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Immunological Analogy Between Allograft Rejection, Recurrent Abortion and Pre-Eclampsia – the Same Basic Mechanism?

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ABSTRACT: There are still controversies concerning the role of immunological mechanisms engaged both in recurrent abortions (RA) and pre-eclampsia (PE). According to some opinions, recurrent miscarriage is comparable to organ-specific autoimmune disease. Analysis of immune reactions shows that graft rejection shares many similar mechanisms with RA and PE. This fact allows us to conclude that rejection of transplanted alloantigenic organs and pregnancy loss have probably the same evolutionary origin. Subsets and functions of immunocompetent cells (T CD4, suppressor γδT, cytotoxic T CD8, Treg, Tr1, uterine NK cells), over-activation of innate immunity (activation of NK cytotoxic cells, macrophages, neutrophils and complement), changes of Th1/Th2 cytokine balance (IL-2, IL-12, IL-15, IL-18, IFNγ, TNFα vs. IL-4, IL-10, TGFβ), importance of HLA-G molecule, CD200/CD200R interaction, over-expression of adhesion molecules, fgl2 prothrombinase activation and stimulation of IDO and HO expression, all suggest that RA and PE are syndromes of fetal allograft rejection, and not organ-specific autoimmune diseases. According to that supposition, an analogy might exist between acute graft rejection and recurrent abortion, and between chronic graft rejection and pre-eclampsia. *Human Immunology 67, 492–511 (2006).* © American Society for Histocompatibility and Immunogenetics, 2006. Published by Elsevier Inc.

KEY WORDS: allograft rejection; recurrent abortion; pre-eclampsia

ABBREVIATIONS

ACA	anticardiolipin antibodies
ANA	antinuclear antibodies
APC	antigen-presenting cells
BAbs	bloking antibodies
CO	carbon oxide
DCs	dendritic cells
DN	double negative T cells
DSBT	donor-specific blood transfusion
FcγR	receptor for Fc fragment of immunoglobulins
Fgl2	fibrinogen-like protein 2 / fibroleukin
GvHD	graft-versus-host disease
HLA	human leukocyte antigen
HO	heme oxygenase
ICAM-1	inter-cellular adhesion molecule-1
IDO	indoleamine 2,3-dioxygenase
IFNγ	interferon-gamma
IgG	immunoglubulin G
IL	interleukin
ILT	immunoglobulin-like transcript
KIR	killing inhibitory receptor
LA	lupus anticoagulant
MHC	main histocompatible complex
MLR	mixed lymphocyte reaction
mRNA	messenger rybonucleic acid
NK	natural killer
NO	nitric oxide
PE	pre-eclampsia
PIBF	progesterone-induced blocking factor
RA	recurrent abortions
TCR	T cell receptor
TGFβ	transforming growth factor-beta
TNFα	tumor necrosis factor-alpha
VCAM-1	vascular-cellular adhesion molecule-1

INTRODUCTION

For many years, the term "fetal allograft" has been widely used for description of fetal immunological status during pregnancy. In such an approach, immunological acceptance describing maternal reaction directed towards fetal antigens is understood as the state of recipient's tolerance to an engrafted organ. Consequently, immunopathological recognition of fetal antigens that occurs in recurrent abortions (and possibly pre-eclampsia), should be viewed as graft rejection-like alloimmune reaction. However, there are still some doubts concerning this approach, as some proofs speak against it. Firstly, the classical HLA antigens are not expressed on the surface of trophoblast

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[1], secondly, the HLA-sharing between partners does not influence fetal survival [2, 3], and lastly, so-called blocking anti-HLA antibodies seem to have no impact on the pregnancy outcome [4, 5, 6]. According to some authors [7], recurrent miscarriage is the result of an increase in activity of the innate immune system, especially NK cells [8, 9, 10], and organ specific autoimmunity, whose contribution is indicated by a higher prevalence of autoantibodies [11, 12] and association with particular maternal class II HLA genotypes [13]. These observations support opinion, that use of the term "allograft" should be viewed as erroneous. However, immunological analysis of both gestation and grafting demonstrates many common mechanisms determining fetal and graft outcome. The question arises if this similarity is only an epiphenomenon, or represents the existence of an evolutionary mechanism of "self-non-self" recognition, which was effectively adopted for regulation of fetal survival. This review attempts to answer this question and presents a comparison between immunopathological mechanisms engaged in allograft rejection and recurrent abortions and pre-eclampsia.

