Antigen-bearing Targets Have Selected the Immune Mechanisms and Their Regulation during Evolution: The Example of Gestation*

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Immunologists are currently trying to understand the bases of the immune regulation on the ground of 2 different concepts, namely

1) The molecular idiotypic network where idiotype specificity is the first concern and antigens would merely be trouble makers, and

2) The cellular T lymphocyte circuitry where the main concerns are the relations and communications between lymphocytes, with positive and negative signals, with help, suppression and contrasuppression.

While these studies are of outmost interest and bring so much to our understanding of the regulatory mechanisms of the immune reaction in mammals, I am convinced that a proper view of the meaning of the immune reaction as well as the bases of its regulation must begin with some understanding of the underlying evolutionary forces.

Beyond doubt, immune reactions are necessary for the survival of individual and species. But, in addition, it appears that they have to rely on a highly sophisticated system in order to maintain the selective advantages and superiority of the highly evolved species such as mammalians and especially the human species. So is also the case of the central nervous system; modern science begins to realize that the immune and nervous systems do communicate with each other and have some mediators in common as well as with the endocrine system.

One is led to consider the possibility that the first two most elaborated systems (dealing with internal communications in order to cope with external stimuli and threats) may have had parallel and possibly interdependent evolution.

Driving forces

What have been the driving forces that have ultimately led to the selection of these systems, as we begin to understand something of their way of functioning?

It appears to me axiomatic that the essential driving force for the selection of the immune agents and the corresponding immune system has to be the final fate of the antigen-bearing targets.

Any target which is dangerous for the survival of the individual and the species must be eliminated or neutralised if the species is to survive and, eventually, to continue its evolution. The relevant targets are bacteria, viruses, fungi, parasites as well as allografted, and possibly, tumour cells. This is at the origin of the immune rejection reaction (RR), i.e. the selection of the immune agents and mechanisms responsible for it.

On the other hand, targets which are necessary to the survival of the individual and the species (such as autoantigen-bearing organs and alloantigen-bearing foetuses) must not be threatened by such a RR or must be protected against it. That reaction, more subtle and more difficult to uncover is what we have named the facilitation reaction (FR).[1,2] In addition, another driving force, common to all physiological reactions, is the necessity of a regulation in order to prevent the immune RR towards invading foreign agents to reach too strong a level and to have too long a duration, which would affect the general balance and preempt the immune system, preventing it to react against other new invaders. This regulation also is insured by the immune agents of the FR.

The main issue and, so to speak, the main purpose of the FR is therefore to maintain the IR in the

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proper limits, reaching a state of balance where foreign invaders are attacked and rejected, and substances and cell from the individual himself are protected against the induction and/or the effects of such an immune RR. The same general mechanisms of the FR may, according to its intensity go from a simple down regulation of an ongoing immune reaction (and its eventual termination) to a state of active immune tolerance.[4,5] This is obtained and observed in highly evolved animals, in mammals.

Aspects of the immune reaction during evolution

A way to try to put some order in our understanding to what happens to the mouse is to follow a few landmarks in the evolution of the immune reaction and its balance.

1. From the beginning, cell-surface recognition seems to be an essential and necessary factor, preserving the cellular individuality. It seems that it can be by-passed through intra-cellular grafting.

2. In multicellular, cell-colony-like organisms such as sponges and coelenterates, transplantation studies show the presence of a self/non-self system of recognition demonstrated by the non-acceptance of cells grafted from foreign colonies. Such a simple binary system does not reach the state allowing cell differentiation with specialised organs as well as the removal of old or altered cells. Cells have therefore to multiply indefinitely, identical to themselves, forming new colonies by separating from the main one.

3. In differentiated phyla such as annelids, earthworms, transplantation studies point to the individual recognition of various foreign colonies with specific second set rejection reactions, indicating the presence of an immunological memory. There are also indications of specialised cells that is to say recognition and removal of altered cells. Whether this can be attributed to recognition substances coded for by a primitive form of MH Locus is not known. But what is known is that this accelerated rejection can be adoptively transferred by cells of the coelom but not passively by its fluid. These facts on earthworm transplantation immunity, demonstrated by Pierrette Chateaureynaud-Duprat from Bordeaux[6] and confimed by Edward Cooper, from California,[7] show the role of sensitised cells in the immune RR.

