T Lymphocyte Subsets During Pregnancy

Thesis

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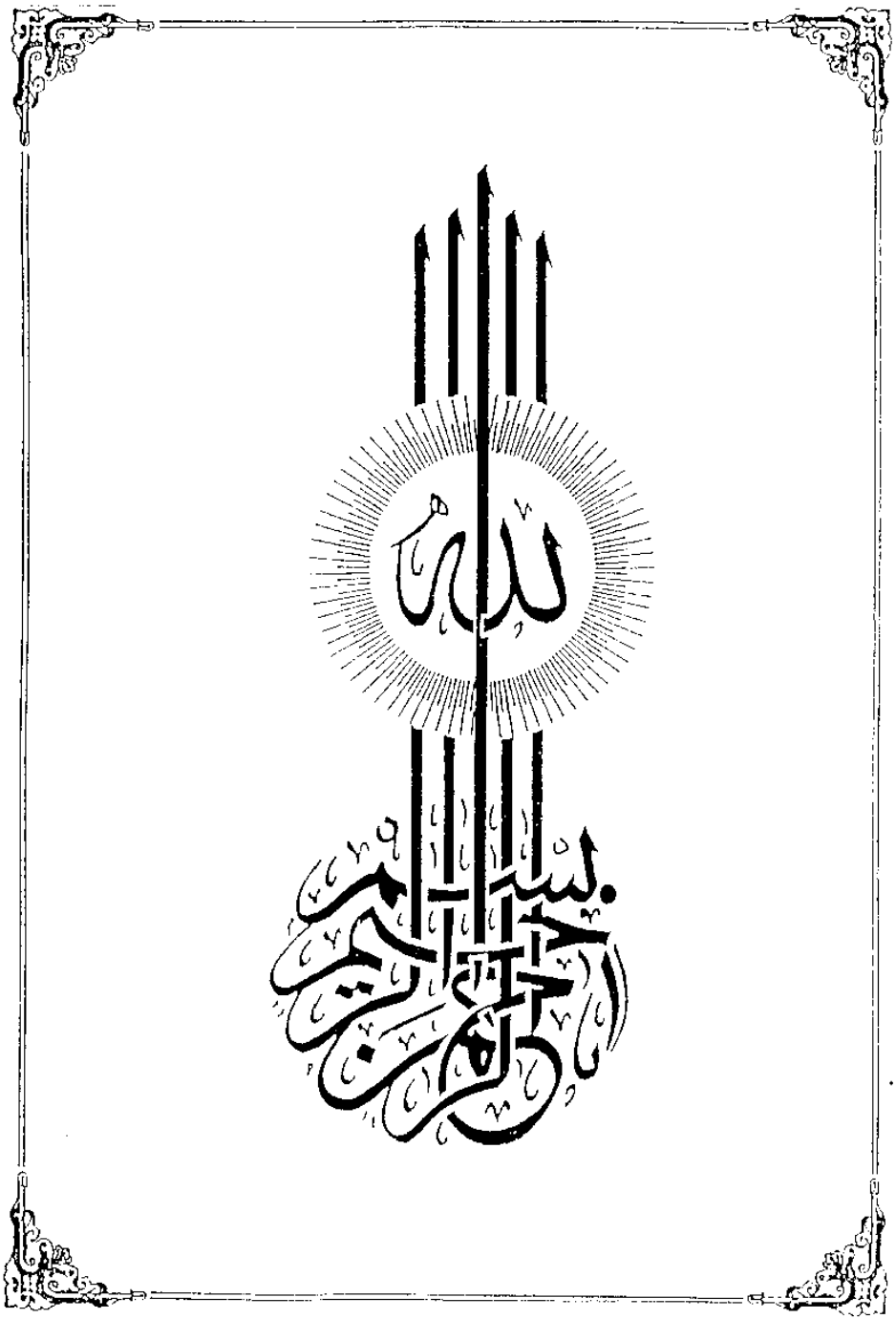

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The pregnant state represents one of the most significant yet at the same time one of the least understood phenomena in biology today. The study of maternal-foetal relationships has generated an enormous number of studies at the experimental as well as the clinical level, aimed at understanding the basic processes involved in normal and abnormal pregnancy.

Normal pregnancy implies a perfect symbiosis of an antigenically foreign foetus and placenta growing in an immunologically foreign environment, and the question therefore arises why such a foreign tissue is not rejected by the mother in the same way that a foreign grafted tissue is rejected (Cauchi, 1981). The mechanisms preventing the immune rejection of the foetus are multiple and not yet clearly explained.

Decreased maternal immune responsiveness during pregnancy may partly explain the survival of the foetus as an allograft (Sridama et al., 1982). Since the recent development of monoclonal antibodies, it has been possible to obtain a more precise evaluation of both the number and the functional characteristics of human T-lymphocytes.

