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News & EFIS

Medawar and the immunological paradox of pregnancy: 60 years on

The Meeting "Medawar and the immunological paradox of pregnancy: 60 years on" was held under the auspices of the Cambridge Centre for Trophoblast Research (CTR) on November 28th-29th 2013 at the University of Cambridge, UK (Fig. 1). The aim of this meeting was to revisit the seminal paper written by Peter Medawar in 1953, which first introduced the concept of the immunological consequences of mammalian pregnancy. The CTR was set up to promote scientific study of the placenta and maternal-fetal interactions during pregnancy.

The invited panel of experts was tasked with the following questions:

1. What is the role of T and NK cells in pregnancy?
2. What is the evidence that maternal T cells and/or NK cells affect the survival of the fetus?
3. Are T-cell and NK-cell responses in pregnancy directed to fetal cells or trophoblast?
4. What effector mechanisms do T cells and NK cells use at the maternal-fetal interface?
5. Has the immune system adapted to different types of placentation in different species?
6. Do uterine NK cells affect the generation of adaptive immune responses at the maternal/fetal interface?
7. Why has NK allo-recognition evolved?
8. What is the contribution and what are the limitations of mouse models to understanding the immune response to trophoblast/fetal antigens?
9. Do pregnancy disorders ever arise in humans as a result of aberrant maternal immune responses?

To put the meeting in perspective, **Bill Seaman** contextualized Medawar's 1953 paper within the history of immunological discoveries. Today we know much more factors and cells at work in the immune system. Examples presented were the growing family of innate lymphoid cells or powerful technology such as mass cytometry.

Leslie Brent, who worked with Peter Medawar, reminded the audience in his historical overview that Peter Medawar became interested in transplant rejection when he saw the results of autologous or allogeneic human skin grafts during the second world war. Medawar went on to contemplate responses to antigens in chimerism, which led to current concepts of immunological tolerance. It is difficult to imagine discussing this complex topic in 1953, before components of the immune system that we take for granted, such as MHC molecules and antibody structure, were fully characterized. Indeed, the thymus was only discovered in the '60s and antibodies were thought to mediate rejection at the time of Medawar's discovery. Medawar died in 1987: What would he have made of our present understanding of maternal-fetal tolerance, 60 years after his famous discussion on the evolution of viviparity in vertebrates? He would have greeted with mixed feelings the finding that the proposed mechanisms underlying placental tolerance, namely: Anatomical separation of mother and fetus; the antigenic immaturity of the fetus; and the immunological unresponsiveness of the mother, have not been fully substantiated. These topics remain controversial and are poorly understood to this day. Brent's personal recollections and photographs also reminded us that research in the 1950's was a hands-on affair, with no recourse to ordering kits and reagents from Commercial catalogues.

Anthony Carter discussed the evolution of placental strategies and speculated that the common ancestor of placental mammals may have had an invasive type of placentation (haemochorial), similar to that found in humans and mice.

Liz Simpson talked about the different ways of keeping the immune system from going into override. The immune system of the mother is not inert to fetal antigens, indeed it responds to them. Examples are maternal antibodies found in multiparous women and specific for paternally inherited Rhesus D, ABO or HLA antigens. Pregnancy indeed immunizes and tolerizes mothers to paternal allogeneic antigens. HY-specific T cells can also, albeit rarely, be found in mothers of sons. As tolerance can be induced with nasally administered HY peptide, similarly, tolerance could be induced with HY peptide in the uterine mucosa.

Immunologists can be forgiven for focusing solely on polymorphic MHC molecules and adaptive immunity. In fact, allorecognition is a feature of metazoan phyla, including sponges. Study of the colonial ascidian *Botryllus schlosseri*, leads to the realization that allorecognition systems appear to have evolved independently. *Botryllus* appears to use a unique system that tells us little about adaptive immunity in vertebrates, except that it exhibits extreme polymorphisms of ligands and receptors. Interestingly, the genes for both ligands and receptors tend to be linked on the same chromosome in *Botryllus*. **Anthony de Tomaso** discussed the fusion histocompatibility (FuHC) gene, which appears to protect against parasitic dividing cells from another sea squirt.

