Journal of Reproductive Immunology 87 (2010) 1–13

Contents lists available at ScienceDirect

Journal of Reproductive Immunology

journal homepage: www.elsevier.com/locate/jreprimm

Review

Utilising T cell receptor transgenic mice to define mechanisms of maternal T cell tolerance in pregnancy☆

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ARTICLE INFO

Article history:
Received 29 January 2010
Received in revised form 19 May 2010
Accepted 31 May 2010

Keywords:
Tolerance
Uterus
Pregnancy
T cell
T cell receptor
Transgenic TCR model

ABSTRACT

Studies in mice demonstrate that the maternal T cell repertoire is aware of paternal antigens during pregnancy, but in healthy pregnancy reactive T cells do not mediate anti-fetal immunity. Mice expressing transgenic T cell receptors (TCRs) specific for paternal and conceptus antigens are powerful tools for elucidating the events surrounding paternal antigen presentation to the maternal T cell repertoire, the nature of the ensuing T cell response and the factors that skew the response towards immune tolerance to allow survival and development of the conceptus. While results from different transgenic TCR models are not always consistent, there is now sufficient data to allow a consensus interpretation that maternal antigen presenting cells present initially seminal fluid antigens and later placenta-derived antigens to both the CD4+ and CD8+ T cell repertoire. T cell proliferation is generally followed by entry into a state of anergy demonstrated by decreased cytokine production and hyporesponsiveness upon restimulation. Some models also demonstrate downregulation of the TCR and co-stimulatory molecules, clonal deletion of paternal antigen-reactive T cells, or alternatively T cell ignorance of paternal antigens. This review will summarise the range of transgenic TCR studies that have shed light on the events surrounding paternal antigen presentation and the various T cell responses to insemination and pregnancy. The benefits, limitations and caveats of these models, and their impact upon data interpretation, are discussed.

1. Introduction

A repertoire of mechanisms is responsible for establishing and maintaining maternal immune tolerance to the semi-allogeneic conceptus during successful pregnancy (Trowsdale and Betz, 2006). While both the innate and adaptive immune compartments are involved in maternal adaptation to pregnancy, recent studies have highlighted the particular importance of the maternal T cell response.

The maternal T cell repertoire has been shown to include cells that interact with paternal antigens (James et al., 2003). In healthy pregnancy, specific immune-deviating mechanisms steer the maternal T cell response away from an activated Type 1 effector state that can be deleterious to the survival and growth of the conceptus. T cells appear to develop a transient state of active paternal antigen-specific tolerance which allows females to accept paternal tumour cell challenges or tissue grafts whilst rejecting third party grafts (Beer and Billingham, 1974; Robertson et al., 1997; Tafuri et al., 1995).

Abbreviations: DC, dendritic cell; APC, antigen presenting cell; OVA, ovalbumin; TCR, T cell receptor; TAP, transporter associated with antigen processing; CTL, cytotoxic lymphocyte; CFSE, carboxyfluorescein succinimidyl ester; pc, post-coitum.

☆ This work was supported by a Program Grant and Fellowship from the National Health and Medical Research Council, Australia (SAR).

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doi:10.1016/j.jri.2010.05.007

The molecular and cellular events underpinning pregnancy and maternal immune tolerance are complex and involve T cell populations that are difficult to identify and track, because of the relatively low frequency of T cells that are reactive to paternal antigens. Genetically manipulated mice expressing transgenic T cell receptors (TCRs) provide powerful tools to address an array of questions that cannot currently be elucidated by examining endogenous T cell populations. Transgenic T cells expressing TCRs specific for a given antigen provide a large pool of antigen-specific T cells, which can be easily manipulated in vivo, in vitro or ex vivo. They are particularly valuable for in vivo studies, where they can be studied as endogenous populations in transgenic TCR mice after identification with antibodies reactive with the TCR. Alternatively, they can be recovered from donor mice, readily labelled with tracking agents such as CFSE and then transferred to naïve recipients to comprise a clearly identifiable population in the host. These strategies allow antigen processing and presentation mechanisms as well as T cell phenotypes to be examined.