In an attempt to contribute to a better understanding of immunoregulation during pregnancy, we used these monoclonal antibodies to characterize the circulating lymphocytes of pregnant females.

REVIEW OF LITERATURE

I- REPRODUCTIVE IMMUNOLOGY

A) Immunology of the Trophoblast

The placenta serves a number of functions including the exchange of gases, transfer of nutrients and metabolites as well as production of a large number of hormones (Cauchi, 1981). In order for the placenta to perform these functions close approximation to maternal blood constituents is essential. Thus the anatomical arrangement of the trophoblast places it in a strategic situation in respect to the foeto-maternal immunological relationship (Billington, 1976; Cauchi, 1981). In this section the reason for non-rejection of the placenta will be examined and the functions of the placenta as an immunological barrier will be analysed.

1. Diversity of Form:

This means that various forms of trophoblast exist both at different phases of pregnancy and as a major component of the organised placenta. It is important to bear in mind that not all immunological properties are shared by these forms from one species to another or indeed from one trophoblast population to another in the same placenta.

The trophoblast invasiveness into the uterine wall varies considerably in different species and this has some influence on its immunological status. Three degrees of invasiveness have been recognised:

a. A completely non invasive state: The trophoblast lies in close apposition to an intact uterine epithelium or causes a minor degree of epithelial breakdown, as in ungulate species; pig, sheep and goat.

b. A moderately invasive state: There is uterine epithelium and stromal tissue erosion, as in carnivores.

c. A complete invasive state: invasion continues deep into the uterine tissues and opens up maternal blood capillaries to bathe the trophoblast surface, as in the haemochorial placenta of man, other primates and rodents. In this type of trophoblast two basic components are present, a cellular tissue and a multinucleate syncytium. The human syncytiotrophoblast arises by differentiation and fusion of cytotrophoblast with an addition of trophoblastic giant cells which may extend beyond the limit of definitive placenta (Billington, 1976).

2. Evidence of Trophoblast antigenicity:

All tissues of the body can be shown to possess a vast array of surface (i.e. cell membrane - related) antigens. A number of these, e.g. organ-specific antigens probably have no significance in relation to rejection phenomena. Other antigens, e.g. histocompatibility, blood group antigens etc., may be relevant in this respect. The different antigens that can be detected on cell surfaces are:

a) Heterophil antigens: shared by different species and show cross relationship (e.g. Forssman type antigens).

b) Xenogeneic antigens: common to one species and recognizable by another.

c) Alloantigens: present on the cells of genetically different individuals of the same species (e.g. histocompatibility antigens).

d) Organ or tissue specific antigens: on a given tissue within an individual (e.g. mouse O antigen on T lymphocytes).

e) Individuality antigens: restricted to a few cells within a tissue or organ (e.g. (TSTA) tumour specific transplantation antigen).

f) Exogenous antigens: introduced by infectious agent (e.g. (MTV) mouse tumour virus antigen).

Antigens of possible relevance to maternal - foetal rejection are:

Histocompatibility antigens:

Whether or not transplantation antigens are expressed on trophoblast became a matter of intense controversy and conflicting data were obtained concerning this matter. Simmons and Russel in 1966 provided evidence that there is either a complete absence or a relative intrinsic deficit of histocompatibility antigens on the cell surface of the early

mouse trophoblast. A more recent study showed that serial transfer of ectoplacental cones (EPC) to ectopic sites in allogenic recipient mice resulted neither in an inhibition of trophoblast growth nor in an alternation in survival time of subsequent skin allografts (Billington, 1973; Billington et al., 1974). Using immunofluorescent technique, a more direct attempt at localizing HLA related antigens to trophoblastic cells in placental tissues could be obtained (Curzen, 1968; Rigby and Curzen, 1969; Koren et al., 1969). Another technique using a mixed agglutination assay was used by Seigler and Metzgar (1970). Both techniques demonstrated that many different types of human foetal tissue possessed antigens controlled by HLA locus but could not obtain positive reactions with the trophoblast. However, Faulk et al. (1974) failed to find any HLA specificity in antibody eluted from placenta. More recently no B_2-microglobulin (a small molecular weight antigenic component intimately associated with HLA antigens) could be shown in trophoblastic cells, although it was present in the villus / stromal cells and foetal endothelial cells (Faulk and Temple, 1976; Faulk and Johnson, 1977). The early claim by Hulka and Mohr (1968) that cone trophoblast is immunogenic (i.e. capable of inducing an immune response), did not allow a distinction to be made between strain-specific and organ-specific antigen. All evidence indicating the presence of transplantation antigens in grafted placental tissue could be attributed to one or other of a wide variety of contaminating cells. With

all these conflicting data it should not be denied that antibodies to histocompatibility antigens are actively produced in a large proportion of multipara. This could be a result of transplacental passage of nucleated foetal cells, rather than as a direct exposure of placenta to the maternal circulation (Pavia and Stites, 1984). Also it was already proved that class I (HLA - A,B,C) antigens were detected on early human placental cyto-trophoblast. However, this was difficult regarding other human trophoblast tissue or the mature chorionic villus. In all cases, class I (H - 2 K/D) rather than class II (Ia) major histocompatibility antigens appear to be selectively expressed on the trophoblast (Pavia and Stites, 1984).