4. Coming now to the vertebrates when lymphocytes with their subpopulations, antibodies with their subclasses definitely appear, the urodele amphibian *Salamandra salamandra* teaches us several things.

Transplantation, although technically uneasy, shows the attributes of a classical immune RR, mainly cellular, but apparently also with a component of cytotoxic antibodies and with some primitive type of C'. This demonstrates a step in the increasing complexity of the RR.

On the other hand, that species represents one of the first attempts at viviparity in tetrapods. Actually, it is an ovo-viviparous species and the study of its *gestation* is particularly rewarding. Embryos are numerous (up to over 40). They may be kept until maturity or rejected while still being larvae, sometimes even dead.

In vitro studies made by P. Chateaureynaud-Duprat and M.T. Badet have shown that spleen cells from the embryo-bearing mothers are able to specifically kill cells from their embryos at an impressive rate. This increases with the number of gestations (and embryos). But, correlatively, the sera of these same mothers can prevent this cytotoxicity and this protective capacity also increases with the number of gestations.[8] It has been shown to be due to 2 factors. One, specific of the embryos, absorbable by them and localised in the IgM fraction (the only Ig present in that species). The other one, non-specific, acting on the effector spleen cells[8] and possibly announcing the mammalian pregnancy associated factors, as the specific component announced the mammalian regulatory FR.[9] No suppressor cells were detected in these reactions. The system therefore is not perfect, although it indicates a very interesting attempt.

5. Coming now to the mammalians with the mouse as the most serious prototype.

In this species one has better defined them.

Immune agents of the rejection and facilitation reactions (Table 1).

While, in the case of an artificial allotransplantation, the RR predominates, it is different in the case of the natural semi-allogeneic transplant. We shall consider in some detail the immunological reactions of the mother to the paternal antigens borne by the conceptus.

Table 1 Immune agents of the rejection reaction (RR) and of the regulatory facilitation reaction (FR).

RR	– T lymphocytes	. T_H & T_{DH} (activating macrophages and NK cells through MAF & IF)
		. Tc (directly cytotoxic)
	– Antibodies activating	. C1 (IgM & murine IgG2)
		. K cells (through ADCC)
FR	– Enhancing antibodies: non-activating C1 or K cells, or complexes to the soluble antigen (blocking factors) or antidiotypic.	
	– Suppressor or regulatory cells (mainly T lymphocytes T_S)	

Immune reactions towards the foetus during pregnancy

These reactions are better (or only) detected in multiparous gestations; they include a double aspect.

*A. **Pregnant mothers elaborate immune agents of a (weak) rejection reaction towards conceptus paternal antigens.***

Signs of a specific alloimmunisation are detected but this does not usually reach a terminal effector stage.

1. Gestation induces a specific alloimmunisation with some components of the RR.

a) Delayed hypersensitivity to father's antigens has been reported.[10,11]

b) Pregnant mother spleen cells may give a secondary type of mixed lymphocyte reaction (MLR) in the presence of paternal type cells.[12]

c) In the H-2 compatible combination BALB/c x DBA/2, BALB/c spleen cells are not able to produce a lethal GVHR when injected into DBA/2 newborn mice, except if the BALB/c donors are preimmunised with DBA/2 cells (92% lethal runting) or if they are pregnant of DBA/2 males (17% of lethal runting) (Janine Voisin *et al,* unpublished data, cited in 13).

d) Spleen cells from allogeneically pregnant mice, injected into isogenic mice can, under favorable conditions, transfer an accelerated rejection reactivity to a tumour allograft of paternal strain origin.[14]

2. However this alloimmunisation does not usually reach the effector stage of CTLs.

a) We have consistently found no trace of anti-paternal CTLs in spleen of primiparous or multiparous pregnant mice.[15]

b) This is at variance with the ovoviviparous amphibian *Salamandra salamandra* in which the spleen cells of the pregnant mothers are extremely cytotoxic *in vitro* for cells of their own embryos.[16]

c) However, CTLs have been described in normal human pregnancy (Noelle Genetet, personal communication) and CTL activity to cells of the conceptus have been described.[17,18]

It is therefore clear that the pregnant mothers do react against the conceptus in the way of a weak rejection reaction.

