LYMPHOCYTOTOXIC ANTIBODIES IN SYSTEMIC LUPUS ERYTHEMATOSUS

THESIS

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Of

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By

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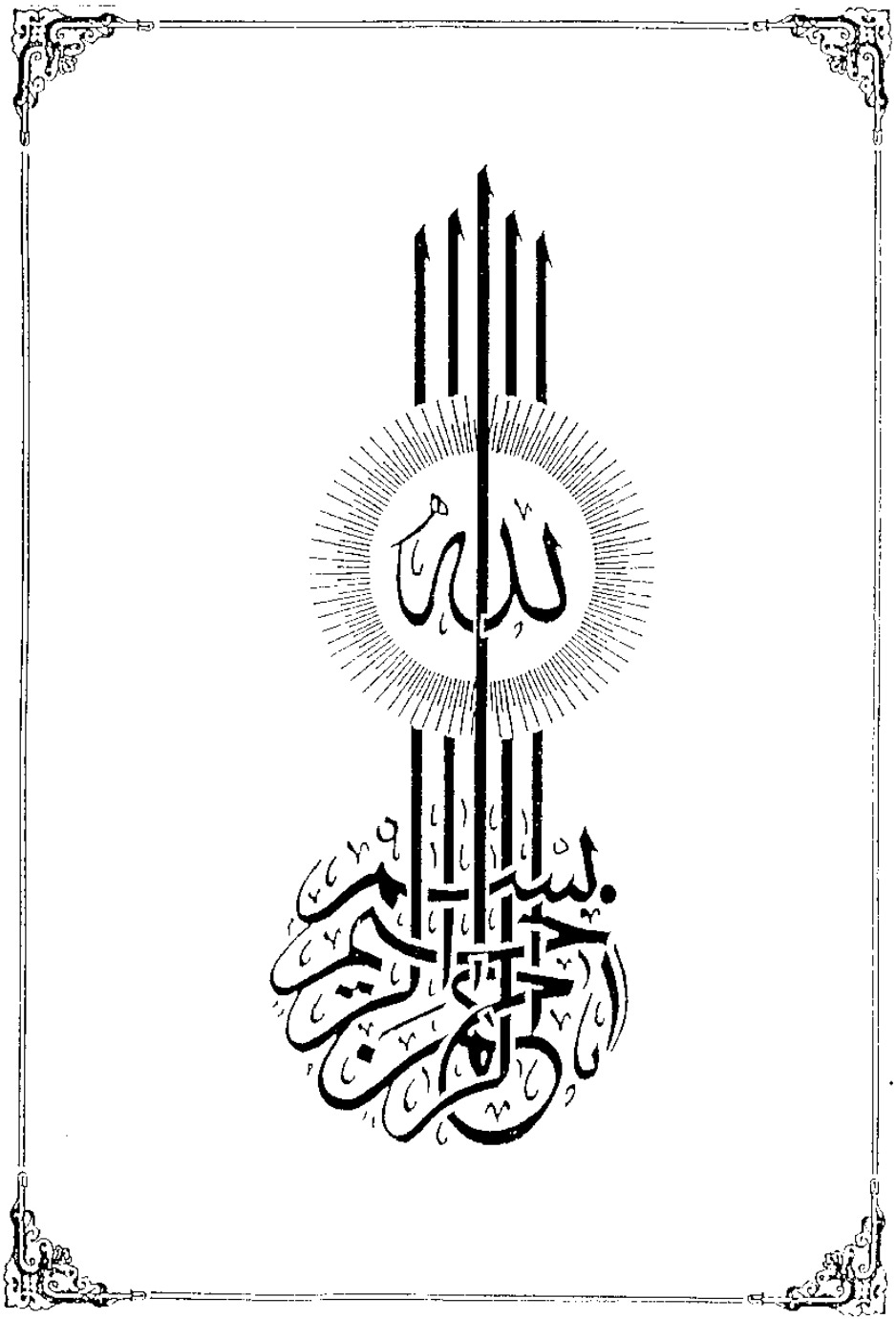
To My Parents



