Effect of vitamin D on Expression of microRNA-22 and microRNA-125b in Behcet Disease

Thesis

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Abstract

Behcet's Disease (BD) is a chronic inflammatory disease with exacerbations and remissions characterized by recurrent orogenital ulcerations, ocular manifestations, arthritis, and vasculitis. In addition, neurological and large vessel involvement can occur. The etiology and pathogenesis of Behcet's Disease have not been clearly defined. However, several genetic, environmental, and immunological factors have been suggested as causative factors in this disease The primary mechanism of the damage is an overactive immune system that seems to target the patient`s own body. The involvement of a subset of T cells seems to be important. Vitamin D has long been known to be important for bone health and turnover. It has major biologic activities including cellular proliferation and differentiation, immune system modulation and muscle strengthening. A growing body of evidence supports the hypothesis that vitamin D is an environmental factor important in the etiology of T-cell-mediated autoimmune diseases. The biological effect of vitamin D is thought to occur by binding to its receptor (VDR) which belongs to the steroid receptor superfamily. VDR gene polymorphisms cause functional differences in immuno-modulatory action of vitamin D. This receptor is widely expressed in many cell types including antigen-presenting and lymphocytes cells. There is significant decrease in the level of Vitamin D in patient with Behcet disease.

Conclusion: The expression of microRNA 125b shows its statistically significant increase in patients of Behcet disease. Although the expression of microRNA 22 shows no significant difference between patients and control however its expression is lower in patients receiving steroid treatment compared to those who do not receive the treatment.

Keywords: vitamin D, microRNA-22, microRNA-125b, Behcet Disease

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List of Abbreviations

AD	Allelic discrimination
Ago	Argonaute
Alb	Albumin
ALK	Alkaline phosphatase
ALT	Alanine transaminase
ANA	Antinuclear antibody
ASO	Anti-sense oligonucleotides
AST	Aspartate transaminase
Bcl-Xl	B-cell lymphoma-extra large
BIC	B-cell integration cluster
Bil	Bilirubin
BD	Behcet`s Disease
bp	Base pair
BT	Breakthrough
CBC	Complete blood count
CD	Cluster of differentiation
CHC	Chronic hepatitis C
CLDN1	Claudin-1
CsA	Cyclosporin A
CYP3A4	cytochrome P450, family 3, subfamily A, polypeptide 4
DAA	Direct acting antiviral
DGAT	Diacylglycerol O-acyltransferase
VDR	Vitamin D Receptors
DNA	Deoxyribonucleic acid
dNTPs	Deoxy-nucleotide triphosphate
miRNA	Micro Ribonucleic acid
ds-RNA	Double stranded RNA
ISG	International Study group
EDTA	Ethylenediaminetetraacetic acid
EGFR	Epidermal growth factor receptor
eIF3	Eukaryotic initiation factor
ELISA	Enzyme-linked immunosorbent assay
VEGF	vascular endothehal growthfactor

ICBD	International Criteria of Behcet`s Disease
ER	Endoplasmic reticulum
RAS	Recurrent aphthous stomatitis
EVR	Early virlogical response
BSAS	Behcet's Syndrome Activity Scale
Glu	Glucose
Gt	Genotype
GWAS	Genome wide association study
ESR	Erythrocyte Sedimentation Rate
CBC	Complete Blood Count
EULAR	European LeagueAgainst Rheumatism
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
TNF	Tumor necrosis factor
HTA	Host targeting antiviral
IgG	Immunoglobulins G
Igf	insulin-like growth factor
IFN	Interferon
IPS-1	Interferon β promoter stimulator
IRES	Internal ribosome entry site
IRF	Interferon regulatory factor
PAAs	Pulmonary artery aneurysms
ISGF	Interferon-stimulated gene factor
IL	Interleukin
IMPDH	Inosine monophosphate dehydrogenase
JAK	Janus kinase
JNK	c-Jun N-terminal kinase
LDs	Lipid droplets
LNA	locked nucleic acid
miRNA	MicroRNAs
mRNA	Messenger ribonucleic acid
AZA	Azathioprine
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
ncRNAs	Non-coding RNAs
NI	Nucleoside analog inhibitor

