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A unified (but in fact not fully testable) model of preeclampsia triggering

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ABSTRACT

In this summary of my presentation in the last Reunion workshop I discuss a few assertions on preeclampsia, then turn on a (not fully testable) model where an embryonic defect in expression of embryo/ placental regulatory proteins results in complement activation, itself responsible for a down regulation of the T regs activity, resulting in a very early lack of complete down regulation of the preimplantation decidual inflammation, causing in the post implantation stage a low grade but chronic inflammatory state.

First, I thank the organisers for i nviting me once again, despite the fact that ocular problems linked to age prevent me from doing a large number of bench work experiments. Thus, I will limit my presentation to "theoretical" considerations.

It is likely my last paper, and somehow a bit testimonial, hence it deals with and questions which may seem far apart, but are not in my opinion. It recapitulates my slide presentation.

First, I would like to challenge a dogma. Myth N° 1 :" Preeclampsia is the result of the need for a big brain which needs a peculiar vascularisation, this brain itself resulting from the apparition of Bipedism which was necessary to make tools a manufacturing capacity linked to co-apparition of hand AND a big brain, at least bigger than in apes (Chaline, 2003)."

In this year of the 50th anniversary of Kubrick's 2001 movie one would like ironically to recall that in the movie tools appeared after bipedism, after intervention of an out of this planet intelligence, and that the almost totipotent "star child".... has no placenta (this has nothing to do with what we know of our real ancestors....except if ....).

More seriously, the "big brain"theory, and some of its consequences for Pre Eclampsia (see Jean Chaline indeed) is in fact also very much linked to Yves Coppens's "East side story" (Coppens, 2003), that I will not summarize here. Even if Jean Chaline was opposed to the East Side story as such, his reflections on the big brain bear, however, in my mind the influence of this theory.

But we now know, first, that Neanderthal had an advanced culture, and in fact one of the theory is that he disappeared by dilution inside homo sapiens as a result of interracial copulations, since, indeed, we all harbour Neanderthal genes. So much for PE leading to its extinction....

Second, Ororin and Tumai have broken the East side story (the "East side story no longer exists" – Coppens himself (interview in La Recherche, 2003), a change of paradigm which,let us be honest, occurred AFTER our Mauritius meeting. Moreover, stone tools (Olduvai Chopper) –sorry for Stanley Kubrick and Arthur C Clarke- were present (Olduvai choppers)..... 1.8 million years ago and even older ones are the Lomekwi 3, West Turkana artefacts.....3.3 million years old, which were certainly NOT linked to a "big brain", at least if we mean restricted to some big apes, hominids by that time having a much smaller brain size than homo sapiens sapiens or Neanderthalensis.

Furthermore, whales, and especially orca, have a big brain and the placenta is .... Epitheliochorial (Carter and Enders, 2004).

And as far as the need for high blood pressure is concerned, their very body size and size of the arteries are compatible with surprinsingly low blood pressure (13 Kpa) vs. human (16- 11 kpa).

Conversely, the 250–300 mm hg highest aortic pressure is linked to a small brain - giraffe (33 kpa, – as high as 53 kpa −400 mm hg - in the feet, but 75 mm Hg in the brain when rised, albeit a giraffe eating herb has a very high blood pressure in the brain without fainting), a fact which testifies by itself that high blood pressures can be implemented, when (height of the neck compelling) they are needed to irrigate the brain, a pressure indeed present at the giraffe utero placental inteface, without requiring uterine trophoblast invasion (Mitchell et al., 2008).

Moreover, In fact animal models of preeclampsia are in rodents with a poorly invasive and not as in higher primates an extensively invasive placenta... though hemochorial, be the models in rats or mice, and be them "natural" (the CBA x DBA/2 system-see Ahmed et al, 2001- for review) or artificially induced.

Now, what is the cause of preeclampsia?

When saying that inflammation or "excess inflammation" is at the root of preeclampsia, one must first recall that post coïtum, pre and peri implantation inflammation is required for successful implantation. This was (after the emphasis put on the POST implantation Th1/Th2 paradigm a relative surprise in the 1992–1994 period, and the Fondation Mérieux devoted a full colloque in Annecy to that topic in the deeply regretted absence of Tom Wegmann who died just a few days before the

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meeting he should have attended. A critical POSITIVE role for TNF, for example, was noted (Kachkache et al., 1991; Mac Master et al., 1992; Noun et al., 1989; Sanford et al., 1992).

