Micro RNA 26a Expression in Peripheral Blood Mononuclear Cells and Correlation with Serum Interleukin-17 in Relapsing Remitting Multiple Sclerosis Patients

Thesis

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Presented by

Fatma Mostafa Mahmmoud
M.B.B.Ch., M.Sc
Faculty of medicine - Ain Shams University

Under Supervision of

Prof. Dr. Nehal Mohamed Anwar Fahim
Professor of Medical Microbiology and Immunology
Faculty of Medicine - Ain Shams University

Dr. Wafaa Khalil Zaki
Assistant Professor of Medical Microbiology and Immunology
Faculty of Medicine - Ain Shams University

Dr. Dina Mohamed Abdelgawad Zamzam
Assistant Professor of Neurology
Faculty of Medicine - Ain Shams University

Dr. Nadia Mohamed Elsheshtawy
Assistant Professor of Medical Microbiology and Immunology
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
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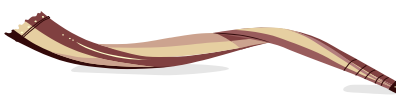

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List of Abbreviations

	Abbrev.	Meaning
A	**AGO**	Argonaute
	ADEM	Acute disseminated encephalomyelitis
	AML	Acute myeloid leukaemia
	APC	Antigen-presenting cells
	AID	Activation-induced cytidine deaminase
B	**Bach 1**	BTB and CNC homology 1
	BBB	Blood brain barrier
	Bcl-2	B-Cell Lymphoma 2
	Breg	Regulatory B cells
	BCR	B cell receptor
	BDNF	Brain- derived neurotrophic factor
C	**CCL**	Chemokine (C-C motif) ligand
	CD	Cluster of differentiation
	CNS	Central nervous system
	CIS	Clinical isolated syndrome
	cDNA	Complementary Dioxyribo Nucleic Acid
	CLEC16A	C-type lectin like domain family 16 A
	CXCL	C-X-C motif chemokine
	CLN	Cervical lymph nodes
	CVC	Central venous catheter
	C/EbPβ	CCAAT/enhancer-binding protein-β
	CSF	Cerebrospinal fluid
	CL	Cortical lesions

	CIITA	MHC class II transactivator
	CT	Threshold cycle
	CS	Corticosteroids
	CTL	Cytotoxic T-Lymphocyte
D	**DCs**	Dendritic Cells
	DMD	Disease-modifying drugs
	DP	Double positive
	DIS	Dissemination in space
	DIT	Dissemination in time
	DMF	Dimethyl Fumarate
	DGCR8	DiGeorge syndrome critical region 8
	DNA	Dioxyribo Nucleic Acid
	dsRNA	Double stranded RNA
	dsRBD	Double stranded RNA binding protein
E	**EBNA**	Epstein Barr nuclear antigen
	EBV	Epstein-Barr virus
	EDSS	Expanded Disability Status Scale
	EXP5	protein exportin 5
	ELISA	Enzyme-Linked Immunosorbent Assay
	EAE	Experimental autoimmune encephalomyelitis
	eIF4E	eukaryotic translation initiation factorE
F	**FDA**	Food and drug adminstartion
	FGF2	Fibroblast growth factor 2
	Foxp3	Forkhead box P3
G	**GA**	Glatiramer acetate
	GWASs	Genome wide association studies
	GVHD	Graft versus host disease

	GTP	Guanosine-5'-triphosphate
	GM- CSF	Granulocyte-macrophage colony stimulating factor
H	**HapMap**	Haplotype map
	hsa	Homo sapiens
	HLA	Human leukocyte antigen
	HSCT	Hematopoietic stem cells transplantation
	Hbl-1	Hunchback-like-1
	HSPB5	Heat shock protein B5
	HHV 6	Human Herpes Virus-6
I	**IFN**	Interferon
	ICAM	Intercellular Adhesion Molecule 1
	IFN γ	Interferon Gamma
	IV	Intravenous
	ILR	Interleukin receptor
	IQR	Interquartile ranges
	IL	Interleukin
	Ig	Immunoglobulin
	IVIG	Intravenous immunoglobulin
L	**LFA-1**	Lymphocyte function-associated antigen 1
	Let	Lethal
	Lin	Lineage defective
	LUX	Light Upon extension
	LNA	Locked Nucleic Acid
	LPS	Lipopolysaccharides
M	**mmu**	murine
	MDCs	Myeloid dendritic cells
	MMP	Matrix metalloproteinase

	MRI	Magnetic resonance imaging
	MHC	Major histocompatibility complex
	MiRNAs	MicroRNAs
	MP	Methylprednisolone
	MAB	Monoclonal antibodies
	MS	Multiple sclerosis
	miRNP	microRNA containing ribonucleoprotein
	miRISC	miRNA inducing silencing complex
	MSP	MiRNA specific primer
	MOG	Myelin oligodendrocyte protein
	MTI	MiRNA target interactions
	MCAM	Melanoma cell adhesion molecule
	MSFC	Multiple Sclerosis Functional Composite scale
	mRNA	Messenger RNA
	MIP	Macrophage inflammatory protein
	MBP	Myelin basic protein
	MSP	MiRNA specific primer
	MICA&B	MHC class I polypeptide-related sequence A *and B*
	µL	microlitre
N	**NK**	Natural killer
	Nrf	Nuclear related factor
	NAB	Neutralizing antibodies
	NF-κβ	Nuclear factor kappa-light-chain enhancer of activated B cells
	NMSS	National Multiple Sclerosis Society
	NKG2D	Natural killer group 2, member D

