THE ROLE OF NATURAL KILLER CELLS IN THE IMMUNEPATHOGENESIS OF RHEUMATOID ARTHRITIS

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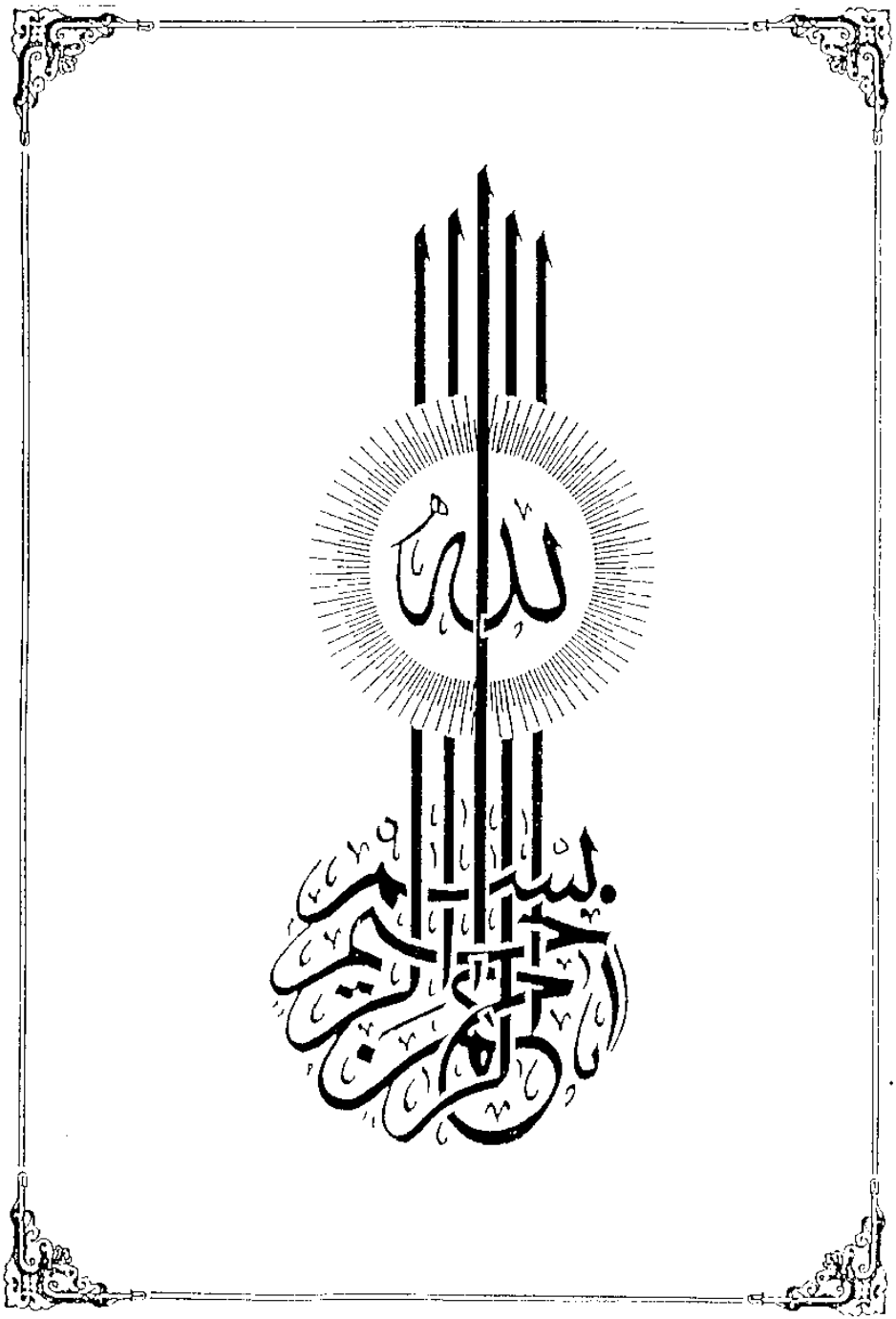