Even more important is the role ascribed to a typical inflammatory molecule, Leukemia Inhibitory Factor (LIF) in mice as well as in human (where LIF mutations cause infertility) as exemplified by Nature's Editorial "Could there be life without LIF?" (Nature Editorial (News and view), 1992; Stewart et al., 1992;Charnock et al., 1994; Giess et al., 1999).

What is important for preeclampsia is the switch in the almost immediate post implantation period from a Th1 dominated environment to what Tom Wegmann called a "Th2 phenomenon" (Wegmann et al., 1993). Failure of such a switch to occur, or presence of a pre coïtum excessive inflammation hampers implantation - see "immuno dystrophism (Hill et al., 1995), but also certain aspects of endometriosis-. Correction of such abnormal parameters is possible in a non negligible number of women, and leads to enhancement of IVF-ET success rate.

It was also surprisingly in that period demonstrated in that period that at opposite to what initially forecasted T cells were NOT the effectors.

Rather, in a natural murine immune abortion model which was also demonstrated by Girardi to be a model for preeclampsia the effectors were (activated) NK cells (Chaouat, 1986; Gendron and Baines, 1988; Baines and Gendron, 1993, 1998). It was demonstrated that activation of peripheral NK cells induced abortions in any strain of mice (Kinsky et al., 1990). Incidentally, this was chosen by therapists as the pathway to down regulate in case of RSA in human (after focusing on the alloantibody response (Beer et al, 1985) even though pregnancy is normal in aggamma globulinic women (see as one of the first case reports Funakoshi et al., 1986) or B cell depleted mice (Mattsson et al., 1985) a fact also recently "ignored" by a German group….).

BUT….concerning uterine NK cells (uNK), there is a consensus that they are normally not cytotoxic. The revolutionary experiments of Anne Croy's group (Guimond et al., 1997, 1998), followed by these of the group of Ofer Mandelböm (see this issue), have led to the concept that they play a key role in angiogenesis, peculiarly being involved in the transformation of uterine arteries into spiral ones. In short, "Killer become builder during pregnancy". As stated by Le Bouteiller and Mandelbom groups.

But I stated elsewhere, (peaceful) cohabitation, sometimes in close and even intimate contact, can be observed without any problem in a variety of placental species without any conflicts, from bryozoa to placental reptiles…. The problem(s) seem to arise almost oly in eutherians mammals. Let us therefore detail the local cohabitation of placenta and "lymphocytes" (the "" are meant because of the age of primitive sharks not to mention bryozoa –see below-).

As stated above, systemic (peripheral) NK cells are normally not a threat for pregnancy, except if cytotoxically activated by (high doses of) interleukin 2, for example, or viral products, and experimentally by viral products, or dsRNA equivalents, such as Poly I Poly C or the less toxic Poly I Poly C12U, leading eventually to 100% resorbtions. Indeed, murine models of spontaneous abortions can be treated by NK cell depletion by anti Asialo GM1 (Baines and de Fougerolles, 1988).

However, in the human, despite claims (expensive) about "treatments" aiming at "dampening NK cells activity" after (costly charged) analysis of peripheral blood activity, there appears to be no correlation between circulating NK cytotoxic potential and RSA, and the Cochrane have concluded that the "treatments" were in fact not effective (Scott, 2000, 2003) and an important placebo effect, linked to the important role of neuro immune interactions in pregnancy, likely accounts for a large part of the success of the initial open studies as well as the still ongoing ones as discussed elsewhere (Chaouat, 2003, 2008).

The situation is different if one regards preeclampsia and uterine NK cells. First, there are reports such as the one of Vinnars et al that inflammation can be linked locally and systematically together with enhanced NK cytotoxicity to preeclampsia, and in this report NKG2D status (Vinnars et al., 2018).

Second, albeit, as stated above, decidual NK cells have a low cytotoxic potential, reports by the group of Le Bouteiller show that strikingly, and in contrast with PB-NK cells, engagement of NKp46- but not NKp30- activating receptor on freshly isolated dNK cells triggers cytotoxicity (El Costa et al., 2008, 2009).Engagement means antigen encounters, and this is happening mostly if not solely at the interface till trophoblast deportation begins.

