The Association of HLA DRB1 Shared Epitope Alleles and Smoking in Rheumatoid Arthritis

Essay

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وأنزل الله عليك
الكتاب والحكمة
وعلَّمَكَ مَا لَمْ تَكُن
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Sally El Leithy

I would like to dedicate this Essay
to my ***Father****, to my* ***Mother*** *and to my* ***Brother****,*
to them I will never find adequate words
to express my gratitude.

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List of Abbreviations

ACPA	: Anti-cyclic citrullinated peptide antibodies
ANA	: Anti-nuclear antibodies
Anti-CCP	: Anti-cyclic citrullinated peptide antibodies
B cell	: B lymphocyte
CCL	: Chemokine ligand
CORRONA	: Consortium of Rheumatology Researches of North America
CRP	: C-reactive protein
CXCL13	: B cell attracting chemokine
CXCR3	: Chemokine receptor
DMARDs	: Disease Modifying Anti-Rheumatic Drugs
DNA	: Deoxyribonucleic acid
EBV	: Epstein bar virus
EORA	: Elderly onset rheumatoid arthritis
ESR	: Erythocyte sedimentation rate
FLS	: Fibroblast-like synovicytes
GM-CSF	: Granulocyte macrophage colony stimulating factor
GST	: Glutathion S transferase
HLA	: Human leukocyte antigen
IgG	: Immunoglobin G
IgM	: Immunoglobin M
IL	: Interleukin
IL-1Ra	: Interleukin 1 receptor antagonist
INF	: Interferon necrosis factor
MCP	: Metacarpophalangeal joint
MHC	: Major Histomptability complex
MIP	: Metatarsophalangeal joint
MMPs	: Matrix Metalloproteinases
MRI	: Magnetic resonance imaging
MT MMP	: Membrane Type Matrix Metalloproteinases
NARAC	: North American Rheumatoid Arthritis Consortium

List of Abbreviations (Cont...)

NK	: Natural killer cells
PIP	: Proximal interphalangeal joint
PMN	: Polymorphonuclear leukocytes (Neutrophils)
PTPN22	: Protein tyrosine phosphatase N22
RA	: Rheumatoid arthritis
RASF	: Rheumatoid arthritis synovial fibroblasts
RF	: Rheumatoid factor
SE	: Shared epitope
SLE	: Systemic lupus erythematosus
SONORA	: Study of New Onset Rheumatoid Arthritis
T cell	: T lymphocyte
Th	: T helper
TLR	: Toll like receptors
TNF	: Tumor necrosis factor
U/S	: Ultrasound

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Introduction

Rheumatoid arthritis is a chronic systemic inflammatory autoimmune disease characterized by bilateral symmetrical polyarticular arthritis which is often erosive ***(Poulsom and Charles, 2007).*** It is one of the most common autoimmune diseases that affect all ethnic groups throughout the world. It is associated with progressive disability, systemic complications, early death and socioeconomic costs ***(Mclnnes and Schett, 2011).***

The disease characterized by acute painful inflammatory episodes, destructive changes of the joints that result in deformity and functional impairment of the joints ***(Goronzy and Weyand, 2001).***

The pathogenesis of RA is characterized by an increased presence of monocytes, macrophages and lymphocytes in the synovial fluid and tissue leading to the release of cytokines and chemokines which activate different proteases leading to the formation of inflammatory pannus ***(Wolfe, 1996).*** Pannus development is related to mononuclear cell infiltration, neo-angiogenesis and abnormal proliferation of type B synoviyctes or fibroblast like synovicytes (FLS) ***(Uzan et al., 2006).*** This hyperplastic invasive tissue culminating in the destruction of bone and cartilage leads to increased disability in RA patients. The severity of the disease is linked to existing joint damage as well as to the extent of ongoing inflammation ***(Van der Heijde, 1995).***

Rheumatoid arthritis is a complex multifactorial disease whose etiology involves both genetic and environmental contributions ***(Lee et al., 2007).*** Several studies that examined the epidemiology of rheumatoid arthritis have shown an association between tobacco smoking and rheumatoid arthritis where smoking appears to be the major environmental risk factor ***(Bang et al., 2010).*** One hypothesis is that long term exposure to cigarette smoke may induce mechanisms that accelerate deimination of arginine to citrulline in auto-antigens present in the lungs. Another possibility concerns the presence of substances in smoke which might act as adjuvants, triggering the innate immune system ***(Lundstrom et al., 2009).***

The most important genetic risk factor for rheumatoid arthritis are HLA DRB1 shared epitope alleles which are primarily a risk factor for anti-cyclic citrullinated peptides (anti-CCP) antibodies where these antibodies are associated with severe rheumatoid arthritis. It was evident that this genetic locus plays a central role in susceptibility of disease in different populations ***(van der Helm-van Mil et al., 2007).***

According to the current state of knowledge, the association between HLA DRB1 variations and susceptibility to anti- CCP positive rheumatoid arthritis is related to more than one allele (0101, 0401, 0404, 0405, 0408, 1001, and 1402). These alleles share a common amino acid in the third hypervariable region of DRB1 molecule and have therefore been denoted shared epitope alleles. The shared epitope

residues constitute a part of the antigen binding site forming the fourth anchoring pocket in the HLA groove. The epitope hypothetically serves as a binding site for arthrogenic peptides, allowing presentation to CD4+ T cells and generation of T cell autoimmune responses and may possibly induce certain B cells to differentiate into plasma cells leading to production of anti-CCP antibodies ***(Klareskog et al., 2006a).***

