Study of RANTES Promoter Polymorphism in Rheumatoid Arthritis and Systemic Lupus Erythematosus Patients

Thesis

Submitted for Partial Fulfillment of
M.D. Degree in Clinical and Chemical Pathology

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2009

Abstract

Rheumatoid arthritis (RA) is a systemic chronic inflammatory disease of the joints. Systemic lupus erythematosus (SLE) is an autoimmune disease which has the potential to involve multiple organs. There are several lines of evidence that chemokines play an important role in the inflammatory development and progression of autoimmune diseases. RANTES is a chemokine that is member of the CC chemokines.

The aim of the work was to evaluate the possible effect of the RANTES gene on the susceptibility to RA and SLE by examining the polymorphism of promoter at position -403 of this gene in RA and SLE patients and ethnically matched controls.

Subjects and methods: The study included 32 rheumatoid arthritis patients and 32 systemic lupus erythematosus patients .Thirty sex and age matched healthy individuals were also included in the study as a control group. All patients were subjected to: careful history taking, assessment of disease activity, laboratory investigations as well as RANTES-403 genotyping by PCR-RFLP.

Results: RANTES -403 A/A genotype frequency was significantly higher in RA (18.75%) and SLE (15.63 %) in comparison to healthy individuals (0%) ($p=0.038$ and $p=0.037$ respectively). However, No significant association was found between clinical aspects and RANTES polymorphism.

Conclusion: These findings suggest that the presence of the A allele in position -403 in the RANTES gene may be a possible risk factor in the pathogenesis of SLE and RA .

The use of RANTES gene therapy appears to be a promising line of treatment for RA and SLE patients.

Key words: Rheumatoid arthritis- Systemic lupus erythematosus-

Chemokines- RANTES –gene polymorphism-- PCR-RFLP.

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ABBREVIATIONS

ACRSRA	The American College of Rheumatology Subcommittee on Rheumatoid Arthritis
ANA	Antinuclear antibodies
APC	Antigen presenting cell
APL	Antibodies to phospholipids
BCA-1	B-cell chemoattractant 1
bp	Base pair
CCP	Cyclic citrullinated peptide
CD	Cluster of differentiation
CHAK	CC-Chemokine-activated killer
Chond/OC	Chondrocytes and osteoclasts
CIA	Collagen induced arthritis
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CR1	Complement receptor 1
CRP	C-reactive protein
CTACK	Cutaneous T-cell- attracting chemokine
CTLA-4	Cytotoxic T lymphocyte antigen -4
DAG	Diacyl glycerol
DARC	Duffy antigen receptor for chemokines
DAS	Disease activity score
DMARD	Disease modifying anti rheumatic drug
DNA	Deoxy-ribonucleic Acid

EBV	Epstein barr virus
ECG	Electrocardiography
EDTA	Ethylene diamine tetracetic acid
ELISPOT	Enzyme-linked immunospot
ENA	Epithelial cell-derived neutrophil-activating peptide
ESR	Erythrocyte sedimentation rate
Fab	Antigen-binding fragment
Fc	Fragment crystallisable
FcγR	Fragment crystallisable gamma receptor
FLS	Fibroblast-like synoviocytes
Foxp3	Forkhead box p3
GCP	Granulocyte chemotactic protein
G-CSF	Granulocyte colony stimulating factor
GM-CSF	Granulocyte-monocyte colony stimulating factor
GPCRs	G protein–coupled receptors
GRO	Growth-regulated oncogene
GRO-α	Growth-related oncogene α
HB	Haemoglobin
HCC	Hemofiltrate chemokine
HIV	Human immunodeficiency virus
HLA	Human leucocyte antigen
HRT	Hormonal replacement therapy
ICOS	Inducible costimulator
IFN	Interferon

Ig	Immunoglobulin
IL	Interleukin
IP-10	Interferon-inducible protein 10
I-TAC	Interferon-inducible T-cell alpha chemoattractant
KDa	Kilo-dalton
LAG3	Lymphocyte activation gene 3
LARC	Liver and activation-related chemokine
LFA	lymphocyte function-associated antigen
LH	luteinizing hormone
MBP	Mannose binding protein
MCAF	Monocyte chemotactic and activating factor
MCP	Metacarpophalyngeal
MCP	Monocyte chemotactic protein
MDC	Macrophage-derived chemokine
MEC	Mammary-enriched chemokine
MHC	Major histocompatibility complex
MIG	Monokine induced by interferon-γ
MIP-1	macrophage inflammatory potein-1
MIP-3α	Macrophage inflammatory protein-3 alpha
Mono/Mac	Monocytes and macrophages
mRNA	Messenger ribonucleic acid
MS	Morning stiffness
MTP	Metatarsophalyngeal
NMDA	N-methyl-D-aspartate