IMMUNOLOGY OF GRAFT REJECTION

Antigen Recognition

The initial step of immunological response directed towards engrafted organ, is antigen recognition that could have either a direct or indirect pattern. Direct recognition means that donor antigens presented with MHC of donor "passenger" leukocytes are recognized by the host immune system. This reaction pattern initiates acute graft rejection [14]. Processed donor antigens presented with MHC on recipient's APC cells are engaged in indirect recognition pattern, which is more important in chronic graft rejection [15, 16].

Cytokines of Th1/Th2 Activity

Allograft-induced activation leads to rejection-type response by stimulation of the surface molecules CD25, CD69, HLA-DR as well as by production of Th1 type cytokines, especially IL-2, IL-12, IFNγ and TNFα [17]. Interferon-γ seems to play a key role in the acute graft rejection process [18, 19, 20, 21]. In animal model alloantigen-specific T lymphocytes secreting IFNγ provoked acute rejection of grafts, whereas Th2 cytokine secretion (IL-4, IL-10) initiated the tolerance of the engrafted organ [22]. Th1-type of activity could be prevented by blocking costimulation pathways with antibody CTLA-4-Ig against CD28/B7 [23, 24, 25] and/or antibody against CD40/CD40L [26]. Such treatment resulted in a decrease of intragraft secretion of IL-2, IFNγ, TNFα, and a concomitant increase in secretion of IL-4 and IL-10 [24, 25, 26], as well as in development of antigen-specific anergy and suppression of NK cell activity [27]. The severity of graft rejection episodes can be also restricted by antibodies against interleukin-2 receptor (IL-2R) [28]. Portal vein immunization with irradiated donor cells [29, 30] or donor-specific blood transfusions (DSBT) before grafting, [31] were shown to be another way to induce tolerance. Regulatory functions of cytokines could be modified by certain cytokine-producing genotypes associated with better or worse transplant survival [32, 33, 34].

Although it has been proved that Th1-type activity could be detrimental to graft survival, one must remember if it occurs in an adequate time and with the proper intensity Th1-type cytokine secretion seems to be necessary for development of protective alloresponses [16]. It was found that an early accumulation of IFNγ took place in grafts destined to be tolerated, and that IL-2 deficient hosts rejected grafts despite IL-4 overbalance, supporting evidence that Th1 cytokine stimulus is necessary for induction of graft tolerance [31, 35, 36, 37]. In pre-treated by DSBT subjects, initial IFNγ up-regulation preceded Th2 response inside grafts, and an addition of immunosuppressive drugs in that early phase of the recipient's response could be harmful for induction of tolerance [38]. In IFN-knockout rodents graft tolerance could not be induced [39]. Macrophage-derived Th1 cytokines (IL-1, TNFα, IFNγ) might also enhance nitric oxide (NO) production, which in turn promotes intragraft Th2 activity [40].

Controversies concerning the mechanism of cytokine-mediated chronic graft rejection still exist. According to some authors, Th2 cytokines mediated chronic rejection, being a "by-product" of earlier protective activity [31]. Interleukin-4 and IL-10 were believed to be the most important cytokines in this process [41, 42, 43], and a high expression of IL-10 was even thought to be a bad prognostic factor for graft success [41]. Th2 cytokines caused B cell-derived alloantibody production and eosinophil activation [44, 45], were capable of activating intragraft endothelial cells, stimulating of interstitial fibrosis and changes in the structure of extracellular matrix [46], followed by vascular obliteration, endothelial IgG deposition and activation of complement [31, 47]. However, concerning the chronic graft rejection as Th2-dependent process seems to be an over-simplification. Physiologically Th2-biased activity of immune system in infants during the first months of life predisposes them to improved graft acceptance at this age [48]. Th2-dependent activity was shown to protect grafted tissue in immunosuppression-free model of chronic renal graft rejection [49]. This model provided the opportunity to study cytokine secretion without the influence of suppressive drugs to ensure, that the observed Th2 protective