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Inflammation, NK cells and implantation: friend and foe (the good, the bad and the ugly?): replacing placental viviparity in an evolutionary perspective

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ABSTRACT

This review summarises an invited talk presented at the 2012 ESRI/ASRI meeting in Hamburg, concerning current views of inflammation in pregnancy, which is timely given that the effects of a local injury in the uterus acts to favour implantation. Recalling that inflammation can be good (it is useful and necessary for implantation), bad (in implantation failure, RSA) and ugly (at the extreme, endometriosis is associated with pain and infertility) leads to consideration of its status in pregnancy. Its role in implantation and the fact that pregnancy maintains some aspects of inflammation throughout, leads to revision of not only concepts of immunosuppression and the Th1/Th2 paradigm, but also the feto-maternal relationship as seen since Medawar's hypotheses were advanced. This is examined from an evolutionary perspective, which should lead to further review of our perception of uterine NK cells, and the emergence of Treg cells to control some aspects of adaptive immunity, which appeared long after placentation.

1. Introduction

This review summarises a talk that I was asked to deliver at the 2012 Hamburg ESRI/ASRI meeting by ESRI President Maciej Kurpisz at the meeting's presidential symposium session. This was likely because I may appear to be a defender of the Th1/Th2 paradigm (Wegmann et al., 1993) in whose conceptual elaboration (by discussions with Wegmann) and demonstration I participated at the time. It was the last paper we wrote together in Goa shortly before his death, "IL-10 in pregnancy" in *Journal of Immunology* (Chaouat et al., 1995). But one should recall that I later briefly (Chaouat et al., 2002) and subsequently in more detail (Chaouat et al., 2004a,b) wrote that the Th1/Th2 paradigm had become an oversimplification, in part because of new understanding of implantation, but not only for that reason.

This revision of concepts has since been reinforced by the involvement of the Th17 pathways and the increasingly important role of inflammation throughout pregnancy. In any case, Maciej sought to have my views in parallel to the talk by Neva Dekel. Her group's belief is that a light injury to the endometrium promotes successful implantation in humans (Gnainsky et al., 2010). This paper is the result of his request.

As such, it is not a data paper, a review, or an opinion paper. It is a mixture of all three and came at a time when I was interrogating myself on reproductive immunology from an evolutionary perspective. The apparently heretic finding that a local injury promotes implantation has been largely confirmed by several teams, although some are reluctant to introduce it into routine practice, for reasons outside the scope of this communication. What seems to make such a finding heretic is, of course, the link that is made to exacerbation or induction of local

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inflammation, as to cut a long story short, the authors come to the conclusion that inflammation is useful for implantation and pregnancy. Since the classical vision of the Th1/Th2 paradigm is that inflammation promotes the "bad guys", while "allogeneic pregnancy is a Th2 phenomenon", the classical visions seem to be shattered.

2. The good (and some evolutionary aspects)

In fact, the view that inflammation is important for implantation is far from entirely new. Interest in local cytokine production was contemporary and partly (but not entirely) an emerging consequence of the role of cytokines as growth factors for the placenta (immunotrophism). The impact of immunotrophism and of Jeff Pollard's group's discoveries on CSF-1 in the uterus at that time was to focus the interest on intrauterine cytokines in the 1980s.

That a new branch of the field was emerging became evident at such meetings as Varna, the ISIR in Toronto, Kiel and Rome, the IUIS in Toronto, Berlin and Budapest, and finally the World Congress on Human Reproduction in Helsinki, and the European Placenta Group in Dourdan (1989), plus of course the Banff meetings, especially the second one in 1990.