Transgenic TCR mice have become extremely useful for dissecting the events surrounding the induction and maintenance of maternal immune tolerance. This review will bring together current information from recent studies utilising T cells expressing transgenic TCRs that recognise either naturally occurring paternal antigens, or transgenic antigens acting as 'surrogate' paternal antigens, to address questions concerning the immune response to pregnancy. We summarise what we have learned about processing and presentation of paternal antigen to the maternal T cell repertoire, the nature of the resulting T cell response and the impact of the response in supporting or interfering with pregnancy success. Finally, we note the caveats and limitations in interpreting data from these models, and indicate research directions for the future use of this important tool in reproductive immunology.

2. Presentation of paternal antigens to maternal T cells

The initial event in any immune response is the processing and presentation of antigens by antigen presenting cells (APCs), and indeed the strength and quality of an immune response is largely governed by the interaction between APCs and T cells. The first section of this review will discuss how T cell transgenic models have shed light on the mechanisms by which paternal antigens in seminal fluid and gestational tissues are processed and presented to the TCR of maternal T cells (Table 1).

2.1. Presentation of seminal fluid antigens

The female is initially and most commonly exposed to paternal antigens in the form of seminal fluid at the time of insemination (Robertson and Sharkey, 2001). This fact is often overlooked in pregnancy studies, which tend to focus on the T cell response to placental antigens. We undertook the first study to demonstrate seminal fluid antigen presentation to the maternal T cell repertoire employing transgenic Act-mOVA mice, which ubiquitously express a membrane-bound form of OVA, providing OVA as a surrogate paternal antigen (Moldenhauer et al., 2009). To investigate OVA antigen processing and presentation, transgenic OVA-reactive CD8+ OT-I T cells and CD4+ OT-II T cells were adoptively transferred into mated or pregnant females.

Both OT-II and OT-I T cells transferred on day 0.5 post-coitum (pc) into females mated with Act-mOVA males were found to be activated in an OVA-specific manner, indicated by upregulation of CD25 and CD69 activation marker expression, proliferation and evidence of IL2 and IFNG production (albeit at low levels) within the uterus-draining para-aortic lymph nodes (Moldenhauer et al., 2009). Utilising the bm1 mouse (H-2K^{bm1}), which is unable to present OVA antigen to OT-I T cells, in a series of bone marrow chimera experiments it was demonstrated that seminal fluid OVA antigen could only be presented to OT-I T cells by females with H-2K^{b} bone marrow, whilst chimeric mice with bm1 bone marrow were unable to activate T cells (Moldenhauer et al., 2009). These experiments showed that presentation of seminal fluid antigens to naïve CD8+ T cells is exclusively performed by maternal bone marrow-derived cells, most likely dendritic cells (DCs), and that neither male cells in seminal fluid or non-hematopoietic cells within the female reproductive tract, such as uterine epithelial cells, can process and present seminal fluid OVA antigen in a form capable of activating an antigen-specific T cell response (Moldenhauer et al., 2009).

Presentation of exogenous paternal OVA antigen via the endogenous antigen presentation pathway results in MHC class I-restricted exogenous antigen presentation, which is referred to as 'cross-presentation'. Cross-presentation is a mechanism known to establish immune tolerance (Kurts et al., 1998) depending upon the APC phenotype and immune environment (Heath and Carbone, 2001; Lutz and Kurts, 2009; Steinman et al., 2003). Cross-presentation is performed by activated CD8+ CD11c+ DCs (Jung et al., 2002), which are amongst the range of DC populations present in the uterus and draining lymph nodes (Bizargity and Bonney, 2009; Blois et al., 2004; Erlebacher et al., 2007). Furthermore, the cross-presentation of OVA antigen requires a mechanism dependent upon transporter associated with antigen processing (TAP), as demonstrated by the lack of seminal fluid OVA presentation in *Tap* null mutant females mated to Act-mOVA males (Moldenhauer et al., 2009).

While OVA is not a native paternal antigen, these findings are consistent with experiments in wild-type mice showing that in the natural T cell repertoire, T cells become activated and proliferate in response to seminal fluid (Johansson et al., 2004). Evidence that paternal MHC antigens drive this response comes from experiments showing that seminal fluid activates functional tolerance specific for paternal MHC antigens apparently mediated by regulatory T cells (Treg cells) (Robertson et al., 2009).

In contrast, another study found no evidence of antigen-specific T cell responses to two native paternal antigens after insemination (Seavey and Mosmann, 2006). This study utilised transgenic 2C T cells which react with a peptide of α-ketoglutarate dehydrogenase when presented in the context of H-2L^{d} and HY-TCR T cells which react with