenetic response
p-CrkL	: Phosphorylated CrkL (CT10 Regulator of Kinase homologue-like)
PD-1	: Programmed cell death receptor-1
PDCD1	: Programmed cell death-1
PDGF	: Platelet derived growth factor

PDGF-R	: Platelet-derived growth factor receptors
PD-L1	: Programmed cell death-ligand 1
PDL-2	: Programmed cell death-ligand 2
Ph	: Philadelphia chromosome
PH	: Pleckstrin homology
PHR	: Partial haematologic response
PI3K	: Phosphatidylinositol 3-kinase
PKC	: Protein kinase C
PP2A	: Protein phosphatase 2A
PTKs	: Protein tyrosine kinases
PTPs	: Protein tyrosine phosphatases
qRT-PCR	: Quantitative reverse-transcription polymerase chain reaction
Rac	: Ras-related C3
Ras	: Rat sarcoma
Rho	: Ras homolog
RICS	: RNA-induced silencing complex
rIFN α	: Recombinant Interferon-alfa
ROS	: Reactive oxygen species
RT-PCR	: Reverse transcription polymerase chain reaction
RUNX1	: Runt-related transcription factor 1
SAHA	: Suberoylanilide hydroxamic acid
SCID	: Severe combined immunodeficiency
SCT	: Stem cell transplantation
SDF-1	: Stroma derived factor-1
Ser/Thr	: Serine/threonine
SH2	: Sarcoma Homology 2
Shc	: Src homology 2 domain-containing
SHP1	: Src homology phosphatase-1
SLE	: Systemic lupus erythematosus

SL-ICs	: SCID leukemia-initiating cells
SNPs	: Single nucleotide polymorphisms
SRCs	: SCID-repopulating cells
STAT	: Signal transducer and activator of transcription
t	: Translocation
<i>T315I</i>	: Threonine-to-isoleucine mutation at position 315
TAM	: Tumor-associated macrophages
TCR	: T-cell receptor
Tg	: Transgenic
TGF- β	: Transforming growth factor β 1
Th1	: T-Helper-1 cells
Th2	: T-Helper-2 cells
TIM-3	: T-cell immunoglobulin and mucin-domain containing-3
TK	: Tyrosine kinase
TKI	: Tyrosine kinase inhibitor
TNF	: Tumor necrosis factor
T-reg	: T regulatory cells
ULBP	: UL16 binding protein-1
UTR	: Untranslated region
v-Crk	: Virus (avian sarcoma) CT10 regulator of Kinase
VEGF	: Vascular endothelial growth factor
WT1	: Wilms' Tumor Antigen 1
ZAP 70	: Zeta-chain-associated protein kinase 70

Abstract:

The aim of this study was to measure plasma levels of the secreted protein Klotho in β -thalassemia major patient and the existence of correlations between the protein level and osteoporosis and fragility fractures. Also, we compared the level of the protein in patients and in healthy controls. 50 patients with β -thalassemia major and 30 healthy volunteers were enrolled. Klotho level in plasma was measured by mean of an ELISA test. CBC, Renal functions, Liver functions, Viral markers (HBs Ag, HCV Ab), Calcium, Phosphorus and Serum ferritin level were measured by standard clinical techniques. DEXA was used to measure bone mineral density (BMD) at the lumbar spine (L2–L4) and femoral neck. We found that the Klotho protein concentration was lower in the blood of patients with β -thalassemia major than in healthy controls. Also, the klotho concentration was lower in patients with osteoporosis or osteopenia than those with normal BMD. Also, lower in patients with history of fragility fractures.

Key words:

Klotho, Osteoporosis, fragility fractures.