Besides, and alternatively, lack of proper interaction between receptors on the "builders" and the polymorphic placental, decidua invading cytotrophoblasts could lead to a deficience in their angiogenic capacity (both in cases of RSA and preeclampsia) (Hiby et al., 2004).

The generalisation of this theory encounters two objections. One, the incidence of pre- eclampsia among couples consisting of Japanese women and Caucasian men does not fit with the prediction (Saito et al., 2006). Second, why should this happen only in the first pregnancy with a given father (the primipaternity concept, amply discussed here since the Lancet paper at origin of these workshops (Robillard et al., 1994)?

I believe, as stated in the introduction, that this is due to persistence at a low level inflammation - (too) high would lead to implantation failure or early pregnancy loss, as early demonstrated by Anderson and Hill (Anderson and Hill, 1992)-. This inflammation, results in a chronic, but low level engagement of dNK cells in a trophoblast attacking/damaging configuration.

But why does it happen? because the adaptive immune system is not enough "controlled /suppressed/regulated" or whatever you would invoke to promote completely a Th1 (pre and peri implantation) switch to a Th2 predominant state. Why? How?

Detour….

Back as announced to evolution…There are « two immune systems the innate and the adaptive. Both have graft rejecting capacities but the early innate one is rather slow in that respect … and from the start does NOT impedes placentation. In that respect, notwithstanding the consideration he deserves for his Nobel prize winning tolerance work-(which was deeply, incidentally, due also to the involvement of RE Billingham, as pointed out righly by Ono (Ono, 1951) - Medawar (Medawar, 1953) was wrong not to look at non eutherian mammals,and indeed before the mammals, such as in placenta harbouring sharks not to mention (Haines et al., 2006), of course, the first placentae such as in bryozoa (Collin H Johnson).

Interestingly, there is in many VERY early placentae as later on in sharks close association locally, in some case in a lining at the interface, of "lymphocytes" progenitors and the placenta, as investigated in depth in the sharks (interestingly enough, some early placental species are hermaphrodites, the placenta display such interactions, and in several early hermaphrodites species where auto fecundation happens SYN placentae are rejected or non accepted BUT (ONLY) ALLO placentae DO THRIVE…(Johnson, 2010).

Later on, albeit we do not know anything of course about histology of placental dinosaurs (there were….) placenta bearing reptiles do not seem to suffer much from immune abortion even if a critical role has been postulated for IL-1 (see the works of Liliana Paulesu for example).

And then we come to mammals…….

But the first mammals were …. mammals….(milk glands... not placenta …) ….? Those were laying eggs (non eutherians). Today remain two monotremes, ornythorinques being the most quoted.

When it came to placenta bearing ones, even in Jurassic, (Zhe-Xi et al., 2011), the adaptive immune system had gained in complexity, and acquired the capacity to HYPER activate the innate immune system in case of, for example, allograft conflict….

Another necessary disquisition: the existence of non rejection of the "foetal allograft" is one of the arguments which lead Polly Matzinger to propose the danger model, which was discussed in several of these workshops (Matzinger, 1994).

As fascinating as it is (and it did predict for example "danger receptors" – the Toll ones being akin to that ….-) it does not fit with

pregnancy : the theory cannot explain –and I asked that question three times in three different meetings- why a CBA mother would see a CBA xDBA/2 embryo as “danger” but not a CBA x BALB/c one. Nor why the equine endometrial cup showing areas of lymphocyte invasion, with in some cases, especially for inter-specific pregnancies such as mule and hinny progeny, areas of necrosis, haemorrhage, is not seen as a “danger”. Nor of course why creating a “danger” response (alloimmunisation in the CBA x DBA/2 model, and of course with the precision of its genetic determination in mice, (Chaouat et al., 1985; Bobé and Kiger, 1989) corrects immune abortion in mice, nor, even more striking than the effects of alloimmunisation in mice the “xeno immunisation” in the donkey embryo in horse system (Chaouat et al., 1983; Allen et al., 1986). And even more, preclampsia and the genetics implied by the primipaternity model and the disparition of the risk in a second pregnancy with the same father ……

The “speed of change” theory (Pradeu et al., 2013) offers a better approach, but it is not the topic of this paper to discuss it….