	NCAM	Neuronal cell-adhesion molecule
	NO	Nitric oxide
	Nt	Nucleotides
	NSC	Neural stem cells
O	**OCP**	Oral contraceptives pills
P	**PU1**	Myeloid transcription factor
	pDCs	Plasmacytoid dendritic cells
	PIAS3	Protein inhibitor of activated STAT
	PBL	Peripheral blood lymphocytes
	Pten	Phosphatase and tension homolog
	PRMS	Progressive relapsing multiple sclerosis
	PPMS	Primary progressive multiple sclerosis
	PBMCs	Peripheral Blood Mononuclear cells
	PCR	Polymerase Chain Reaction
	PSD-95	Postsynaptic density protein 95
	PML	Progressive multifocal leukoencephalopathy
	PMR1	Polysomal ribonuclease1
	Poly (A) tail	Polyadenylation tail
	Pre-miRNA	Precursor miRNA
	Pri-miRNA	Primary miRNA
Q	**qRT-PCR**	Quantitative real-time PCR
R	**RAR**	Retinoic acid response
	RA	Rheumatoid arthritis
	RRMS	Relapsing remitting multiple sclerosis

	RIS	Radiologically isolated syndrome
	ROR	RAR related orphan receptor
	RORγt	RAR related orphan receptor gamma t
	RISC	RNA-Induced Silencing Complex
	RITS	RNA-induced transcriptional silencing
	RIIIDs	RNase III domain
	RNA	Ribo Nucleic Acid
	RT	Reverse Transcription
	RT-PCR	Reverse Transcription- PCR
S	**SD**	Standard Deviation
	STAT	Signal transducer and activator of transcription
	SMAD	Mothers against decapentaplegic
	SPMS	Secondary progressive multiple sclerosis
	SHIP	Scr homology 2 containing inositol phosphatase
	SH2	Scr homology 2
	SOCS1	Suppressor of cytokine signaling 1
	SNP	Single nucleotide polymorphism
	SPSS	Statistical Program for Social Science
T	**TAR**	Transactive response
	TRBP	(TAR) RNA-binding protein
	T reg	Regulatory T lymphocytes
	TGF-β	Transforming growth factor-β
	TH	T-helper type
	TCR	T cell receptor
	TNFR1	Tumor necrosis factor receptor 1
	TNF-α	Tumor necrosis factor- α
	TLR	Toll like receptor

	TCR	T cell receptors
	Tc 17	Interleukin-17A-producing CD8 subset
	TYK	Tyrosine kinase
U	**UTR**	Untranslated region
	UV	Ultraviolet rays
	USP25	Ubiquitin-specific protease 25
V	**VZV**	Varicella zoster virus
	VDR	Vitamin D receptor
	VDRE	Vitamin D receptor element
	VCAM	Vascular cell-adhesion molecules-1
	VLA4	Very late antigen-4
W	**WBC**	White blood cells

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Introduction

Multiple sclerosis (MS) is defined as inflammatory autoimmune disease of the central nervous system (CNS) which is widely characterized by the brain and spinal cord myelin destruction ***(Calabresi, 2004; Bendszus and Storch-Hagenlocher, 2013).***

Prevalence rates for MS vary between 2 and 160 per 100,000 in different countries, and more than 2 million individuals are affected by this disease worldwide ***(Tufekci et al., 2011).*** MS disease onset usually occurs in young adults, and it is more common in women than men ***(Milo and Kahana, 2010).*** The geographic prevalence of multiple sclerosis is reported to be heterogeneous with more cases in Western Europe, and northern side of the USA. There are some reports about increase in the incidence of MS in the Mediterranean Basin, and some developing countries ***(Etemadifar and Maghzi, 2011; Benito-Le´on, 2011).*** In Egypt the prevalence is about 25/100,000 with more familial cases ***(Hashem et al., 2010).***

The factors that initiate inflammation are still unknown, but it is believed that MS is caused by environmental factors in the host that has genetic susceptibility which trigger a T-cell autoimmune response

against the CNS ***(Tufekci et al., 2011).*** The auto reactive T cells migrate across the blood-brain barrier (BBB) and mediate damage particularly against the central neurones and their myelin sheaths, but also against their axons. The key morphological feature of MS is primary demyelination of nerve axons leading to signal conduction block or conduction slowing at the site of demyelination ***(Fletcher et al., 2010)***.

Primarily it was supposed that a subset of CD4+ T cells (T helper 1 {Th1}) which produce interferon γ (IFN-γ) is critical in autoimmunity of MS, however it is now clear that interleukin (IL)-17 producing CD4+ T cells (Th17), are the main responsible cells for inflammation and pathogenesis of MS ***(Naghavian et al., 2015).*** Th17 cells mainly do their effects through secreting IL-17, IL-21, IL-22 and granulocyte monocyte colony stimulating factor (GM-CSF), which are essential for autoimmune neuro-inflammation ***(Zhu et al., 2010; Codarri et al., 2011).***

There is also evidence that endothelial cells express high levels of IL-17 receptors and are more permeable to IL-17. This microenvironment favors the differentiation of naïve CD4+ T cells into Th17 cells that transmigrate efficiently across BBB endothelial cells, leading to the destruction of human neurons and initiating CNS inflammation ***(Larochelle et al., 2011).*** Various studies