ACCELERATED IN VITRO APOPTOSIS OF LYMPHOCYTES FROM PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Thesis

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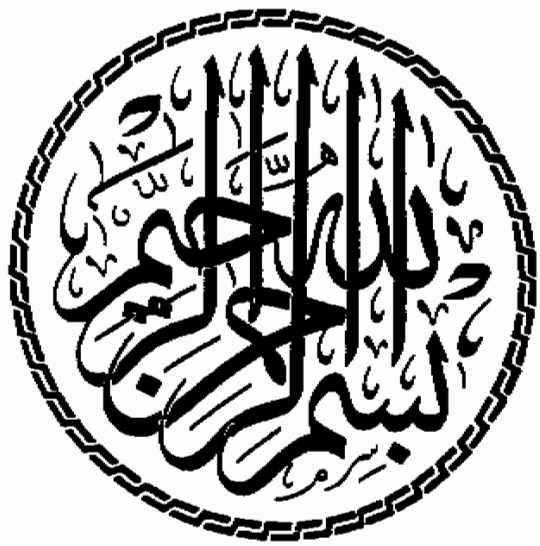
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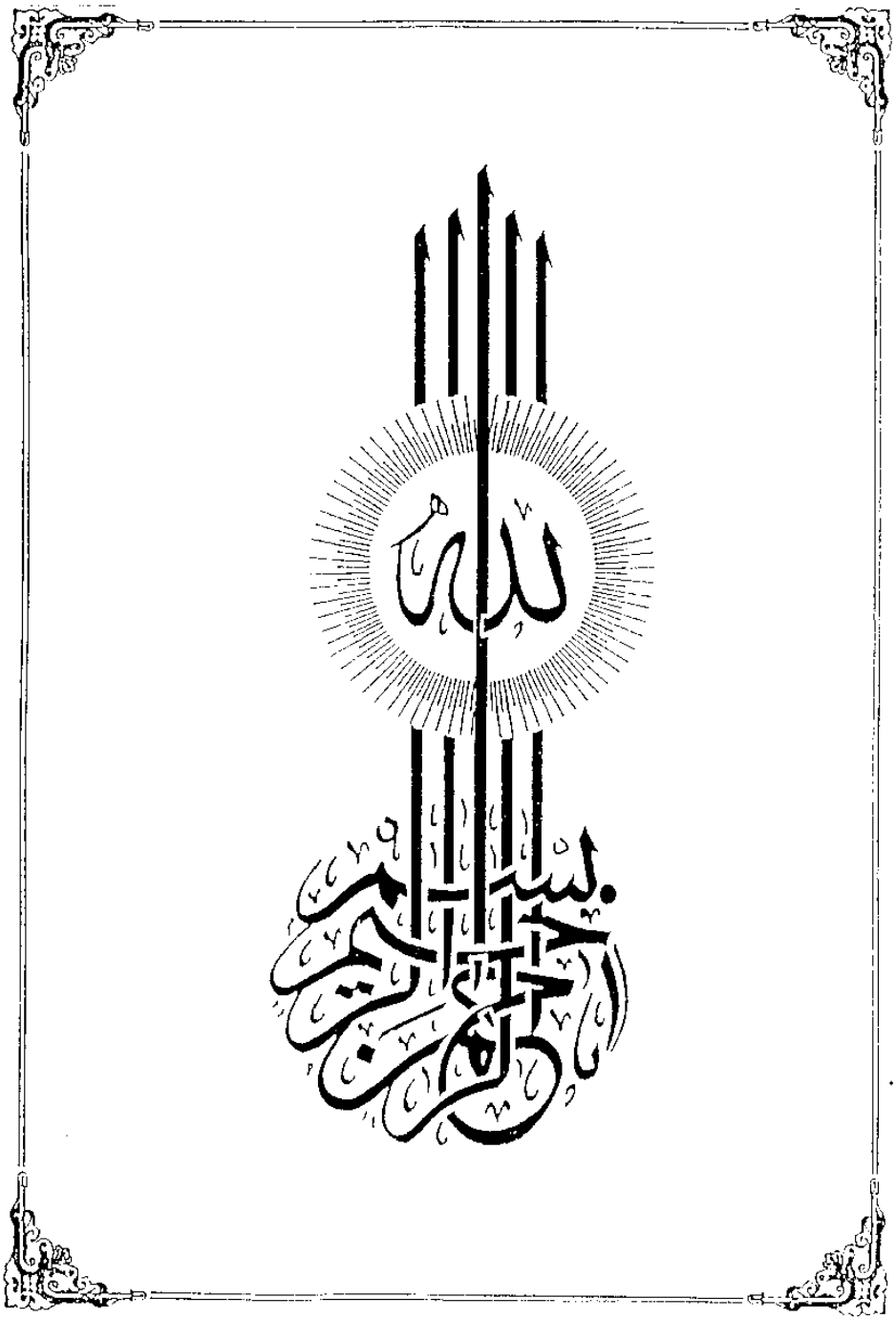

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ABSTRACT

Apoptosis is a form of cell death in which the cell actively participates by providing molecules that are directly or indirectly involved in the process.