Kalle Malberg attempted to simplify the complexity of the variables regulating how NK cells modulate the outcome of mismatched hematopoietic stem cell transplantation, which, to some extent, can be compared to the mismatch between the mother (the lymphocyte "donor") and the fetus. Diversity, in terms of both the HLA and KIR genes involved, and the NK-cell

Figure 1. The 16 speakers and 20 discussants who participated in the meeting on the loan of King's College, Cambridge, UK.

subpopulations, could be harnessed and used as a metric, or even as a biomarker.

Francesco Colucci discussed the usefulness and limits of mouse models to study allorecognition, in general, and immunogenetics of pregnancy in particular, and presented evidence that the mouse, despite differences in reproduction and in the genes coding for NK receptors and their MHC ligands, is a powerful tool to understand how NK-cell biology contributes to the immunology of reproduction.

Jean-Francois Bach reviewed the lessons that could be learnt about maternal tolerance in the context of induction of tolerance to autoantigens and alloantigens in autoimmune diabetes.

Patrice Nancy reviewed the work done in the Erlebacher lab, which has elucidated, using transgenic mouse models, key epigenetic silencing of T cell-attracting inflammatory chemokine genes in decidual stromal cells that prevent effector T cells with fetal-antigen specificity from rejecting the allogeneic fetus.

Sing Sing Way demonstrated that ablation of mouse Treg cells results in the loss of pups. Down regulation of T-cell activity has to be carefully controlled as it may be exploited by pathogens. His recent work also shows that the susceptibility of newborn infants to infection is compromised by $CD71^+$ cells that express arginase, which is essential for immunosuppression.

Paul Moss has demonstrated the presence of HY-specific T cells with a memory effector phenotype in women. These cells are functional and persist for many years. The persistence of fetal cells in women post-natally, a form of chimerism, may have long term consequences that have not been appreciated. The effects of the pregnancy hormone, progesterone, on a range of T-cell functions illustrate how systemic T cells may change during pregnancy.

John Trowsdale discussed the role of KIR, LILR and HLA genes in disease association studies. He also shared new data from his laboratory suggesting that a newly identified member of the antigen processing machinery might contribute to some of the unique aspects of HLA-C, which is the only polymorphic HLA class I molecules expressed on extravillous trophoblast.

Richard Apps presented new data suggesting that the products of some KIR genes, in combination with paternal HLA-C2, modulate birth weight across the whole human birth weight spectrum. Women who possess the activating KIR2DS1 in combination with a paternal HLA-C2 are at risk of a macrosomic baby. This leads to pregnancy complications such as obstructed labor and birth asphyxia. The KIR and HLA-C genes are under stabilizing selection and the pressures resulting from either very low birth weight or macrosomia may be partly responsible for this.

Maternal immunomodulation by HLA-G has been extensively investigated since it is uniquely expressed at a high level on trophoblast. The problem is that HLA-G has two different proposed ligands. One is LILRB1, a molecule related to KIR but expressed on decidual macrophages. The other proposed HLA-G ligand is another KIR, KIR2DL4. **Sumi Rajagopalan's** data suggest that soluble HLA-G induces a proinflammatory response in resting NK cells by being endocytosed to early endosomes where it encounters KIR2DL4. The consequence of the encounter is a DNA damage response and morphological changes consistent with senescence. These signals are thought to mediate vascular remodeling and angiogenesis of maternal vasculature in early pregnancy.

A related function for dNK cells is suggested by the genetic and functional studies from **Ashley Moffett's** laboratory. Their studies indicate that interactions of fetal

HLA-C molecules with of KIR receptors expressed by dNK cells fine-tune fetal-maternal interaction. The purpose of this conversation between the two genetically different beings is to ensure an even-handed transaction and definition of the maternal-fetal territorial boundary – the baby gets sufficient resources without compromising the mother's survival.