*B. **Pregnant mothers elaborate immune agents of a (stronger) facilitation reaction towards the conceptus paternal alloantigens.***

The immune agents of this FR being enhancing antibodies and suppressor cells.

1. Anti-paternal transplantation alloantibodies.

a) Their elaboration during pregnancy is well established in mice (H-2) and humans (HLA) although the phenomenon is not detected in all strain combinations or all individuals in the mouse strain combinations studied here,

b) They have been shown to be trapped on the placenta.[14,19,20]

c) They are paternal alloantigen-specific.

d) They are predominantly IgG1,[14,19,21] i.e. of an anaphylactic, non-C1 fixing, non-cytotoxic class.

e) They have enhancing properties i.e. they promote a father-strain tumor growth in a maternal-strain-recipient.[14,19]

2. Regulatory cells (mainly suppressor T cells) able to reduce the response to paternal alloantigens are also elaborated by the pregnant mother.

a) First detected in uterus draining nodes, then in the spleen.[12,22,23]

b) They are able to partially and specifically inhibit a) a relevant allograft rejection when transferred to the recipient (maternal-strain-recipient of a father-strain-tumour allograft,[14]) b) a maternal anti-paternal (or I-region-sharing)[12,24] MLR and c) the *in vitro* generation of maternal strain anti-paternal strain cytotoxic T lymphocytes (CTLs).[15]

c) The responsible regulatory (suppressor) cells which we have studies are lymphocytes Thy 1^+, Ly 2^+3^+, Ia^+, genetically restricted in the I region (mainly IC).[12,24]

d) They act through soluble factors, themselves Ia^+ and genetically restricted.[25]

e) Other types of suppressor cells found during pregnancy have been described also in other laboratories: non-specific suppressor lymphocytes,[26] non-T suppressor cells,[27] local suppressor cells, in the decidua.[27] Suppressor cells have also been described in human pregnancy[28] and in cord blood.[29]

It is worth mentioning that a physiological role of these agents (especially antibodies with protective capacities) is suggested in the BALB/c – DBA/2 strain combination, since DBA/2 newborns of less than 24 hours (physiologically and immunologically close to foetuses) are protected against a lethal GVHR triggered by spleen cells of BALB/c-pregnant of DBA/2, by the simultaneous injection of serum from the same pregnant mouse – appropriate controls being done – (Janine Voisin and Paulette Monnot, unpublished data cited in 13).

The presence of enhancing antibodies and suppressor cells active towards paternal inherited antigens, together with the absence or paucity of cytotoxic cells and antibodies against antigens of same origin in pregnant mice clearly point to an immune deviation from a predominant elaboration of immune agents of the rejection reaction (as it is usually observed in "artificial" allografts) to a predominant elaboration of immune agents of the protective and regulatory facilitation reaction.

It was therefore of interest to understand something of the mechanisms responsible for this immunodeviation. In view of the outstanding role of placenta, regulating the exchanges between mother and foetus, the hypothesis was put forward that the conceptus itself, through the placenta and depending substances, delivered a message to the immune system of the mother, which, in association with the conceptus antigens, induced the speci-

fic reaction towards these antigens to be directed predominantly towards regulatory and protective rather than cytotoxic and aggressive immune agents.

This hypothesis is tested in the following section.

C. Placental extracts injected with allogeneic cells induce an immunodeviated response mimicking the one induced by a state of gestation

Such a response consists in an alloimmune response where the formation of suppressor cells and enhancing antibodies predominates over the formation of cytotoxic T cells and cytotoxic antibodies (the latter predominates in a classical alloimmunisation with spleen cells in the absence of placental extracts).