NSAID	Non steroidal anti-inflammatory drug
PCR	Polymerase chain reaction
PF	Platelet factor
PI3Kγ	Phosphatidylinositol-3'-kinase γ
PIP	Proximal interphalyngeal
PLC	Phospholipase-C
RA	Rheumatoid arthritis
RANK	Receptor activator of nuclear factor-kappa B
RANTES	Regulated upon activation, normal T-cell expressed and secreted
RF	Rheumatoid factor
RFLP	Restriction fragment length polymorphism
RNP	Ribonucleoprotein
SCLE	Subacute cutaneous lupus erythematosus
SD	Standard deviation
SDF	Stromal-cell-derived factor
SE	Shared epitope
SJC	Swollen joint count
SLC	Secondary lymphoid tissue chemokine
SLE	Systemic lupus erythematosus
SLEDAI	SLE Disease Activity Index
Sm	Smith
SNP_S	single nucleotide polymorphisms
SR-PSOX	Scavenger receptor for phosphatidylserine-containing oxidized lipids

T reg	Regulatory T
TARC	Thymus and activation-related chemokine
TCR	T cell receptor
TECK	Thymus-expressed chemokine
TGF-β	Transforming growth factor Beta
Th	T helper
TJC	Tender joint count
TLC	Total leukocytic count
TNF	Tumor necrosis factor
UV light	Ultra violet light
VEGF	Vascular endothelial growth factor

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ACKNOWLEDGEMENT

First and foremost thanks to "God" the source of all good.

Then I would like to express my deep thanks and appreciation to ***Prof Dr. Omayma Abdel Kader Gohar:*** *professor of Clinical and Chemical Pathology, faculty of medicine, Cairo university, for giving me a lot of her precious time and support and for her constructive guidance and valuable observations.*

I am also grateful to ***Prof.Dr. Mona Salah El-Din Hamdy:*** *professor of Clinical and Chemical Pathology, faculty of medicine, Cairo university, for her great help, continuous supervision and effort with me throughout this study. She supplied me with valuable information which were important pillars in my thesis.*

My sincere appreciation to ***Dr. Rasha El Sayed Gheith:*** *lecturer of Rheumatology and Rehabilitation, faculty of medicine, Cairo university. She kindly guided my steps and was always providing me with valuable suggestions, advice, experience and constant support which were the cornerstone in the completion of this study.*

I wish to thank all my patients, without whom this work would have never been completed.

Finally whatever I say will never be enough to thank my husband and family. I greatly appreciate their moral help, they were always supplying me with the feeling of hope, love and encouragement.

This thesis is dedicated to a great and special father, mother, aunt and uncle. It is also dedicated to a cooperative kind husband and to my beloved family.

Introduction

Chemotactic cytokines (chemokines) are small signaling proteins that are released by a variety of cells and are involved in the pathophysiology of inflammatory processes, through the process of attracting and stimulating specific subsets of leucocytes. ***(Liao et al., 2004)***

Chemokines, such as regulated upon activation, normal T cell expressed and secreted (RANTES) are responsible for the recruitment of monocytes and T lymphocytes in both the acute and chronic phases of inflammation. ***(Rovin and Phan, 1998)***

RANTES is produced from various cell types, including CD8+T cells, CD4+T cells, monocyte/macrophages and renal tubular epithelium after cellular activation by stimuli and cytokines such as tumor necrosis factor-α and interleukin 1β stimulation. ***(Canque et al., 1996)***

The RANTES gene is located on human chromosome 17. Two single nucleotide polymorphisms (SNP_S) in the RANTES promoter region (-28C→G and -403G→A) have been found affecting the transcription of RANTES gene. ***(Mehrabian et al., 1991)***

In human cell lines the -28G and the -403 A were shown to increase promoter activity of RANTES compared to the more frequent -28C and the-403G, respectively, suggesting that these polymorphisms increase RANTES expression in the human body. ***(Liu et al., 1999)***

Rheumatoid arthritis (RA) is a systemic chronic inflammatory disease with synovial tissue invasion by inflammatory cells. These cells and associated products such as chemokines play an essential role in synovitis, pannus formation and eventually joint destruction. ***(Szekaneez et al., 2003)***