The aim of this study is to demonstrate the role of altered apoptosis of lymphocytes in the pathogenesis of systemic lupus erythematosus.

This study was performed on 30 SLE patients in activity and 17 control subjects of matching age and sex.

Apoptosis of lymphocytes cultured for 48 hours was detected by examining nuclear morphology under the fluorescent microscope after staining by acridine orange and flow cytometric DNA quantitation after propidium iodide staining.

Accelerated in vitro apoptosis of lymphocytes was found in the patients group when compared to normal individuals. Both methods used for detection of apoptosis showed highly significant positive correlation.

We recommend in vitro double staining with marker of apoptosis and markers of both T and B lymphocytes to clearly define the role of altered lymphocyte apoptosis in the pathogenesis of the disease. Either one of both methods applied in this study could be used for detection of apoptosis.

LIST OF ABBREVIATIONS

RA:	Rheumatoid arthritis.
AIDS:	Acquired immunodeficiency syndrome.
ALL:	Acute lymphoblastic leukemia.
A.O:	Acridine orange.
Ca^{2+}:	Calcium ions.
ced:	Cell death abnormal.
ces:	Cell death specification.
CTL:	Cytotoxic T lymphocytes.
DEX:	Dexamethasone.
dNTP:	Terminal deoxynucleotide transferase with biotin.
EBV-LMP1:	Epstein-Barr latent membrane protein-1.
egl-1:	Egg-laying defective.
ELISA:	Enzyme linked immunosorbent assay.
HIV:	Human immunodeficiency virus.
HSP-70:	Heat shock protein-70.
IAP:	Inhibitor of apoptosis.
IgG:	Immunoglobulin G.
MHC:	Major histocompatibility complex.
MNC:	Mononuclear cells.
NGFR:	Nerve growth factor receptor.
NK cells:	Natural killer cells.
nuc-1:	Nuclease-1.
OA:	Osteoarthritis.
PBS:	Phosphate buffered saline.
PCD:	Programmed cell death.
P.I:	Propidium iodide.
PS:	Phosphatidyl-serine.
RNP:	Ribonucleoprotein.
sFas/Apo-1:	Soluble Fas/Apo-1.
SGP-2:	Sulphated glycoprotein-2.
SLAM:	Systemic lupus activity measure.
SLE:	Systemic lupus erythematosus.
Sm:	Smith antigen.
SS:	Sjogren's syndrome.

TCR:	T cell receptor.
TGFB:	Transforming growth factor beta.
TIMP:	Tissue inhibitor of metalloproteinase.
TNF:	Tmour necrosis factor.
TNFRI,CD120a:	Tmour necrosis factor receptor I.
TNFRII:	Tmour necrosis factor receptor II.
tPA:	Tissue plasminogen activator.
TRPM-2:	Testosterone repressed message-2.
TSP:	Thrombospondin.
uPA:	Urokinase-type plasminogen activator.
USA:	United States of America.
UV:	Ultraviolet.
VnR:	Vitronectin receptor.

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Systemic lupus erythematosus (SLE) is characterized by the production of antibodies to intact nuclear antigens, including antibodies to DNA and histones. Production of these antibodies appears to be antigen driven. Antinuclear antibodies in SLE are frequently IgG isotype of high avidity **(Carson, 1991)**. Analysis of fine specificity of these antibodies has shown that the epitopes recognized by many antinuclear antibodies are on the exposed surfaces of intact nuclear antigens **(Potanova et al., 1990)**.

These observations suggest that nuclear antigens must interface with the immune system to drive the antinuclear antibody response, and to provide antigen for the formation of immune complexes, nuclear antigens must become available in the extracellular space. A major mechanism by which undigested, intact nuclear antigens are generated and released in vivo is by the process of programmed cell death or "apoptosis" **(Franek and Dolnikova, 1991)**.

In contrast to necrosis, in which cell lysis and digestion of cellular contents are early events, apoptosis is characterized by the ordered digestion of nuclear chromatin yielding intact oligonucleosomes **(Green and Cotter, 1992)**.

Apoptosis may be abnormal in autoimmune diseases and may play a role in the induction of autoimmunity **(Watanabe et al., 1992)**.

AIM OF THE WORK