The hypothesis is that some substance(s) in the placental extract (or supernatant) are able to modify (qualitatively, quantitatively or both) the immune response towards the alloantigens simultaneously injected. This suggestion can be formulated as follows: *addition of (strain "B") placental extract or fraction to alloantigenic (strain "A") spleen cells injected into (strain B) mice results in an immunodeviated response to "A" alloantigens.*

This suggestion can be supported by the following sets of experiments which show the alterations of the rejection reaction and analyse the elements of its deviation.

1. In B mice, alloimmunised against A and simultaneously treated with placental extracts, strain A tumour grafts are no longer rejected by strain B mice in an accelerated way (second set) but may even sometimes enjoy a lethal growth.

B mice (CBA or C57BL/Ks) are subcutaneously injected with 3 to 5 $x10^6$ A tumour cells (Sa 1, A/J) 14 days after having receiving 10^4 to 4 $x10^7$ immunising A (A/J) cells mixed with placental extracts (2 to 8 mg proteins) or fractions. The controls, with placental extracts replaced by liver extracts or medium, show an accelerated rejection (10-15 days) of the graft. Placenta-treated animals show no accelerated rejection (rejection in 15-20 days) or a delayed rejection ($>$ 20 days) or even the allografted tumours reach the stage of lethal growth.[30,31] This has mainly been observed within a narrow range of spleen cells immunising dose of $5x10^5$ to 10^6.[31] This test, expressing the results of the balance between several types of alloimmune reactions and agents has been retained as a selection test for placental extracts and fractions. The observed effects are presummably due to an immunodeviating effect akin a FR, with preferential induction of suppressor cells and enhancing antibodies over the agents of a RR. This is suggested by the following two sets of facts concerned with cellular and humoral alloreactions respectively.

2. Spleen cell from alloimmunised and placenta-treated B mice are less reactive and less cytotoxic towards A cells; they are suppressive of the reactions against the latter.

a) They are less reactive as tested in GVHR, local or systemic, in the BALB/c x DBA/2 H-2 compatible strain combination. In local GVHR ($5x10^6$ BALB/c preimmunised spleen cells injected in F_1 hybrid foot-pad, followed by the popliteal lymph node specific growth index), the reactivity is reduced to about none by the use of placental extract. In systemic GVHR ($1.3x10^7$ BALB/c preimmunised spleen cells injected intravenously to DBA/2 newborn mice followed by lethal reactivity assessment) the reducing activity of placental extracts is less intense (14% instead of 40% within a narrow range of immunising cell dose ($2 - 2.5x10^7$).[32]

b) They are significantly less cytotoxic to A (A/J) cells when mixed with them (after ^{51}Cr labelling) in a CMC assay made 20 days after *in vivo* immunisation.[33]

c) They are suppressive when added to *in vitro* reactions or to allografted recipients.

In vitro reactions are concerned with the CMC effector phase and MLR inductor phase. In CMC when spleen cells of day 20 treated B animals are added to *in vivo*-raised CTLs mixed with ^{51}Cr labelled A target cells there is a clear inhibition of the cytotoxicity.[33] In MLR, when spleen cells of B treated animals are added to a conventional B anti-A MLR, there is a significant decrease of the stimulation index.[30]

In more recent studies, the MLR inhibitory capacity was found not to be higher (and even usually lower) in placental extract-treated alloimmunised animals than in simply alloimmunised ones.[31]

However, the *in vivo* experiments made with the same cells show that the only *in vivo* biologically significant suppression is brought about by the experimental, placenta-treated group. Indeed B mice grafted with A sarcoma (Sa 1) supported a sarcoma enhanced growth (or a mere first set type of rejection) when and only when they received the spleen cells from placenta-treated alloimmunised B animals. In the absence of placenta treatment the animals gave rise to cells able to transfer not an enhancement of Sa 1 growth but an accelerated rejection of the allografted tumour.[31]

Therefore placental extracts injected with alloantigens favour the induction of suppressor cells against these alloantigens.

