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Foetal-maternal immune interactions

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There is little doubt that any gestation in mammalians (and thus also any new human life from its biological inception) can be considered as an haploidentical allo-transplant, due to the antigenic disparity existing between the pregnant mother (the host) and the embryo-foetus (the graft). Indeed in its obvious biological reality, the embryo-foetus, due to its antigenic constitution, is one half of paternal origin, thus foreign to the mother who, however, physiologically tolerates it. Therefore, little doubt exists that the concept, *life itself is also an immunological phenomenon*, may be extended also to prenatal life.[1,2]

A look at the past

Half a century has elapsed since Billingham, Brent and Medawar[3] faced the enigmatic question of maternal tolerance of a half-compatible allogeneic transplant and formulated four possible explicative hypotheses. The physiological foetal engraftment could be made possible by: a reduced immunogenicity of the conceptus; a scarce reactivity on the part of the mother; an organic characteristic of the uterus, as an *immunologically-privileged* site; or a function such as the *immune-barrier* inherent to the placenta. Based on knowledge acquired over time, it is in fact the placenta, with its maternal *decidual* component and embryonic *trophoblast* which has been recognised to hold a position of principal importance in interpreting the *physiological life in common* of the mother-embryo, mother-foetus. In fact, over time, the placenta has been demonstrated to play a fundamental barrier role reciprocally limiting the cellular interchange between mother and foetus.[4]

In addition, the hormonal activities of the placenta (chorionic gonadotropin, possibly somatomammotropin, and, most importantly, progesterone and other various steroids) that favour the general protection of the foetus during pregnancy must be taken into consideration. In particular, among steroids, the relevant placental production of progesterone,[4] as well as the immune suppressive effect of this hormone were already demonstrated several years ago.[5]

Beginning in the late 60's and early 70's, the antigenic-immunologic aspects, in particular those pertinent to the HLA antigens, of the placental component of embryonic, trophoblastic origin, namely the trophoblast, have been extensively investigated in depth, with very controversial results. However, their functional implications remained unclear, at least until the end of the 80's when it was recognised that *a presupposition for a maternal immune-cytotoxic-lymphocyte-mediated rejection of the embryo-foetus* is lacking since the cyto- and the syncytio-trophoblast do not express MHC class I antigens, even though the *extra-villous cytotrophoblast presents the antigens HLA-A, -B, -C*, although, of somewhat rudimental structure.[6,7] Evidence that all trophoblastic structures instead lack class II antigens (HLA-DR, -DP, -DQ) supports, together with the previous data, the hypothesis of the scarce immunogenicity of trophoblastic tissue, and this easily correlates with *the absence of cytotoxic maternal cells* directed against the foetus.[7] Nor has the antigen H-Y (histocompatibility-Y) naturally originating only from the male foetus, received due credit over time for its ability to stimulate the mother's immune system.

The function of the maternal, *decidual*, placental component, in limiting or in controlling the invasive penetration of the trophoblast in uterine tissue was underlined in the early 70's, as well as the possible immunologic role of the conspicuous lymphocytic component associated with specific decidual cells, first demonstrated in mares, but also successively in the human uterus.[4] These first data were then integrated by specifying that *around 50% of the decidual cells result as CD45 positive lymphocytes*, morphologically similar to natural killer (NK) cells.[7] These lymphocytes were defined as *decidual granulated lymphocytes* and have been actually recognized to possess strong immune suppressing activity, mediated by the secretion of a factor that blocks IL-2 activity on lymphocytes; this

readily suggests an immune regulating role of the embryo-placental entity.[8] It should be recognized then, that we are already at this time, facing significant new horizons of research related to the clarification of immune tolerance existing in the interaction between mother and foetus.

On the other hand, less recent studies (1977) accredited the role of an immune depressed environment favouring the course of the pregnancy due to the participation of other non-specific factors; molecular complexes produced by the mother and foetus: the Pregnancy Associated Plasma Protein A and the Early Pregnancy Factor, as well as the alpha-foetal protein and transferrin (whose activity has at least been demonstrated *in vitro*).[9] And still from the literature of the latter thirty years of the XX century emerged the importance of investigations, aimed at evaluating the immune characteristics of neonatal lymphocytes, in particular their response against the mother's lymphocytes.

