Pathways of paternal antigen presentation to initiate antigen-specific immune responses in pregnancy

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Abstract

The fetus and its placenta, collectively called the conceptus, are semi-allogeneic to the mother, as they express transplantation antigens of paternal origin. Foreign tissues generally experience immunological rejection by the host immune system; however in a normal healthy pregnancy the conceptus does not undergo immune attack. Emerging evidence indicates the conceptus avoids rejection through a number of mechanisms including the induction of active maternal immune tolerance specific for paternal antigens. However, the mechanisms responsible for establishing this tolerance remain undefined, including the timing of the first encounter with paternal antigen and the cellular processes by which paternal antigen is presented to the maternal immune system. Exposure to paternal transplantation antigens occurs in two waves: initially in the context of male seminal fluid at conception, and secondly after placental trophoblast invasion of maternal tissues in mid-gestation pregnancy. Therefore the aim of this research was to evaluate the female immune response to paternal antigens in seminal fluid and those associated with the conceptus. The mechanisms of antigen presentation, the impact of the cytokine environment and the consequences of T cell activation on pregnancy were also investigated.

A transgenic system using ovalbumin (OVA) as the model paternal antigen was established. The transgenic Act-mOVA mouse expresses OVA constitutively and ubiquitously under a β-actin promoter and OVA was shown to be present in seminal fluid and in the fetal and placental tissue of sired progeny. The OVA-reactive CD8+ OT-I and CD4+ OT-II T cells were employed to gauge the relative amount of OVA antigen presented, with the strength of the maternal immune response quantified based upon the extent of T cell proliferation, as assessed by CFSE dye-dilution.

Utilising bone marrow chimeric mice, it was demonstrated that upon insemination by an Act-mOVA male, seminal fluid-derived OVA was processed and indirectly presented by maternal bone marrow-derived antigen presenting cells to induce activation and proliferation of the CD8+ OT-I T cells within the uterine-draining para-aortic lymph nodes of the female. Likewise, OT-II T cells were responsive to MHC class II-restricted presentation of seminal fluid OVA. Post-implantation conceptus-derived OVA was detected within peripheral lymph nodes and the spleen where it was presented via the MHC class I and class II-restricted pathways to induce systemic proliferation of both OT-I and OT-II T cells. Furthermore, as gestation
advanced the extent of OVA presentation and hence T cell proliferation intensified. Conceptus-derived OVA was still presented systemically until 20 days pp.

The impact of the uterine cytokine environment was assessed to determine its influence on seminal OVA antigen processing and presentation. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a key factor in regulating the leukocyte population of the female reproductive tract. GM-CSF-deficient female mice were unable to process and present seminal fluid OVA as effectively or efficiently as their wildtype counterparts, as assessed by their reduced capacity to drive OT-I and OT-II T cell proliferation following insemination by an Act-mOVA male.

Finally, with highly-reactive OVA-specific T cells activated in response to seminal and conceptus OVA antigen, it was of interest to determine the effect of OT-I T cell activation on fetal survival and pregnancy success. It was found that OT-I T cells activated in vivo to paternal OVA antigen in the context of seminal fluid and pregnancy were not deleterious to pregnancy outcomes. However the transfer of cytotoxic OT-I T cells generated in vitro in the presence of an IL-2 into female mice carrying OVA-expressing conceptuses was detrimental to fetal survival.

Collectively these experiments demonstrated that the initial exposure to paternal antigen, and hence the first opportunity to develop paternal antigen-specific tolerance, occurs at insemination. Paternal antigen is presented to the maternal T cell repertoire throughout gestation and may play a role in maintaining immune tolerance during pregnancy. The processing and presentation of paternal-derived antigen is chiefly performed by female bone marrow-derived antigen presenting cells. The cytokine environment of the mated female reproductive tract is critical in allowing optimal antigen processing and presentation, to generate an immune response consistent with maternal immune tolerance of the conceptus.
Declaration

This work contains no material which has been accepted for the award of any other degree or diploma at any University or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I further grant my consent to the University of Adelaide to make this thesis available in all forms of media, now or hereafter known.

