THE ROLE OF IMMUNOREGULATORY CELLS IN SOME CHRONIC LIVER DISEASES

THESIS

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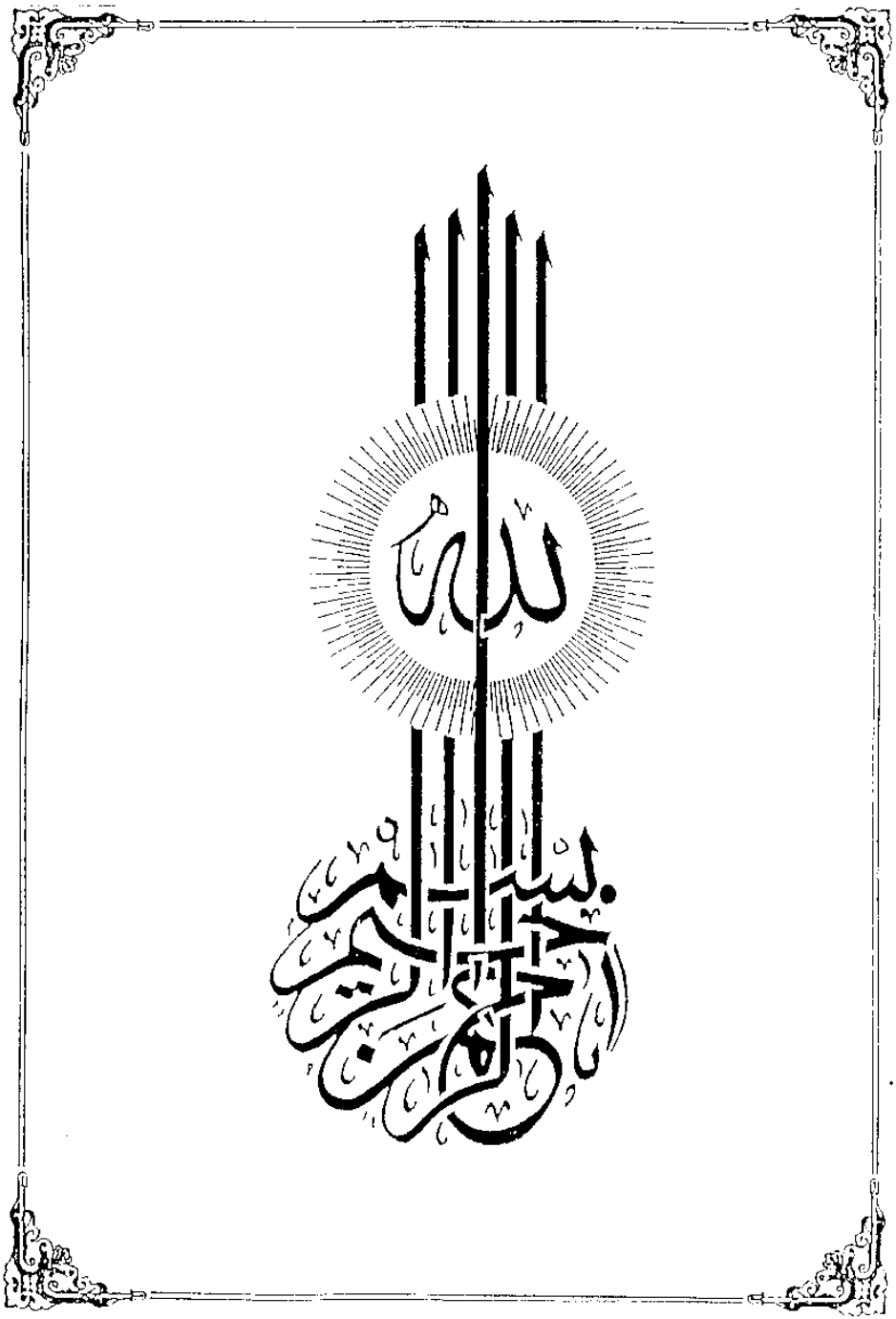

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Schistosomiasis is the most prevalent disease in Egypt affecting about 11 millions of population (Ayad, 1974 and Zakaria et al., 1988). Viral hepatitis is also an important endemosporadic disease in Egypt (El Akkad, 1973, El-Razzky et al., 1974; Sherif et al., 1985 and Abdel Azim et al., 1987).