In this regard, we should remember for example, that some studies suggested that neonatal lymphocytes are capable of inducing the production of the Migration Inhibitory Factor (MIF) by lymphocytes of pluriparous women, thereby demonstrating their previous sensitization.[10] On the other hand, lymphocytes of women experiencing spontaneous idiopathic chronic abortion demonstrate *in vitro* reactivity towards paternal alloantigens through the production of MIF, but do not produce a factor that blocks MIF, which instead is produced by women capable of bringing pregnancy full term.[11]

These observations are from the 1970s, but previously (1965-69), it was noted that a passage of leukocytes (also lymphocytes) takes place *naturally* from the mother to the foetus and that these cells survive in the foetal circulation, usually, for 6 months; and even much longer if the foetus is immune suppressed.[4,12-14] Not less significant, is the passage into the maternal circulation of foetal trophoblastic cells, as well as blood cells and lymphocytes; the latter in particular were extensively analyzed as early as the 1970s.[4] According to some more recent research (1998), the presence of these cells in the mother's circulation might suggest a possible role played by foetal lymphocytes in the development of some maternal autoimmune disorders many years after delivery, but also, vice versa, during the pregnancy, a role in the establishment of a *microchimerism* perhaps immunologically favouring the course of the pregnancy.[15]

Moreover, regarding neonatal lymphocytes, we must remember that (we are in the 1990s) these lymphocytes rarely express cytotoxic activity against maternal cells, while they express activity (low to normal) against paternal or (i.e. third party) foreign cells.[16, 17]

More recent years

A significant turning point in studies of the maternal-foetal immune interaction was realized just at the beginning of the 1990's after revisiting the peculiar HLA pattern previously demonstrated in the trophoblast and in particular with the demonstration that syncytiotrophoblast cells express HLA-G,[18] an HLA Class I molecule able to bind the *killer-cell immunoglobulin like receptors* (KIRs) expressed on natural killer (NK) lymphocytes present in the maternal part of the placenta. This interaction between KIR molecules and their ligands (i.e. HLA-G), blocks NK cell function, possibly contributing to tolerance of the foetus by the mother.[19]

The 1990s resulted very fertile in research and offered clarifications (in part speculative and in part experimental) of this yet *enigmatic* tolerance that is at the basis of every renewal (and continuation) of the human life and mammalian life in general.

Through the years, virtually every biological mechanism, hypothesized or demonstrated to be involved in the maintenance of immune tolerance towards self or non-self antigens, has also been investigated in the context of foetal-maternal interaction. As a result of these studies, all the below listed mechanisms, working actively in synergy, have been hypothesized, and sometimes also documented, to contribute to the foetal-maternal immune barrier, thus promoting reciprocal foetal-maternal immune tolerance and favouring the successful growth of the foetus.[20-22]

Peculiar HLA expression pattern

As already mentioned, the syncytiotrophoblast does not express, unlike adult tissues, surface HLA-A and HLA-B molecules and only weakly displays HLA-C antigens. Taking into account the *missing self* theory,[23,24] this pattern of expression should potentially defend the foetus from the immune reactivity mediated by HLA class I-restricted maternal T lymphocytes, specific for alloantigens expressed by the foetus, while permitting the attack of alloreactive NK cells. However, trophoblastic cells peculiarly express HLA-G and HLA-E, monomorphic HLA-class I variants, which have been documented to be ligands of inhibitory receptors present on the NK-lymphocyte surface, such as KIR or CD94/NKG2A. The inhibitory signal, delivered by the interaction between inhibitory receptors with HLA class I, and in particular with HLA-G and HLA-E, is known to inhibit NK lymphocyte-mediated cytotoxic activity.[25] Therefore, selective expression of HLA-G and HLA-E on the trophoblast is thought to protect the foetus from maternal NK lymphocyte attack at the foetal-maternal interface.