Two solutions were found when placentation reappeared: one, a very short period inside the uterus followed by an intra pouch mammotrophy: this was chosen by the marsupials, when a kind of delivery occurs almost exactly (and it is not an hazard) when paternal MHC class I polymorphic antigens appear expressed on trophoblasts. An almost larva gets out, gropes the mother fur and skin and climbs to take refuge in the marsupial pouch.

The eutherians have chosen to tame locally the adaptive T cell response - and then systemically, since multiparity induces H-Y specific tolerance or specific hypo-responsiveness to paternal MHC antigens in rodents and human- (see for H-Y the pioneer reports of Smith and Powell (Smith and Powell, 1977) and of Simpson and Chandler (Simpson et al., 1981). They do this by mobilising locally Tregs (Ts at that time…) which I myself extended to alloantigenic paternal strain antigen tumour challenge (Chaouat et al., 1977). But after the opprobre thrown on suppressor T cells by the ignominious end of the I-J story, one had to wait Sakaguchi and as would say (and said) Hermann Waldmann resurrection of Ts in T regs….

The experiments of the Betz’s group (Aluvihare et al., 2004; Kallikourdis and Betz, 2007; Kallikourdis et al., 2007) are pioneer in that respect for pregnancy, and it came to the Samstein group to demonstrate that in eutherian an otherwise non coding sequence has been used to build an eutherian specific, of expression restricted to the placenta, CNS- 1, which governs paternal antigen specific pTreg accumulation in the placenta ….(Samstein et al., 2012).

A deficiency in Treg accumulation/ function has been noted in cases of recurrent abortion or implantation failure in mice and human, be it quantitative or qualitative. (see for examples Jasper et al., 2006; Arruvito et al., 2007)

This deficiency has been noted also in the CBA x DBA/2 murine mating combination which is not only a model of model of natural immune mediated abortion but also since the pioneer work of Guillermina Girardi a model of pre eclampsia (see for review Ahmed et al., 2010). In such a model, transfer of properly triggered alloimmune Tregs, of their activation by low doses of IL-2 prevents an high resorbtion rate as well as the 1st pregnancy preeclamptic symptoms (Zenclussen et al., 2005; Darrasse-Jeze et al., 2006; Chen et al., 2013; Ruocco et al., 2014).

But the very same work by Girardi and colleagues has nicely demonstrated that early neutralisation of complement prevents the abortion and preeclamptic symptoms in the CBA x DBA/2 mating compbination. This is completed by studies showing a crucial role for MBL-2 in such pathologic complement activation (Chaouat et al., 2009; Oger et al., 2009; Petitbarat et al., 2015)

It is noteworthy that this action is efficient (as is transfer of properly activated Tregs) only if performed very early in pregnancy. This supports the hypothesis that preeclampsia starts very early by a deficiency of the regulation of the transition from a Th1 predominant state to a Th2 phenomenon. This has lead to reconsider the initially thought kinetics of both RSA and PE, based on the curative effects of tailored anti Th1 treatments, at least in the murine models (albeit the anti TNF treatment proposed by Winger and Reed and colleagues (Winger et al., 2012) also enters in the category of early actions, as are also the pre-implantation treatments proposed in case of IVF by Ledée’s group (Lédée et al., 2016).

It remains to understand why are T regs down regulated in Pre eclamptic women.

Here, we must recall that complement activation happens if NOT regulated at the materno foetal interface by complement regulatory proteins expressed by the early embryo and placenta. These are ccry in mice, MCP and DAF in human.

Quantitative deregulation of such materials leads to complement activation and 100% abortion in mice (Xu et al., 2000; Holmes et al., 1990; Lokki and Laitinen, 2001).