Significant higher incidence of viral hepatitis in schistosomal hepatosplenomegalic cases was demonstrated by many workers (Guimaraes, 1973; Ata et al., 1977; Nooman et al., 1977, Shoeb and Madwar, 1981 and El-Dayadi et al., 1984). They concluded that schistosomal infection predisposed to retention of hepatitis B antigen after subsidence of the acute attack and attributed this to local defect in cell mediated immunity (El-Dayadi et al., 1984 and Zakaria et al., 1988).

In previous studies cell mediated immunity in schistosomal hepatosplenomegaly was found to be depressed using E-rosette assay (Zakaria et al., 1978 and Khalil et al., 1987); hypersensitivity skin tests (Zakaria et al., 1978; Saif El Din et al., 1982 and Shoeb et al., 1983); by migration inhibition test (Saif El Din, 1981) and by E-rosette assay with blast transformation (Abd El Ganil, 1986).

Recently monoclonal antibodies are available to identify and enumerate T lymphocytes and their functional subsets, helper/inducer and suppressor/cytotoxic cells (OKT_3+, OKT_4+ and OKT_8 + cells respectively) (Reinherz & Schlossman, 1980; Borre et al., 1982 and Khalil et al., 1987). Monoclonal antibodies are considered to be indespensible tools for delineating communicative inter-actions between lymphocytes subsets (Thomas et al., 1982; Talal, 1986 and Khalil et al., 1987).

In this study our AIM was to do more advanced and specific studies on T-lymphocytes, in pure schistosomal and mixed schistosomal post viral hepatitis hepatosplenomegaly. Also, our AIM was to utilize the highly sensitive technique of immunofluorescence using the most recently developed monoclonal antibodies in identification and enumeration of T-lymphocyte and its subpopulation.

REVIEW OF LITERATURE

BASIC IMMUNOLOGY

Various functions of the immune system are controlled in a precise way through a system of regulatory cells and factors. These include the B-lymphocytes, helper and suppressor T-lymphocytes, the specific and non specific helper and suppressor factors and lymphokines Paul, 1980; Talal, 1986 and Abd El Azim et al., 1987..

Macrophages are known to play a central role in initiation of immune responses through antigen-presentation and triggering of I helper cells (Th cells) (Rosenthal, 1978.. Antigen taken up by macrophages is thought to be displayed on the cell surface in association with self-MHC products coded by the I-region in mice or the homologous HLA- D locus in man Miller, 1978 . Antigen specific Th recognise both the antigenic and self Ia determinants (Abd El Azim et al.,1987).

The number of effector Th cells increases exponentially, so that B cells of appropriate specificity which have bound antigen via their surface immunoglobulin receptors are triggered to differentiate into antibody forming cells. When the Th population has expanded sufficiently, amplifying feedback induction signals augment suppressor activity. The sequential appearance of helper followed by suppressor activity

is a phenomenon which has often been noted (Rich & Pierce, 1974; Yamamoto et al., 1977 and Sercarz et al., 1978). The delayed appearance of a wave of suppression serves a dual purpose: to limit further Th recruitment and to inhibit the continuing activation of B cells under the influence of already differentiated Th effector cells. Those B-cells triggered during the early wave of helper activity are refractory to the action of Ts (Lobley et al., 1978) and continue to differentiate into fully mature antibody forming cells (Miller, 1973; Talal, 1986 and Abd El Azim et al., 1987).

One of the major category of T cell function is the development of responses which produce soluble proteins (lymphokines) with the capacity to engage the inflammatory system, to destroy target cells, and to increase viral resistance. Among the lymphokines are materials that inhibit the migration of macrophages (Macrophage inhibition factor, MIF); products that activate macrophages, MAF; products that are chemotactic for monocytes, granulocytes, and eosinophils; interferon; and products that directly destroy certain tumor cells and cell lines (lymphotoxin) (Mocklin et al., 1980a and Abd El Azim et al., 1987).

Monoclonal antibodies are produced by somatic cell hybrids. They are used for differentiation of T-lymphocytes. The use of monoclonal antibodies depends

upon their ability to bind to the surface of viable cells expressing the unique antigenic determinants (Brooks et al., 1980 and Talal, 1986). These cells become coated with monoclonal antibody and can be visualized and enumerated by staining with fluorescein labelled antimouse immunoglobins (Zola et al., 1980 and Abd El Aziz et al., 1987).