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LISTS OF ABBREVIATIONS

ADCC	:	Antibody dependent cellular cytotoxicity.
AIDS	:	Acquired immune deficiency syndrome
ALA	:	Antilymphocyte antibodies.
ANA	:	Antinculear antibodies.
ANTI-H	:	Antihistone
ANTI-N-DNA	:	Anti-native DNA.
ANTI-RNp	:	Antiriponucleoprotein.
BCRs	:	B-cell receptors.
C	:	Complement.
Con-A	:	Concanavalian-A
CHF	:	Congestive heart failure.
CLA	:	Complement dependent lymphocytotoxic antibodies.
CML	:	Chronic myelogenous leukemia.
CNS	:	Central nervous system.
CPK	:	Creatinine Phosphokinase.
CSF	:	Cerebrospinal fluid.
CVA	:	Cerebrovascular accidents.
DEJ	:	Dermal epidermal junction.
DIC	:	Disseminated intravascular coagulation.
dS-DNA	:	double stranded-DNA antibodies
EBv	:	Epestein-Barr virus.
ESR	:	Erythrocyte sedimentation rate
Ig	:	Immunoglobulin.
IL	:	Interleukin
JRA	:	Juvenile rheumatoid arthritis.
LBT	:	Lupus Band test

LCTA	:	Lymphocytotoxic antibodies.
LE	:	Lupus erythematosus.
MCTD	:	Mixed connective tissue disease
MHC	:	Major histocompatability complex.
MI	:	Myocardial infarction.
MLR	:	Mixed leukocyte reaction.
MNC	:	Mononuclear cells.
MW	:	Molecular weight
NK	:	Natural Killer
PBS	:	Phosphate buffered saline
PHA	:	Phytohaemagglutinin.
PPD	:	Protein purified derivatives
PWM	:	Pook weed Mitogen
RA	:	Rheumatoid arthritis
RBCs	:	Red blood cells.
SLE	:	Systemic lupus erythematosus
SS-A	:	Streptolysin S-A.
SS-B	:	Streptolysin S-B.
T_H	:	T-helper
T_S	:	T-suppressor.
TCRs	:	T-cell receptors.
VDRL	:	Venereal disease research laboratory.

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Introduction and Aim of the Work

INTRODUCTION

Systemic lupus erythematosus (SLE) is a disease with a more immunologic cause. Among the various etiologic factors of SLE is the infective theory. One of the most important points which favoured this theory is the prescence of lympho-cytotoxic antibodies (LCTA) in sera from patients with SLE. These antibodies were often seen following viral infections e.g. measles, Mumps, and infectious mononucleosis, and are not only seen in these patients but also in their household contacts.

The aim of the present work is to evaluate the presence of these lymphocytotoxic antibodies in Egyptian lupus patients and their households contacts.

Review of Literature

LYMPHOCYTE

The lymphocyte is a spherical cell (7-12 µm diameter) with scanty cytoplasm and a round, slightly indented and somewhat eccentrically located nucleus, containing course masses of chromatin (Kristic, 1984).

Lymphocytes carry out many functionsbut one of these is unmistakably and is unique to them. It is the lymphocyte's ability to re-shuffle its genes in such a way that they can then produce receptors for antigens and via these receptors initiates a specific immune response. The receptors also provide the basis for distinguishing two kinds of lymphocytes:

T-lymphocytes differentiating largely in the thymus and B-lymphocytes differentiating largely in the bone marrow (in mammals) or in the bursa of fabricius (in birds). The receptors of the T-lymphocyte , the T-cell receptors (TCR) is characterized by its ability to recognize two molecules or molecular fragments at the same time: an antigen (non self) and a molecule encoded in the genes of the major histocompatibility complex (MHC; self in the physiologic situation) (Shwartz, 1985). The receptors of the B-lymphocyte, the immunoglobulin (Ig) molecule, on the other hand, recognize one molecule only - the foreign antigen (non self). The two kinds of receptors also differ in the form in which they are produced by their respective cells. The B-cell receptor (BCR) is secreted by the lymphocyte and the TCR is

not. This distinction is however not absolute, in certain stages of B-cell development, the BCR, like the TCR, is integrated in the membrane and only acquires a secretory piece in the latter phase (Kronenberg, et al.,1986).

The two kinds of receptors also differ in their structure, but this difference is in detail rather than in the overall design. (Kronenberg, et al., 1986). Both receptors consist of two kinds of chain (heavy and light in BCR, α and B in TCR), each chain is assembled from very similar basic molecules (domains), the receptor genes are assembled from similar elements (The V.D.J. and C. Segments).