3. Anti-A alloimmune sera from placenta-treated alloimmunised B mice are not modified for their haemagglutinating activity; they are less (or not) cytotoxic and more (or at least as much) anaphylactic *(in vitro)* and enhancing *(in vivo)*.[31]

a) Treating the CBA alloimmunised (anti-A/J) mice with placental extracts did not modify the titres of serum agglutinating antibodies tested on days 5, 10 and 15 after immunisation. This indicates that the overall anti-class I MHC antigens reactivity is not impaired (and therefore that the

Table 2 Relations between alloimmune agents elaborated during pregnancy: those induced by alloimmunisation in the presence or absence of placental extracts and those induced by classical procedures of enhancement or "positive" tolerance

Agents specific for the antigen-bearing target	Observed in pregnancy (murine)	Induced by allotransplantation or cell alloimmunisation	Similarly induced but in the presence of placental extracts	Induced by classical procedures of enhancement
Cytotoxic T cells	∿ absent	present ++	strongly ↘	↘
Cytotoxic antibodies	∿ absent	present ++	strongly ↘	↘
Suppressor T cells	present ++	present	strongly ↗	↗
Anaphylactic antibodies	present ++	present	↗ (some preparations)	↗

placental extracts had not destroyed the A/J spleen cell antigens).

b) In contradistinction, the complement-dependent cytotoxic activity of the same sera was reduced and/or delayed in appearance. It was even reduced to none with some glycoprotein fractions.

c) As for the *in vitro* anaphylactic activity, it was tested by the direct allogeneic anaphylactic degranulation described in this laboratory[34] and due to a "bipolar bridging activation".[35] Anti-A/J (class I) anaphylactic alloantibodies were found increased under the influence of some placental preparations and fractions.

As a whole, the cellular and humoral behavior of animals alloimmunised in the presence of placental extracts or fractions mimicks the one of pregnant mice on the one hand. On the other hand, it is similar to the immunodeviation characteristic of the regulatory FR (Table 2).

4. Origin and nature of responsible placental substances.

This can be considered from three points of view: histocytological, subcellular and biochemical.

a) Histological origin.[36] Placentas and their surrounding have been dissected and fractionated into labyrinth, spongiotrophoblast and maternal decidua. Preliminary results (obtained with 1 mg protein preparations) suggest that, while the spongiotrophoblast shows activity which is not very different from the one described for total placental extracts, the labyrinth appears devoid of activity and decidual fractions are clearly active (Sa 1 allograft growth inhibition of cytotoxic and increase of anaphylactic antibody production).

B) Subcellular fraction.[37] After elimination of the cytosol and washings, the deoxycholate solubilised placental pellet exhibited the same immunomodulatory properties as just above described.

c) Biochemical nature.[37] Although it is too early to draw any firm conclusion, a few number of points may be made: there exists several glycoproteins (Con A bound) Sephacryl S-200 fractions of various molecular weights (from 8 to over 400 KD) endowed with different immunomodulatory properties. The small molecular weight ones appear to possess most of the properties. Increase in anaphylactic alloantibody production seems not to exist in Con A unbound fraction. One single fraction (possibly linked to a 105 KD band) showed a significant *increase* in C-dependent-cytotoxicity antibody production. This is to be compared to some results mentioned below.

5. Immunomodulatory action of placental extracts on other antigens.

MHC antigens were especially studied because of their outstanding importance in self-recognition, cell-communications and possibly differentiation, and because of the extensive experimental possibilities that they offer, having been so much worked out on immunological and genetic basis. They have allowed us to analyse immunophysiological mechanisms which we believe to hold true for other antigens: minor histocompatibility loci antigens (as shown in the BALB/c-DBA/2 combination, possibly placental antigens (such a Faulk's TA antigens) and differentiation antigens. On the other hand, although alloantigens active in allotransplantation have been used in these "placental-extract-driven" experiments in order to mimick the alloantigenic situation of gestation, we have also shown[23,36,38] that the placental extracts are able to modify the immune response to heterospecific antigens such as red blood cells (RBC) and to induce regulatory cells specific of the immunising antigen: i.e. sheep RBC versus pigeon RBC and *vice versa.*

The dose effect curve on IgM PFCs together with fractionation on Sephadex G-200 as well as Sephacryl S-200 led to the conclusion that there were 2 fractions: one (∿ 40 KD) decreasing the production of PFC number and one (∿ 60 KD) increasing it.