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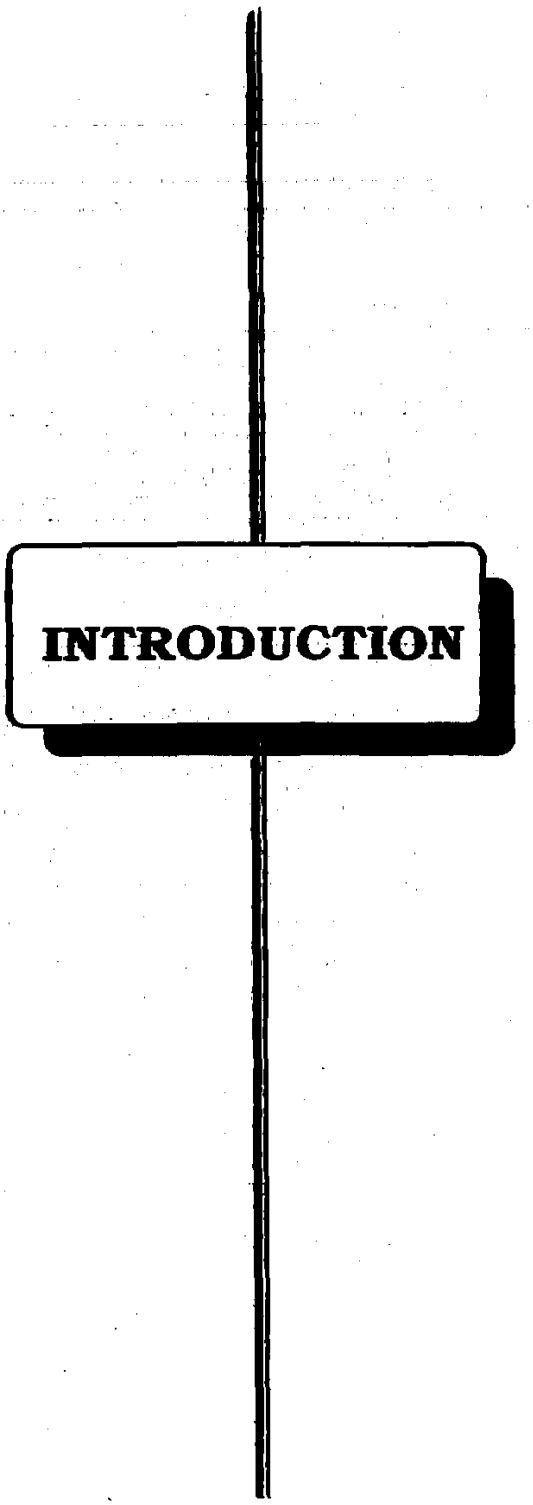
Hala Issa Mohamed

LIST OF ABBREVIATIONS

ADCC	Antibody dependent cell mediated cytotoxicity.
Aza	Azathioprine
BCGF	B cell growth factor
CD	Cluster of differentiation
CRP	C-reactive protein
DMARD	Disease modifying anti-inflammatory drug
ELISA	Enzyme linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
GSTG	Gold sodium thioglucose
GSTM	Gold sodium thiomalate
IL	Interleukin
IL-2	Interleukin 2
IL-2R	Interleukin 2 receptor
LAK	Lymphokine activated killer cell
LGL	Large granular lymphocyte
mAB	Monoclonal antibody
MHC	Major histocompatibility complex
MICC	Mitogen induced cellular cytotoxicity
MLR	Mixed lymphocyte reaction
Mtx	Methotrexate
NHS	Normal human serum
NK	Natural killer cell
NSAIDs	Non-steroidal anti-inflammatory drugs
PBL	Peripheral blood lymphocytes
PBMC	Peripheral blood mononuclear cell
PHA	Phytohaemaglutinin

PLG	Phosphetidy linositol glycan
PTS's	Parallel tubular arrays
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SAARD	Slow acting anti-rheumatic drug
SFL	Synovial fluid lymphocyte
TCGF	T cell growth factor

CONTENTS



INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disorder of unknown etiology that affects articular as well as extraarticular structures. Its major distinctive feature is chronic, symmetric, and erosive synovitis of peripheral joints. Associated monoarticular manifestations may include subcutaneous nodules, vasculitis, pericarditis, pulmonary nodules or interstitial fibrosis, mononeuritis multiplex, episcleritis or, less commonly scleritis. The severity of the disease fluctuates over time, and the most common outcome of established disease is progressive development of various degrees of joint destruction, deformity, and disability. (Roland, 1993).