Lymphocyte Function and Structure

The main physiologic function of lymphocyte is to distinguish self from nonself and to mount specific attack on non self. The recognition occurs via three sets of molecules TCR,BCR and MHC molecules. The TCR of T-lymphocytes recognises protein in the context of MHC molecules, normally self MHC molecules, (Roitt , et al., 1989). If the recognition occurs at a certain stage of development of the organism or a certain phase of T-cell differentiation, in which only self molecules are present, the recognising cell is inactivated or eliminated. If it occurs outside this stage or phase and involves non self proteins, the T-cell develops into an effector cell which can influence the development of other cell (T-lymphocyte, B-lymphocyte

and other cells) or can kill the target cell with which it reacts specifically (Roitt, et al., 1989). The B-lymphocytes probably recognise self and non self antigens indiscriminately and also recognise a large spectrum of substances. They normally avoid response against self by being dependent on signals from activated T-cells for stimulation. Even when they bind to a substance via their antigen receptors, most of them do not develop into effector cells (antibody-secreting plasma cells) until they recieved the go-ahead from T-cells which have encountered the same substance (Mitchison, 1971).

In addition to this main function (initiation of specific immune response) lymphocytes also carry out a host of other functions, largely through soluble substances (lymphokines) which they secrete. Most of the lymphokines are produced only after activation of the lymphocytes which normally occurs when the lymphocyte encounters an antigens.

Lymphocyte Surface membrane: structure and function:

The lymphocyte surface (plasma) membrane as for cells in general consists of lipid bilayer, integral membrane proteins and peripheral proteins. The lipid bilayer provides a surface barrier separating the cell contents from the extracellular environment regulating the flow of ions and nutrients/ metabolites between these compartments. It is composed of equal amounts of cholesterol and

phospholipids, but the exact composition is variable and reflects the lipid composition of the environment (Levis, et al., 1976). In lymphocytes, the peripheral membrane proteins are apparently located exclusively on the plasma membrane's cytoplasmic face. The integral proteins exposed on the cell surface mediate in particular the regonition of specific antigen either alone (B-cells) or in association with class I & II MHC antigens (T-cells) (Selvaraj, et al., 1987).

I. The T-cell receptors (TCRS):

T-cells recognise different antigen entities than do B-cells (Kronenberg, et al., 1986).

The T-cell marker is the T-cell antigen receptor TCR, there are two defined types of TCR, TCR_2 is a heterodimer of two disulphide linked polypeptide (α and B), TCR_1 is structurally similar to TCR2 but consists of γ and δ polypeptides. Both receptors are associated with a complex of polypeptides making up the CD3 complex. Thus a T-cell is defined either by TCR1 or TCR2 which is associated with CD3 . Approximately 95% of blood T-cell express TCR_2 and up to 5% have TCR1. The TCR2 bearing cells can be sub-divided further into T-helper (T_H) subset which is CD4+ and T- cytotoxic/suppressor subset (Tc/s) which is CD8 +. CD4+ T-cells recognise antigens in association with MHC class II molecules. While CD 8 + T-cells recognise antigens in association with MHC class I molecules (Roitt, et al.,1989).

Two potential funtions of TCR1 bearing cells are surveillance of epithelia and differentiation of T-cell, TCR_2 (α,B receptors) in the thymus (owen, 1988).

The CD_4 + set can be furthur subdivided functionally into:

1. Cells which positively influence the immune response of T-cells and B-cells - the helper cell function, which are CDW 29+
2. Cells inducing suppressor/cytotoxic functions in CD8+ cells- the suppressor inducer function which are themselves CD45 R+.

CD8 + cells can also subdivided by a number of criteria and a variety of monoclonal antibodies into specific functional subsets. For example cells which recognise antigen in association with MHC molecules and produce IL-2 (CD 28+) and cells which do not recognise antigen in association with MHC molecules or produce IL-2 (CD11 b+). CD3 +/TCR 1 cells represent a minority of circulating T-cells which are also CD4, CD8. These cells house into surface epithelia such as epidermis and are termed intra-epithelial lymphocytes (IEL) In interstitial mucosal epithelium TCR1 + cells also express CD8. It is probable that these cells represent a primitive cytotoxic popualtion operating at the sites of entery of pathogens (Roitt, et al., 1989).

II. B-cells:

B-lymphocytes represent about 5-15% of the circulating lymphoid pool and are classically defined by the prescence