In addition to this modulatory action on the systemic immune reactions,

D. The placenta plays an essential local role in preventing an efficient RR to take place against the conceptus.

This action is exerted both at the induction and effector levels and is due to both immunologically speci-

Table 3 Local intervention of placenta on maternal immune reactions to the foetus. (immunologically specific)

Main fact. Maternal alloantibodies specific of paternal antigens are absorbed on the placenta (murine).

Consequences:

1. They do not pass into the foetus.
2. They mask alloantigens to alloreactive lymphocytes (at both afferent and effector levels).
3. They form immune complexes that are presumed to:
   a) deliver signals to specific lymphocytes through bipolar bridging
   b) inactivate effector cells
   c) activate suppressor cells

Table 4 Local interventions of placenta decreasing detrimental immune reactions to the conceptus. (non immunologically specific).

I – *Anatomical barriers.*
Separated circulation, fibrin layer, sialomucin coating, trophoblast tight junctions.

II – *Decreased expression of MHC antigens at the interface.*
Class II absent. Class I absent at implantation.

III – *Non-specific local immunosuppression.*
Placenta proteins, glycoproteins and/or hormones able to non specifically inhibit MLR and CML (eg progesterone, steroids).

IV – *? Role in the induction of local (decidual) suppressor cells.*

Table 5 Target-structures and type of predominant reaction.

Antigen-bearing target-structure and survival value	Predominant elements of the immune reaction	
	in normal physiological situation	in pathological or experimental situations
I-Dangerous (Bacteria, viruses, fungi, parasites, allografted and tumour cells.)	Rejection	Facilitation
II-Necessary (Paternal alloantigen bearing foetus, autoantigen-bearing organs.)	Facilitation	Rejection

fic and non-specific mechanisms as summarised in Table 3 and 4.

Conclusion

The preceding data (as well as many other ones) can be integrated in a general simplified scheme where the antigen-bearing target is not simply a superimposed troublemaker but the "raison d'etre" of this highly sophisticated system, the intimate mechanisms of which are exquisitely analysed by immunologists, but the general meaning of which is its surivival value through its action on the antigen-bearing target eliminating it if it threatens the survival of the species or protecting it if it is necessary to that surivival.

This is what happens in normal physiological conditions while the opposite may be observed in pathological situations or experimentally created through a functional unbalance of the immune system (Table 5).

Summary

It is argued that the essential evolutionary pressure leading to the selection of the immune agents of the immune reaction is the fate of the antigen-bearing targets: the dangerous ones, that threaten the survival, must be eliminate (hence the immune agents of the rejection reaction), while the ones useful or necessary to the survival must be protected against such a RR (hence the regulatory agents of the facilitation reaction, the action of which go from a simple regulation to an operationally complete tolerance).

Examples are given, through the animal kingdom of the retention of more and more sophisticated immune agents of these two aspects of the IR.

Attempts of gestation and mammalian gestation, as well as artifical allotransplantations, are taken as models of different states of balance between RR and FR. The case of mouse gestation is detailed showing evidence of a low RR and

a higher FR. Such a state of immune deviation (as compared to artifical allografts with a highly predominant RR) can be artificially reproduced by utilising placental extracts or fractions mixed with alloantigenic cells. The local roles of placenta in inhibiting the RR at the induction as well as at the effector level is also recognised.

Finally, a general scheme is drawn accounting for immunophysiological as well as immunopathological situations in the frame of such a balance (or unbalance) between RR and FR facing a threatening or a necessary antigen-bearing target.

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