Lachlan Millhouse Moldenhauer

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2008

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Abbreviations

♂ male
♀ female
°C degrees Celsius
%CD25+ percentage of CD25 positive cells in the parent peak
%CD69+ percentage of CD69 positive cells in the parent peak
am ante meridiem
APC antigen presenting cell
B6 C57Bl/6 mouse strain
B6.SJL B6.SJL-PtprcaPep3b/BoyJArc mouse strain
B6.SJL → B6.SJL B6.SJL mouse donor bone marrow into B6.SJL host
B6.SJL → bm1 B6.SJL mouse donor bone marrow into bm1 host
bm1 bm1 mouse strain
bm1 → B6.SJL bm1 mouse donor bone marrow into B6.SJL host
bm1 → bm1 bm1 mouse donor bone marrow into bm1 host
BSA bovine serum albumin
cDNA complementary deoxyribonucleic acid
CFSE 5,6 - carboxyfluorescein diacetate succinimidyl ester
CLN cervical lymph node
CpG DNA cytosine-guanine island deoxyribonucleic acid
CSF colony stimulating factor
CSF-1R colony stimulating factor 1 receptor
Crry complement receptor related protein
CTL cytotoxic lymphocyte
CTLA-4 cytotoxic T lymphocyte-associated protein 4
CTLA4-CR cytotoxic T lymphocyte-associated protein 4 counter receptor
DC dendritic cell
DES-TCR Désiré T cell receptor transgenic mouse
dpc days post-coitum
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Meaning</th>
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<tr>
<td>KHCO₃</td>
<td>potassium bicarbonate</td>
</tr>
<tr>
<td>KLH</td>
<td>keyhole limpet hemocyanin</td>
</tr>
<tr>
<td>LCMV</td>
<td>lymphocytic choriomeningitis virus</td>
</tr>
<tr>
<td>LN</td>
<td>lymph node</td>
</tr>
<tr>
<td>LPS</td>
<td>lipopolysaccharide</td>
</tr>
<tr>
<td>µg</td>
<td>microgram</td>
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<tr>
<td>µl</td>
<td>microlitre</td>
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<td>µM</td>
<td>micromolar</td>
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<tr>
<td>M</td>
<td>molar</td>
</tr>
<tr>
<td>MCP</td>
<td>monocyte chemoattractant protein</td>
</tr>
<tr>
<td>MES</td>
<td>mesenteric lymph nodes</td>
</tr>
<tr>
<td>MgCl₂</td>
<td>magnesium chloride</td>
</tr>
<tr>
<td>MHC</td>
<td>major histocompatibility complex</td>
</tr>
<tr>
<td>min</td>
<td>minute</td>
</tr>
<tr>
<td>MIP</td>
<td>macrophage inflammatory protein</td>
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<td>ml</td>
<td>millilitre</td>
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<td>millimetre</td>
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<tr>
<td>mM</td>
<td>millimolar</td>
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<tr>
<td>MMP</td>
<td>matrix metalloproteinases</td>
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<tr>
<td>mRNA</td>
<td>messenger ribonucleic acid</td>
</tr>
<tr>
<td>MUC</td>
<td>mucin</td>
</tr>
<tr>
<td>n</td>
<td>number</td>
</tr>
<tr>
<td>Na₂HPO₄</td>
<td>disodium hydrogen phosphate</td>
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<tr>
<td>NF</td>
<td>nuclear factor</td>
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<td>ng</td>
<td>nanograms</td>
</tr>
<tr>
<td>NH₄Cl</td>
<td>ammonium chloride</td>
</tr>
<tr>
<td>NK</td>
<td>natural killer</td>
</tr>
<tr>
<td>NLR</td>
<td>NOD-like receptors</td>
</tr>
<tr>
<td>nm</td>
<td>nanometres</td>
</tr>
<tr>
<td>NP-40</td>
<td>nonyl phenoxylpolyethoxylethanol</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
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</tr>
<tr>
<td>OVA</td>
<td>chicken ovalbumin</td>
</tr>
<tr>
<td>PALN</td>
<td>para-aortic lymph nodes</td>
</tr>
<tr>
<td>PBS</td>
<td>phosphate buffered saline</td>
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<td>pc</td>
<td>post-coitum</td>
</tr>
<tr>
<td>PE</td>
<td>phycoerythrin</td>
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<td>PE-Cy</td>
<td>phycoerythrin-cyanine</td>
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<tr>
<td>PGE</td>
<td>prostaglandin</td>
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<tr>
<td>PI</td>
<td>proliferation index</td>
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<td>pm</td>
<td>post-meridiem</td>
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<tr>
<td>PMSF</td>
<td>phenylmethanesulphonylfluoride</td>
</tr>
<tr>
<td>pp</td>
<td>post-partum</td>
</tr>
<tr>
<td>PRR</td>
<td>pattern recognition receptor</td>
</tr>
<tr>
<td>RANTES</td>
<td>regulated upon activation normal T cell expressed and secreted</td>
</tr>
<tr>
<td>RBC</td>
<td>red blood cell</td>
</tr>
<tr>
<td>RER</td>
<td>rough endoplasmic reticulum</td>
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<tr>
<td>RLR</td>
<td>retinoid-inducible gene 1-like receptors</td>
</tr>
<tr>
<td>s.c.</td>
<td>subcutaneous</td>
</tr>
<tr>
<td>SEM</td>
<td>standard error of mean</td>
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<tr>
<td>SIINFEKL</td>
<td>ovalbumin peptide amino acids 258-265</td>
</tr>
<tr>
<td>SOCS</td>
<td>suppressor of cytokine signalling</td>
</tr>
<tr>
<td>SPL</td>
<td>spleen</td>
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<td>ssRNA</td>
<td>single stranded ribonucleic acid</td>
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<td>SV</td>
<td>simian virus</td>
</tr>
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<td>SVX</td>
<td>seminal vesicle-deficient</td>
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<td>TAP</td>
<td>transporter associated with antigen processing</td>
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<td>TCR</td>
<td>T cell receptor</td>
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<tr>
<td>TGF</td>
<td>transforming growth factor</td>
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<tr>
<td>Th</td>
<td>T helper</td>
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<tr>
<td>TIMP</td>
<td>tissue inhibitors of metalloproteinase</td>
</tr>
<tr>
<td>TLR</td>
<td>Toll-like receptor</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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</tr>
<tr>
<td>Tris-HCl</td>
<td>Tris (hydroxymethyl) aminomethane hydrochloride</td>
</tr>
<tr>
<td>uNK</td>
<td>uterine natural killer</td>
</tr>
<tr>
<td>VAS</td>
<td>vasectomised</td>
</tr>
<tr>
<td>VEGF</td>
<td>vascular endothelial growth factor</td>
</tr>
<tr>
<td>VSV</td>
<td>vesicular stomatitis virus</td>
</tr>
</tbody>
</table>