Antibodies to cyclic citrullinated peptide (anti-CCP) are highly specific for rheumatoid arthritis; precede the development of rheumatoid arthritis. These antibodies occur in 60% of rheumatoid arthritis patients, in 2% of healthy populations and rare with other inflammatory diseases ***(Klareskog et al., 2006b).*** It has been suggested that these antibodies play a causative role in pathogenesis of rheumatoid arthritis and it is closely linked to the presence of shared epitope alleles. The association of rheumatoid arthritis is observed with anti-CCP positivity (***Van Gaalen et al., 2005)***.

Epidemiological investigations have shown a striking interaction between smoking and HLA DRB1 shared epitope alleles (01,04,10 groups) in conferring risk for development of anti-CCP positive and RF positive ***(Klareskog et al., 2006b).*** In our study we will report findings from analyses of different groups separately as well subtypes of 04 group in the context of smoking and anti-CCP status in rheumatoid arthritis.

Aim of the Work

This study aims to review the association of HLA DRB1 shared epitope alleles and smoking in rheumatoid arthritis.

Chapter (1):
Rheumatoid Arthritis

Rheumatoid arthritis is a chronic systemic autoimmune inflammatory disease that affects all ethnic groups throughout the world. It has a considerable impact on patient's life, on their families and on society as a whole ***(Majithia and Geraci, 2007)***. It principally attacks the joints in a systemic pattern producing inflammatory synovitis that often progress to destruction of the articular cartilage and ankylosis of the joints ***(Hekmat et al., 2011)***. Females are 3 times more likely to be affected than males. The reasons for this over representation of women are not clear but genetic (X-linked) factors and hormonal aspects are likely to be involved ***(Oslen and Kovacs, 2002).*** The onset of the disease can occur at any age but peak incidence occurs within the fourth and the fifth decades of lives ***(Drosos, 2004)***.

Genetic factors contribute 50% to 60% of the risk of developing rheumatoid arthritis. The most strongly associated gene with rheumatoid arthritis (RA) is the human leukocyte antigen HLADRB1 gene in the major histocompatability complex where specific alleles clusters encoding the shared epitope sequences within the expressed DRB1 molecule. HLA DRB1 contributes up to one third of the genetic susceptibility to rheumatoid arthritis ***(Begovich et al., 2004).*** Exposure to various environmental factors increase the risk for rheumatoid

arthritis and cigratte smoke is one of the best characterized ***(Klareskog et al., 2006a)***. Infectious agents such as bacterial DNA and bacterial peptidoglycans can activate Toll like receptors (TLR) and stimulate synovial innate immune responses. Several viruses have been implicated as possible etiological factors in rheumatoid arthritis such as Epstein Bar virus (EBV), Cytomegalovirus proteus and Parovirus 19 where they lead to inappropriate immune response ***(Waldburger and Firestein, 2008)***.

The formation of immune complexes during infection may trigger the induction of rheumatoid factor (RF) which has long served as a diagnostic marker of rheumatoid arthritis and is implicated in its pathogenesis. Also, the gastrointestinal microbiome is now recognized to influence the development of autoimmunity and specific clinical bacterial signatures that are associated with autoantibody positive rheumatoid arthritis are emerging ***(Mclnnes and Schett, 2011)***.

Rheumatoid arthritis is one of the most common inflammatory arthritides characterized by erosive synovitis. It primarily affects the small diarthroidal joints of the hands and feet although larger weight bearing and appendicular joints can also be involved where synovium is the primary site of inflammation ***(Waldburger and Firestein, 2008)***. This chronic inflammation induces changes in the cellular composition and in the gene expression profile of the synovial membrane resulting in hyperplasia of intimal lining fibroblast like

synoviocytes and infilteration with mono nuclear cells especially $CD4^+$ T cells, macrophages and B cells ***(Wolfe, 1996).*** With the thickening and proliferation of synovium, the joint is filled by the thickened and abnormally proliferated tissue called pannus, which spreads across the articular cartilage and subsequently causes erosions and structural damage of the cartilage, bones and ligaments leading to disability and substantial loss of mobility due to pain and joint destruction ***(Goronzy and Weyand, 2011).***

Also, it is important to recognize that rheumatoid arthritis is a systemic disease affecting extra-articular tissues throughout the body including the skin, blood vessels, heart, lungs and muscles (***Firesfin, 2001).***

Pathophysiology:

The normal synovium consists of an intimal lining layer, one to two layers which are a loosly organized collection of cells that form an interface between the synovium and the synovial fluid space. The intimal lining cells lack tight junctions and a definite basement membrane. The sublining below the intima contains blood vessels, lymphatics, nerves and adipocytes distributed within a less cellular fibrous matrix. The intimal lining layer comprises two different cell types, type A synovicytes (macrophage like synoviocytes) and type B synovicytes (fibroblast like synoviocytes) ***(Waldburger and Firestein, 2008)*** (figure1).