The primary cause of RA is unknown. Utsinger et al., (1985) suggested that there is no single primary cause of RA, and speculated that this clinical syndrome defined as RA may be induced, in genetically predisposed individuals, by many arthritogenic agents. Since the understanding of RA pathogenesis is important for succefull treatment, every effort was done to investigate the implicated factors in the pathogenesis of this disease.

Heberman et al., (1986) stated that the understanding of RA owes much to immunologic studies. In the 1950s and 1960s, emphasis was on the antibodies present in the blood, particularly the antibody to IgG known as rheumatoid factor (RF). Later attention shifted to the cellular immune findings that has accumulated in the last 15 years and, where appropriate, try to relate it to the immunopathogenesis of rheumatoid synovitis. They added that although RA is primarily a disease of the joints, lymphoid cells in blood have been studied more than those in the synovial membrane. There are two reasons for this: firstly, the concept that RA is a systemic disease characterized by arthritis justifies the use of blood rather than joint cells;

secondly blood mononuclear cells are more easily obtained, separated and purified into their sub-populations.

The role of natural killer cells (NK) which are large granular lymphocytes (LGL) possess characteristic phenotypic markers and are distinguishable from T and B- lymphocytes in RA, remains unclear. Recent reports have indicated that NK cells may be involved in the pathogenesis of some autoimmune disorders, either by normal NK activity (Goto et al., 1980), reduced (Neighbour et al., 1982) and enhanced activity. (Spina, 1984).

In 1991, Satybaldyev et al. studied the activity of peripheral blood NK cells in 25 patients with RA. Data on the comparative clinico-immunological analysis by the cytotoxicity index were submitted. They found a relation between the nature of RA course and the presence of systemic manifestations such as nodules, polyneuropathy, proteinuria, carditis, levels of the RF, anti-DNA, CRP, cryoglobulinemia and changed activity of peripheral blood NK cells. Finally, they added that patients with RA having a combination of marked changes of humoral immunity with changed cytotoxicity of the peripheral blood NK cells activity can be referred to the group of risk.

In the study of Hendrich et al., (1991) NK cells were examined as a model for Fc gamma receptor type III positive cells, with regard to their interaction with RF. NK cell antigen CD16 and CD56 expression and functional NK and antibody-dependent cell-mediated cytotoxicity (ADCC) activity were compared in peripheral blood lymphocytes (PBL) and autologous synovial fluid lymphocytes (SFL) of RA patients. PBL and SFL showed normal CD56 expression. In contrast, both the frequency and the density of CD16 antigen were decreased in PBL & SFL. Furthermore, diminished NK cytotoxicity and a significant decrease in ADCC were observed in PB & SF NK cells.

Schwarz et al., (1992) showed that RA serum or synovial fluid increases the growth capacity of normal, interlukin-2 (IL-2) driven cell preparations, compared to normal human serum (NHS). Proliferation in RA serum and SF cultures was primarily associated with expansion of NK cells (CD16), and in NHS cultures, with T-cell growth. The capacity of RA serum to promote NK cell growth was related to patient global clinical activity and RF titers. The NK cells, but not the T cells, induced high levels of IgM RF synthesis in autologous B cells. Thus, alteration in NK cell growth may disrupt NK-B cell circuits in RA and contribute to B cell dysfunction.

Karsh, (1992) examined the effects of immune complexes on Nk activity. They demonstrated that RF as naturally occurring immune complexes in RA are able to modulate NK cell function via Fcγ RIII, not only with regard to natural killing and ADCC, but especially with regard to the capacity of NK cells to potentiate inflammation by the production of cytokines. They also found that non- RF containing immune complexes were also found to be potent inhibitors of NK activity.Thus, these data demonstrates how immune complexes and NK cells can interact and contribute to the process of rheumatoid inflammation.

However, the reason for these observations remains unclear and little is known about possible regulatory functions of NK cells in RA.