Tissue specific antigens:

The possible existence of an organ-specific antigen in the placenta was considered for many years. A number of organ related antigens were described in the placental trophoblastic cells including mitochondrial and microsomal antigens (Beer and Billingham, 1971). These are antigenically related to renal proximal cells. The findings that rabbit antirat trophoblast serum had a powerful abortificient influence in pregnancy in rats strengthened the thesis that there was a highly tissue-specific antigen associated with trophoblast (Beer et al., 1972). This heterogenous anti-trophoblast serum might have some applications in trophoblast neoplasia, particularly choriocarcinoma, as it was

susceptible to immune attack in vitro (Currie and Bagshawe, 1967). Another interesting finding is that in the sera of pregnant women there is a trophoblast related antigen detected by immunodiffusion which is absent in non pregnant females (Aw and Chan, 1973).

Species specific antigens:

It is clear that species-specific antigenic determinants on the trophoblast cell membrane render the tissue susceptible to immune attack under suitable conditions. The pre-immunization of rats with mouse skin grafts inhibited the growth of subsequently transferred mouse ectoplacental cone (EPC) trophoblast (Simmons and Russel, 1967).

In vitro, cultures of mouse trophoblast showed lysis following incubation with xenogeneic antiserum (Billington and Jenkinson, 1975). A similar complement dependant lysing reaction against human trophoblastic chorionic gonadotrophins was demonstrated by Currie (1967). At the same time there is early evidence that the trophoblast can withstand xenogeneic transplantation and produce flourishing growth from one species to another (Kirby, 1962; Billington, 1966).

Blood group antigens:

The original investigations by Withebsky and his colleagues in 1928 and 1932 suggested that blood group A and B antigens were absent from placental villi (Beer and Billingham, 1971).

Additional evidence for this report using immunofluorescence technique was done later (Thiede et al., 1965; Szulman, 1972). However the endothelium of vessels of the chorion, villi and umbilical cord possessed only basic H antigens (Szulman, 1972). Localization of blood group A antigen on both normal human trophoblast and on hydatidiform mole was claimed by Gross (1966) and later was supported by Loke and Ballard (1973). They suggested its presence at low surface density. This was confirmed by electromicroscopic localization of separated patches of antigen (Cauchi,1981). It is to be concluded that as with histocompatibility antigens, blood group antigens are present in reduced concentration on trophoblast compared to other foetal and normal adult tissue.

3. Antigen Transfer Across The Placenta "an incomplete immunologic barrier":

Trophoblastic tissue serves as an anatomic barrier between foetal and maternal tissues and thereby serves as the first line of defense against maternal antifoetal alloimmunity. Anderson (1971) pointed out that the placenta might more aptly be described as a filter than a barrier because it is responsible both for the transmission of materials essential for foetal development and for the exclusion of a variety of potentially deleterious agents from the maternal side.

Passage of cells through the placenta: Although it is relatively easy to envisage the free transfer, passive or active, of metabolites from mother to foetus and vice versa, it is more difficult to establish the traffic of cells in this way.

a. *Passage of foetal cells into the maternal circulation*:

Trophoblast: it was documented that up to one gram of trophoblastic tissue per day could be found in the maternal circulation (Ikle, 1964). This phenomenon is known as "trophoblastic deportation." Entrapment of these cells in the lung and other tissues occurred with no apparent host reaction (Park, 1965).

Foetal red cells: can be shown in the maternal circulation from the eighth week onwards using Kleihauer technique or immunofluorescent staining of foetal Hb. It varies from minute quantities to massive foetal bleeds (Cauchi, 1981). They are increased in number after delivery and to a lesser extent following foetal manipulation (Hay et al., 1979).

Leucocytes: this was proved by techniques involving cytogenetic analysis (Walkanowska et al., 1969). The male type Y chromosome was present in 19 out of 21 women bearing male foeti. The male type cells in the maternal circulation were first detectable at fourteenth to fifteenth week using Y chromosome fluorescence (Schroder and De la Chapelle, 1972).