Peculiar distribution of leukocyte subsets at the foetal-maternal interface

NK- and T-lymphocytes, as well as macrophages, are the most abundant immune cells included in the deciduas, while B-lymphocytes are virtually absent. Early during pregnancy, NK cells comprise the majority of leukocytes (about 50-80%) present in uterine mucosa. Distribution of NK cell subsets in the deciduas is different from that of peripheral blood[26] and more similar to that observed in normal non-inflamed lymph nodes.[27] Indeed, the maternal deciduas includes $CD16^{neg}CD56^{bright}$ NK lymphocytes, co-expressing both inhibitory (e.g. CD94/NKG2A) and activating (e.g. CD94/NKG2C) receptors, while circulating peripheral blood NK cells display a $CD16^{+}CD56^{dim}$ phenotype and reciprocally express either inhibitory or activation receptors.[28] Decidual NK cell subsets come into close contact with extravillous trophoblastic cells, which have the function to invade and destroy the walls of the uterine spiral arteries, in order to guarantee an efficacious blood flow to the foetus.[21,26,29] The balance between inhibitory and activation receptors expressed by decidual NK cells is supposed to play an important role in controlling the growth of trophoblasts and in preventing an overwhelming foetal cell invasion of maternal tissues.

The T helper type 2 (TH-2) pattern of cytokine response in the placenta has been shown to dominate during successful pregnancy, while a TH-1 reaction, which mainly elicits inflammatory phenomena, has been associated with miscarriage.[20,21,30]

Naturally elicited $CD4^{+}CD25^{high}Foxp3^{+}$ regulatory T cells[22] endowed with immune suppressive function (Treg) were shown to increase in number, in both deciduas and peripheral blood, during early pregnancy.[31] It is also worth considering that, following activation, Treg produce at least two anti-inflammatory cytokines, namely interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), and up-regulate surface CTLA-4, a molecule known to deliver a negative signal to both T lymphocytes and antigen presenting cells (APC).[19] In particular, CTLA-4 interaction with its ligands (CD80, CD86), expressed on APC, induces IDO (indoleamine 2,3-dioxygenase) production by the APC. IDO, a tryptophan-catabolizing enzyme expressed by macrophages, dendritic cells (DC) and extravillous trophoblastic cells is known to prevent immune cell activation by means of tryptophan deprivation, and might thus actively contribute to induction and maintenance of foetal-maternal tolerance. Altogether, these data support the hypothesis that the presence of Treg at the foetal-maternal interface may promote the differentiation of tolerogenic APC.[31-33] Moreover, animal models and *in vitro* observations in humans strongly suggest that the action of Treg may prevent miscarriage and control the foetal T cell response during pregnancy, while a reduced number and/or function of this subset of suppressor immune cells are associated with unexplained infertility.[31-35]

Peculiar cytokine pattern

Both membrane-expressed HLA-G and a soluble form of the molecule (sHLA-G1 protein) abundantly secreted by trophoblastic cells and circulating in the amniotic liquid, as well as in maternal blood during pregnancy, are able to modulate the pattern of cytokines produced by decidual mononuclear cells. In particular, the signal delivered by the interaction between HLA-G and mononuclear cells shifts the TH1/TH2 cytokine balance towards a TH2 polarization.[20] Among its well-described immune suppressive effects, progesterone, secreted in large quantities by the placenta, has been documented to stimulate the endometrium to synthesize leukaemia inhibitory factor (LIF). While during implantation LIF is produced by endometrium and blastocyst expresses surface LIF-receptor (LIF-R), during pregnancy, LIF is secreted by deciduas and, in particular, by TH2 lymphocytes. Even though the precise role of the LIF/LIF-R interaction has not been fully clarified, it is conceivable to hypothesize that binding of LIF to its ligand favors trophoblast growth.[20]

Tolerogenic APC, and in particular suppressive macrophages and DC up-regulate the production of anti-inflammatory cytokines, such as IL-10 and TGF-β. Altogether, studies focusing on cytokine balance at the foetal-maternal interface strongly suggest the dominance of an anti-inflammatory, immune tollerogenic, pattern of secretion.