A series of monoclonal antibodies have now been developed which are reactive with thymocyte and or peripheral T lymphocyte cell surface antigens.

OKT_3 monoclonal antibodies are reactive with 95% of peripheral T lymphocytes, 20% of thymocytes and 30% of splenocytes. It is used for identification of human peripheral T lymphocytes.

Evidence has been provided that the OKT_4 cells which are reactive with approximately 50 to 60% of peripheral human T-lymphocytes, contain helper cells capable of assisting the differentiation of B-cells into antibody forming cells and also capable of inducing lymphotoxic (killer) and cytotoxic effector cells (Reinherz et al., 1979).

OKT_8 is reactive with about 35% of peripheral T-lymphocytes. It identifies a reciprocal subset of T-cells that lack helper functions but do contain the cytotoxic precursors and effector cells involved in cell mediated lymphocytosis. OKT_8 cells also contain at least one subset of cells important in suppressing B-cells differentiation (Thomas et al., 1980 and Khalil et al., 1987).

THE LIVER AS AN IMMUNOREGULATORY ORGAN

Kupffer cells As Antigen Inactivators:

The liver plays a dominant role in the clearance of bacteria (Beeson et al., 1945) and viruses (Sabesin & Koff, 1974).

In man, endothelial cells lining the sinusoids of the liver comprise about 15% of the total number of liver cells (Gates et al., 1961). Some of these are phagocytic and are known as Kupffer cells. Although they are probably bone marrow-derived (Stuart, 1970), their turnover is relatively slow and their activity for particulate material is very high (Portmann et al., 1976). Cells of mononuclear phagocytic system are found in many other organs but Kupffer cells are in many way quite distinct.

Most of macrophages are capable of increasing the immunogenicity of antigens, but Kupffer cells are highly specialized in their inability to perform this function. In fact their prime function from an immunologic point of view seems to be destinction of antigens (Paul, 1980).

In cirrhosis, the extraction rate of colloidal materials in a single passage through the liver is

decreased (Rankin et al., 1961), possibly owing to decreased Kupffer cell function or intrahepatic collateral circulation, bypassing the liver sinusoids. The development of portosystemic collaterals in association with portal hypertension would further reduce the effectiveness of Kupffer cells in clearing particulate material, and this would lead to increased delivery to other phagocytic cells in the spleen and bone marrow. These would increase the immunogenicity of any particulate antigens (Grun et al., 1977).

The Immunoregulatory Network in Liver Diseases:

It has become apparent that more than one type of immune reaction mediated by different cells, may be responsible for the initiation, progression or healing of liver disease.

Three major types of immune reactions may be of importance in liver diseases. The first immune reaction is mediated by T-cells and may be of major importance in the early stages of viral infection. Hepatitis B viral antigens and most likely other viral antigens located on the surface of hepatocytes are recognized by sensitized T cells (Alberti et al., 1977 and El-Sheikh et al., 1978). This reaction, as in other viral infections (Ennis et al., 1981), may be HLA-restricted, that is, lymphocytes cytotoxic for

antigens of viral origin can only kill virus coated target cells of the same HLA constitution.

The second type of reactivity is a B-cell immune reaction directed to viral antigens. Antibodies may combine with various antigens on the surface of liver cells or outside. These antibodies, especially those directed to HBsAg, may be helpful because they may neutralize or prevent multiplication of the viral agent (Macdonald, 1981). In addition, some antibodies may elicit systemic manifestation by forming immune complexes (Madalinski & Brugal, 1979 and Pernice et al., 1979) or may interfere with the modulation of the immune response (Theofilopoulos & Dixon, 1980). The significance of other antibodies, especially those coating antigens on the nuclei is not yet clear (Gerber et al., 1976; Biquetto et al., 1976 and Paronetto, 1981).

The third type of cell destruction an antibody dependent cellular cytotoxicity, ADCC, became apparent from in vitro studies of cytotoxicity of lymphocytes (Cochrane et al., 1976). In this situation, autoantigens, or modified cell surface antigens, may be involved. Antibodies bind to the hepatocytic antigens with either Fab parts, thus rendering their Fc portion available for interaction with K lymphocytes, which are cells