TROPHOBLAST RESTRICTION OF MATERNO-FOETAL IMMUNITY

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One of the great unsolved problems in human biology today is the almost total lack of immunological understanding about the materno-foetal relationship. Genetically dissimilar tissues are normally unable to co-exist, yet foetal growth normally occurs uninterrupted within the mother throughout gestation. This striking exception to contemporary concepts in transplantation immunology suggests that a unique mechanism developed during evolution to allow the intra-uterine development of fertilized eggs and the subsequent birth of living young, i.e. viviparity. There are also several reasons to expect that aspects of this phenomenon have been adopted by certain tumour cells to enhance their survival, and a growing body of information on certain diseases of pregnancy such as spontaneous abortion and pre-eclamptic toxaemia suggests that some of these might represent immunological imbalances between mother and foetus. There is also the hope, as yet unfulfilled, that an explanation of the mechanisms responsible for the survival of the placental homograft will be useful in organ transplantation. In order to understand the transplantation analogies of pregnancy, it is necessary to study the events which occur at the interface between mother and embryo. This interface in humans is composed of the trophoblast cell membrane, and some progress has recently been made in understanding the interplay between trophoblast antigens and maternal lymphocytes within the placental bed. Lymphocytes are normally responsible for the recognition and rejection of foreign cells, and this process can be reproduced in the laboratory by the mixed-lymphocyte culture reaction. This tool has been modified to study the interaction of lymphocytes with trophoblast antigens, thus providing a model of the materno-foetal relationship. We have used this approach during the past three years, and the results of these studies have revealed that trophoblast membranes produce a unique glycoprotein which inhibits the rejection reaction of lymphocytes while having no measurable effects on other lymphocyte reactions. This glycoprotein is species-specific and it is not found on other normal cells except amnion epithelium. Interestingly, it is however found on certain tumours such as human breast cancer cells. It thus seems as though the two major biological exceptions to immunosurveillance in natural selection,i.e. viviparity and tumour development, utilize a common mechanism to insure their survival in potentially immunologically hostile hosts, and several aspects of this mechanism will be presented and discussed.

FOETAL-MATERNAL RELATIONSHIPS: ENDOCRINOLOGY

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Although the growth and development of the fetus is hormonally modulated, there is little evidence to suggest that maternal hormones play a major role. Thus a relatively impermeable placenta preserves an autonomous status for the endocrine regulation of fetal growth. However indirect effects such as the influence of maternal diabetes upon fetal pancreatic function and of maternal thyrotoxicosis should not be overlooked.

On the other hand, the intervention of chorionic hormones into the physiology of the mother is well established, varied, and in some species such as the human and rat, highly complex. It would seem that in gaining the advantages of a longer gestation mammals have faced greater evolutionary pressures to develop mechanisms to safeguard the endometrial-chorial relationship. Although in some species this has been accomplished by mechanisms which simply extend the life of the corpus luteum, in others, chorionic hormones themselves not only ensure the continuation of the progestational state, but actually marshall maternal intermediary metabolism for the benefit of the fetus.

Luteotrophic responsibility resides in chorionic gonadotrophins such as hCG and PMSG. It may also be a property of placental lactogen, as for example in the rat where it replaces maternal pituitary hormones on about day 12, and possibly in the human female.

More striking roles for placental lactogens are (1) in the alteration of maternal metabolism to fetal advantage and (2) in the stimulation of lobulo-alveolar growth in the mammary gland. In one species at least the subsequent lactational performance is dependent upon the intensity of this chorionic stimulus.

Control of chorionic polypeptide hormone secretion is poorly understood. There is little doubt that it is influenced by fetal genotype as in the control of PMSG output in the mare, bPL in the cow and possibly hCG in man.

The steroidogenic capability of the conceptus has permitted the fetus to participate in the control of birth. The influence is most complete in sheep where adrenal glucocorticoid induction of placental enzymes permits oestrogen synthesis to increase markedly at the expense of that of progesterone. In rats, where there is evidence of strong maternal influence on the onset of labour, the key event, namely the reduction of ovarian progesterone secretion, may again be determined by the conceptus. In man a fall in progesterone is not obligatory for labour but fetal adrenal participation in chorionic oestrogen biosynthesis may be important. The significance of oestrogen is not clear but may reside in actions on the myometrium and on the cervix, both of which may involve the participation of relaxin.

TRANSPORT MECHANISMS IN THE PLACENTA

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The mammalian conceptus is surrounded by, and entirely supported by, maternal extracellular fluid, an environment whose stability is well regulated by the mother's own homeostatic mechanisms. However, it appears to be necessary for a fetus to maintain some independence from its mother. The placenta provides such a barrier; the fetus can enjoy a separate 'milieu interieur', which may be an advantage from immunological, endocrinological or nutritional aspects.

Animal experiments suggest that the placental barrier is epithelial in nature. In common with other epithelia, it is relatively permeable to substances of high lipid solubility, such as gases. There is good evidence for the presence of special transfer mechanisms for those lipid-insoluble substances of biological importance such as sugars, aminoacids and at least some electrolytes. The development of such transfer mechanisms would have been an evolutionary necessity in the presence of an otherwise relatively impermeable barrier, as transfer of adequate quantities of anabolic substrates needs to be guaranteed. Little is yet known of the selectivity of these mechanisms or of what controls them - or if they are controlled at all; and there is no evidence concerning whether their failure contributes to materno-fetal disease. At present, the placental epithelium may be considered to have a transport function in search of a pathology.

Most experimental data have been obtained in animals, but observations in man suggest that, while there are differences in detail, there is considerable similarity in the overall pattern of placental epithelial function. Experiments made by man occur whenever medication is prescribed. The different patterns of permeability to drugs of differing properties provide support for the relative impermeability to lipid insoluble molecules, while the neonatal hyponatremia following intravenous glucose infusions to women in labour reflects the high placental permeability to water.

Experiments of nature often depend on the constitutional differences between mother and the genetically different fetus. The markedly different protein phenotypes in mother and fetus implies a very low passive permeability to protein. Similarly the relative impermeability to thyroxine is evident from the delayed osseous maturation of the hypothyroid fetus in spite of normal maternal thyroxine levels. In some cases placental transfer functions contribute to fetal disease; for example, the placenta fails to protect the fetus from the hostile environment of maternal diabetes, phenylketonuria or rhesus isoimmunisation.

Most such observations pose more questions than they answer. Yet these answers must be sought if we are fully to understand, and perhaps modify, the contribution of placental transfer mechanisms to fetal health and disease.

Abstracts

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Heterozygote-diagnosis of GSD II and GSD III by quantitation of a urinary glycogen fragment.

A glucose-containing tetrasaccharide characterized as a-D-Glc-(1-6)-a-D-Glc-(1-4)-a-D-Glc-(1-4)-D-Glc was first found in normal human urine and has a normal excretion rate of 0,1-2,5 mg per 24 hrs. The structure of this oligosaccharide strongly indicates a glycogen origin. The excretion of the glucose tetrasaccharide have been studied in several diseases in which an abnormal glycogen metabolism is known. Greatly increased amounts were found in the urine of patients with glycogen storage disease types II and III. A moderate increase was observed in glycogen storage disease type VI while normal excretion was found in cases with glycogen storage disease type I.

New results indicate that the quantitative determination of this compound is of value in the identification of GSD type II and III heterozygotes which in hitherto studied families show a clearly increased urinary excretion of the tetrasaccharide.

The tetrasaccharide is reduced to its alditol derivative and methylated. The permethylated derivative is quantitated by gas-liquid chromatography and identified by its retention time on GLC and its mass spectrum.