In this context, it is important to recall that “signalling through C5a receptor and C3a receptor diminishes function of murine natural regulatory T cells” (C3aR/C5aR signaling regulating Foxp3 expression) or that “Receptors for C3a and C5a modulate stability of alloantigen-reactive induced regulatory T cells”, C3aR/C5aR-induced Foxp3 down-regulation resulting in diminished suppressive capacity This, initially demonstrated in mice, is also true in human. (Wing-hong Kwan et al., 2013; Kwan et al., 2013);

Even more relevant is the demonstration of the role of complement regulatory factors in the spontaneous abortion model of CBA/J × DBA/2 mice (Takeshita et al., 2014). Compared to control mice, the CBA/J × DBA/2 model mice had higher expression levels of adipsin in the placenta and serum, and, most important, Crry was consistently expressed in the placenta and serum BUT reduced in the resorption sites of CBA/J × DBA/2 mice as compared to normal sites.

Incidentally, this deficiency as a cause of preeclampsia and immune abortion in the CBA x DBA/2 murine mating combination at last solves a question asked by Pr Peter Johnson in the 1992 Serono meeting in Florence : “What is special in the CBA x DBA/2 mating? “. Such a uniqueness of the triggering event explains why the anti IL-10 treatment –or later on IL-10 KO – enhances resorbtion rates in this mating combination, whereas r IL-10 prevents them, whereas no such effects can be observed in other mating combinations –see complete Fg 4 in.(Chaouat et al., 1995) -.This differential effect is too often neglected.

This absence of abortive effect of IL-10 KO in non abortion prone mating was indeed noted by Sarah Robertson’ group (White et al., 2004).

This fact strongly suggests that Th1/Th2 cytokines can correct or enhance resorbtion rates or more subtly affect pregnancy, but reinforces the concept that normally their deregulation is not the triggering event in immune abortion pregnancy.

The link to microbiote, suspected for Pe and testefd partly in the CBA x DBA/2 model (Clark et al., 2008) can be established via MBL2 and communication of gut flora induced phenomena with the uterus, part of regulation in the gut being very close to pregnancy and the gut and utero vaginal immune systems being linked. This explains the old environmental effects first noted by Hamilton and Hamilton (Hamilton and Hamilton, 1987)….in the CBA x DBA/2 system.

Thus I would predict as an initial triggering agent that THOSE embryos of PE women are qualitatively of quantitatively deficient in expression of complement regulatory proteins.

In the second pregnancy with the SAME father, Treg activity is boosted anyhow after delivery as well as memory Tregs being present (this phenomenon is at the root of multiparity induced paternal antigen specific T cell tolerance as seen in mice-see above- and human (see for example Engleman et al., 1978a, 1978b)

To summarise the unified model.;

a) Preeclampsia is triggered by an EMBRYO DEPENDENT LACK OF EXPRESSION OF EMBRYONIC COMPLEMENT REGULATORY PROTEINS and thus complement activation

b) THEN Complement activation down regulates Tregs, which are "weak" any how in the First pregnancy (Pregnancy induced H-Y or alloantigen systemic tolerance requires multiparity)

This results in a early post implantation chronic inflammation

- DELIVERY UP REGULATES in PE as well as in normal pregnancy ALLO SPECIFIC (Here I differs from David Klatzman) MEMORY Ts, T regs, and NK memory cells, explaining the lack of 2nd pregnancies same paternity pathologies, but not when there is a de novo alloantigen challenge (we lack studies concerning what happens if there is enough cross reactivity with the second father.
- Theoretically, one could test the model by pre IVF-ET screening in a prospective study …. Ethical constraints renders such a study utopic, at least in France, and I am not fool enough to propose it to the Comité National d'éthique….
- Theoretically also, quantitative si RNA (half, or rather 30%, chosen arbitrarily : complete Down Regulation would of course induce 100/% abortion) down regulation of CCRY in IVF generated B or C embryos transferred to an A mother should induce preeclampsia like syndrome (high blood pressure, albuminuria) in ANY STRAIN of mice in a first A x B pregnancy and in a second pregnancy where A is sired by C but not in a 2nd A x C pregnancy. Preliminary experiments using C3H mothers and BAL/C or C57BL/6 father suggest it might be the case, but I will likely not be able to complete the protocol for personal medical reasons. The suggestion is thus made here…

Finally, this opens the possibility of Treg therapy for PE….as discussed nicely in a recent review…(Robertson et al., 2019, in press) (and previously; Ruocco et al., 2014).

Conflicts of interest

None.

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