Peter Parham's view of Medawar's analogy between transplantation and pregnancy was to look at the evolution of all the major components of the immune system that were in place ~500 million years ago, well before the appearance of placental mammals ~150 million years ago. There is no possibility that there would have been selection for mothers rejecting their babies. Instead, there must have been a harmonious co-evolution of placentation with the existing immune system. The great diversity of types of placentation is mirrored by the various receptors used by NK cells in different species. His focus on primates with the emergence of KIRs in simian primates and HLA-C2 groups in the great apes correlates with increasingly vigorous placental invasion.

Graham Burton offered the view of a non-immunologist and shared recent discoveries in physiology, which show that histiotrophic nutrition from the uterine glands sustains the human embryo until the end of first trimester, when maternal blood takes over. Uterine secretions are found in intervillous space, where some immune cells can also be found. The extent of vascular remodeling was appreciated by quantifying it: uterine arteries increase their diameter by 5 fold between 9 and 40 weeks of gestation. The dilation of the mouth of the artery reduces the speed of flow from 2-3 m/s to 0.1 m/s.

Discussion

It was clear that many questions remain, for example what is the role of endogenous retroviruses in the placenta and do these trigger activation of maternal immune cells? It was also notable that the majority of experiments have been performed using species that have haemochorial placentation and not those (the majority) that have less invasive epitheliochorial or endotheliochorial forms of placentation. The impact on the maternal immune system is likely to be very different in these species.

The discussion addressed the elusive potential effector mechanisms by which allogeneic T cells cause pregnancy complications in humans. The elegant murine models of pregnancy in which the fetus expresses a paternal transgene have still not allowed a distinction between maternal systemic or local decidual T-cell responses to the fetus. Whether maternal T cells recognize fetal and/or trophoblast cells and what effector mechanisms are used are also still unresolved. While it is clear that the maternal immune system senses the fetal allograft, how it might 'attack' it is unclear, as nicely put in the Janeway's Immunobiology textbook [1]:

> *"The mysterious lack of rejection of the fetus has puzzled generations of immunologists, and no comprehensive explanation has yet emerged. One problem is that acceptance of the fetal allograft is so much the norm that it is difficult to study the mechanism that prevents rejection: if the mechanism for rejecting the fetus is rarely activated, how can one analyze the mechanism that controls it?"*

Because the evolution of the immune system predated the evolution of the placenta, it is likely that placentation and immunity have adapted to one another. Maternal immune cells at the maternal fetal interface may have been co-opted to mediate tissue homeostasis (as many innate lymphoid cells do in other tissues) and trophic functions, such as the effect of uterine NK cells on vascular remodeling, rather than immune functions targeted at the invading placental cells. T cells at the maternal fetal interface may be dedicated mainly to protecting against infectious agents and a compromise is mediated by Treg cells, which keeps the balance between infectious immunity and fetal tolerance.

In contrast, there has been progress on NK allorecognition where a range of NK receptor systems with known trophoblast cognate ligands have been described. The variable KIR and Ly49 families that bind MHC class I molecules are a particular focus as both human genetic studies and mouse models have shown that there is a definite impact on reproductive success.

The talks are available online at http://sms.cam.ac.uk/collection/1636116

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Reference

1 **Ken Murphy (Eds.)**, *Janeway's Immunobiology textbook– 8th Edition Garland Science*, New York, NY, 2008.

Women in Immunology database

EFIS has recently launched the "Women in Immunology" database. The aim of this project is to help scientists, universities, research institutions, political institutions, conference organizers and journal editors identifying qualified female immunologists, and therefore, facilitating the gender balance of scientists at all levels.

The experts will be classified according to sub-discipline and experience. They will be listed by keywords that reflect their research foci, location (cities, institutions, etc.), and the search results may be filtered by research area, position, or country. This database will help in promoting young investigators as well as senior female scientists in relevant organizations by increasing their visibility.

We encourage female immunologist to register and create a profile in the "Women in Immunology" database.

Find more details about the "Women in Immunology" database at **https://www.efis.org/the-federation/women-in-immunology/about/index.html?nav=true**