Induction of an apoptosis pathway

Trophoblastic cells cultured *in vitro* express CD95-ligand (CD95-L), a molecule that can also be secreted in a bioactive soluble form. It is well known that an interaction between CD95-L (membrane or soluble form) with the CD95 molecule which is up-regulated on activated immune cells, such as activated T lymphocytes, induces apoptosis of CD95-expressing cells. Therefore, it has been hypothesized that trophoblastic cells expressing and/or producing CD95-L are endowed with the capacity to promote apoptosis in CD95-expressing, activated blood cells homing to the foetal-maternal interface and are potentially harmful for the conceptus. Even though trophoblastic cells also express CD95, it is of note that they are apparently refractory to apoptosis mediated by the CD95L/CD95 pathway. However, it cannot be excluded that some other apoptotic pathways, such as that mediated by the tumour necrosis factor/TNF-R interaction might be involved in the control of trophoblast proliferation.

Moreover, it has been hypothesized that:
(i) trophoblastic antigens expressed by syncytiotrophoblasts are in some way camouflaged (for instance by blocking antibodies or fibrinoid material), thus they escape maternal immune surveillance (a very speculative hypothesis);
(ii) certain molecules (e.g. membrane complement protein, MCP; decay accelerating factor, DAF) might block or strongly reduce the complement cascade, activated by antibodies specific for paternal antigens, potentially able to reach the foetal-maternal interface;
(iii) annexin II secreted by the placenta could play a role in foetal-maternal tolerance by means of its capacity to inhibit maternal lymphocyte proliferation and/or maternal antibody production.

Foetal-maternal immune interaction continues beyond pregnancy

The passage of foetal cells into the maternal circulation documented already more than a century ago by Schmorl in 1893,[36] and more recently further confirmed.[37] More recent studies have documented a cell passage from the mother to the foetus.[38-41] In particular, as mentioned above, the presence of maternal cells was initially documented in patients affected by severe combined immunodeficiency; thereafter, it has been demonstrated that maternal cells can be detected in a relevant percentage of cord blood samples derived from healthy neonates. Cells of foetal origin transferred to the mother may survive for decades and are responsible for the microchimerism observable in tissues of women who have experienced pregnancy.[15,42-43] Transferred foetal cells include mature leukocytes (T–, B–, NK–lymphocytes, monocytes) and haematopoietic, as well as mesenchymal progenitor cells.[42-45] Moreover, microchimerism of foetal origin has been described in multiple tissues (skin, liver, thyroid) in both women affected by autoimmune disease and in healthy individuals. In particular, it has been postulated that the foetal-maternal microchimerism of immune cells may play a role in the development of some types of autoimmune disease; nevertheless, no concrete data have been obtained to definitively prove this hypothesis. On the other hand, it has also been hypothesized that foetal progenitor cells homing to the mother and endowed with trans-differentiation capacity could play a role in the repair of damaged maternal tissues, thus offering a benefit to the host.

Transmission of maternal cells to the foetus may also go along with transfer of soluble maternal HLA, this last phenomenon in particular is favoured, in the neonate, by breast-feeding. Confrontation of the foetal and neonatal immune system with non-inherited maternal antigens (NIMA) may have a long-term impact on modulation of childhood immune responses.[46,47] Indeed, it has been documented that highly allosensitized patients were less prone to develop allo-antibodies specific for NIMA as compared to allo-antibodies directed towards non-inherited paternal antigens (NIPA).[48] Moreover, it has been demonstrated, at least *in vitro*, that alloantigen-reactive cytotoxic lymphocytes specific for NIMA are undetectable or present at a low frequency in the neonate, as compared to the frequency of the same cells directed towards NIPA.[16,17] This differential immune reactivity against NIMA when compared with NIPA or unrelated alloantigens may theoretically have a favourable impact in the context of allogeneic transplantation, especially on the occurrence of graft-versus-host disease in patients given an allogeneic hematopoietic stem cell transplantation from a family HLA-disparate donor.[46,47]

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