Since then, uterine cytokine study has led to a series of important papers in the late 1980s and early 1990s, including the mandatory role of leucocyte inhibitory factor (LIF) in rodents (Stewart et al., 1992), the first reports by Carlos Simon, which would lead to his endocrinology paper (Simon et al., 1994), and the results from Loke's group, which would lead to the famous "blue book" (Loke and King, 1995). René Frydman and myself organised a meeting devoted to the by then established status of immunology of embryo implantation, with the help of the late Marcel Mérieux, in the wonderful setting of Les Pensières, near Annecy (Colloque Université Paris Sud/Inserm Fondation Mérieux, May 1994) where for example, as far as I remember, the recently published findings from Jeff Pollard's group on colony stimulating factors, especially CSF-1, stemming from papers such as Arceci et al. (1989), G.K. Andrews' group (MacMaster et al., 1992), Gary Wood's group (Sanford et al., 1992) and Michèle Garabedian's group (Kachkache et al., 1991) were presented (the latter in close cooperation with our own).

Very clearly, almost all of the communications pointed out that there were both pre-implantation cellular movements and expression of inflammatory cytokines in the pre-implantation uterus. We were there with Tom Wegmann and Jacques Martal preparing some of the final experiments that would lead to publication of our joint IL-10/oTP[1] data in the aforementioned *Journal of Immunology* paper (Zourbas et al., 2001), one that is often seen to be one of the key publications on the Th1/Th2 paradigm in mice.[2] But Wegmann, as James Mowbray and Jennifer Underwood who were also present in Annecy can testify, was very interested in this type of data and had no problem admitting that the Th1/Th2 paradigm had to be restricted to established pregnancy. A few years afterwards, data from Sandrine Zourbas would lead to re-evaluation, even for that period (Zourbas et al., 2001; Chaouat et al., 2002, 2004a,b).

2.1. Inflammation poses problems for the "danger model" of the immune system

The data obtained by reproductive immunologists as well as by placental and uterine development specialists since this meeting in my mind pose problems for the "danger theory" (Matzinger, 1994), which is an irony since the danger model arose itself partly as a consequence of the discussions that Polly Matzinger had on pregnancy and immunity with Prof. Robert Schwab at the time, as do effectively the current results of the effects of local injury on implantation rates in humans.

Incidentally, local injury or local injection of oil was a very well-known technique for creating a deciduoma in mice – see for example studies in mast cell-deficient mice (we will come back to them) (Wordinger et al., 1986). Indeed, this technique was used by some labs as an alternative to mating with vasectomised mice as one of the components for obtaining pseudo-pregnancy in mice after hormonal treatments prior to murine embryo transfer in the old days. Thus, the danger theory predicts that the Medawar paradigm (Medawar, 1953) is fundamentally wrong, for there is no immunological problem with pregnancy (Matzinger, 1994), since "Reproduction cannot be a danger, it does not make evolutionary sense" (interview with Polly Matzinger explaining how consideration of the immunology of pregnancy led her to propose a new vision of the immune system, and thus quit her job as Playboy Bunny bartender to become a world famous immunologist). On that point, she is right (see below). Once the relation between the immune system and reproduction is placed in that context, there is (tautologically) no threat of rejection of the embryo, since there is no danger. The absence of threat to the embryo is embedded in the definition of the danger (at least, if one has a restricted view of mammalian pregnancy).

For if the real function of the immune system is "tolerance and the 4 Ds" (danger, death, destruction and distress), how can a deliberate local injury (destruction, local distress, local death) improve grafting rather than promoting rejection? What about a quasi-inflammatory response at implantation (see above and below), and indeed later on throughout pregnancy (as first demonstrated by a very nice paper from Oxford) (Sacks et al., 2003), which I described at the time as "innately moving away from the Th1/Th2 paradigm" (Chaouat, 2003)?

Moreover, although the term "danger" is often used in papers I co-authored with David Clark, in an extended sense dealing with the CBA × DBA/2, CBA × BALB/c

[1] OTP: ovine trophoblast protein. Discovered by Martal et al. (1998) as "trophoblastin", the material maintaining corpus luteum in ovine species, thus re-named trophoblastin. Sequencing has revealed that it was a bona fide interferon, highly conserved between species, and defining a new class of interferons, interferon τ (tau). See the article on placental interferons in this journal.

[2] Except that the anti IL-10 has *no* effect on non-abortion-prone murine matings, a finding that is too often omitted.