NL	Null response
nt	Nucleotide
NTC	Non template control
OCLN	Occludin
ORF	Open reading frame
P-bodies	processing bodies
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PEG	Polyethylene glycol
PegIFN	Pegylated interferon
pH	Potential hydrogen
PIs	Protease inhibitors
PI-KA	Phosphatidyl inositol kinase A
Pol II	Polymerase II
PPAR	Peroxisome proliferator-activated receptor
pre-miRNA	precursor miRNA
pri-miRNA	primary miRNA
PRKRA	protein kinase, interferon-inducible double- stranded RNA-dependent activator
PR	Partial response
PT	Prothrombin time
Q	Quencher
R	Reporter
RBV	Ribavarin
RFLP	Restriction fragment length polymorphism
RIG-I	Retenoic acid inducible gene I
RISC	RNA-induced silencing complex
RLC	RISC loading complex
RNA	Ribonucleic acid
rpm	Revolutions per minute
RT-PCR	Reverse transcriptase polymerase chain reaction
RVR	Rapid virological response
S	Standard
SDS	Sodium dodecyl sulphate
SHP	Src(sarcoma) homology 2-domain containing tyrosine phosphatase
SL	Stem loop

SNP	Single nucleotide polymorphism
SOCS	Suppressor of cytokine signaling
SP	Specificity protein
SR-BI	Scavenger receptor type B class I
STAT	Signal transducer and Activator of transcription
SVC	Spontaneous viral clearance
SVR	Sustained viralological response
T	Test
Taq	Thermus aquaticus
TGF-*β*	Transforming growth factor beta
TH	T helper
TIR	Toll/interleukin 1 receptor
TLR	Toll like receptor
TNF	Tumor necrosis factor
TPV	telaprevir
TRIF	TIR domain-containing adapter-inducing interferon β
TRBP	Trans-activation response RNA-binding protein
TSH	Thyroid stimulating hormone
TU	transcription unit
TyK	Tyrosine kinase
UTRs	Untranslated regions
UVB	Ultra violet B
VLDL	Very low-density lipoprotein
WHO	World Health Organization

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INTRODUCTION

Behcet's Disease (BD) is a chronic inflammatory disease with exacerbations and remissions characterized by recurrent orogenital ulcerations, ocular manifestations, arthritis, and vasculitis. In addition, neurological and large vessel involvement can occur. The etiology and pathogenesis of Behcet's Disease have not been clearly defined. However, several genetic, environmental, and immunological factors have been suggested as causative factors in this disease. The primary mechanism of the damage is an overactive immune system that seems to target the patient`s own body. The involvement of a subset of T cells seems to be important.

Vitamin D has long been known to be important for bone health and turnover. It has major biologic activities including cellular proliferation and differentiation, immune system modulation and muscle strengthening. A growing body of evidence supports the hypothesis that vitamin D is an environmental factor important in the etiology of T-cell-mediated autoimmune diseases.

The biological effect of vitamin D is thought to occur by binding to its receptor (VDR) which belongs to the steroid receptor superfamily. VDR gene polymorphisms cause functional differences in immuno-modulatory action of vitamin D. This receptor is widely expressed in many cell types including antigen-presenting and lymphocytes cells.

MicroRNAs (miRNAs) are short non-coding RNAs with wide gene regulatory activity at the posttranscriptional level. MiRNAs associate with

several proteins in RNA silencing complexes that cause mRNA degradation or translation inhibition, or both processes.

In recent years, miRNAs have been shown to play key roles in cancer as they control the expression of crucial oncogenes and tumour suppressor genes and, accordingly, several miRNAs are either over-expressed or silenced affecting many diseases.

MiRNA-22 augments tumour suppressor activity. 1,25(OH)2D3 modulates cell proliferation: it usually has a mild to medium cell-type-dependent inhibitory effect, although stimulatory effects have also been reported. miR-22 is induced by 1,25(OH)2D3 and contributes to its inhibitory effects on the proliferation and migration of cells.

Moreover, anti-miR-22 expression abrogates the regulation by 1,25(OH)2D3 of the RNA levels of several target genes. Importantly, miR-22 is downregulated in a high proportion of colon tumours and its expression correlates directly with that of VDR. Together, miR-22 is a target of 1,25(OH)2D3 and mediates in part its protective action against many diseases.

The microRNA miR-125b is multi-faceted, with the ability to function as a tumor suppressor or an oncogene, depending on the cellular context. To date, the pro-apoptotic role of miR-125b and its underlying mechanisms are unexplored. miR-125b level was positively associated with the rate of apoptosis in HCC tissues.

AIM OF THE WORK

The aim of our study is to investigate serum levels of vitamin D and its effect on miRNA22 and miRNA125B gene expression in Egyptian patients with BD and to evaluate their relationship to disease activity.