Chimerism 1:1, 19-20; July/August/September 2010; © 2010 Landes Bioscience

Breast milk and transplantation tolerance

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Recent experimental and clinical studies suggest that exposure of the fetus to noninherited maternal antigens (NIMAs) during pregnancy has an impact on allogeneic transplantations performed later in life. We have reported that NIMA exposure by breastfeeding further potentiates the tolerogenic NIMA effect mediated by in utero NIMA exposure during pregnancy in mice of allogeneic hematopoietic stem cell transplantation (HSCT). Breastfeeding generates Foxp3$^+$ regulatory T cells that suppress anti-maternal immunity and persist until adulthood. These results reveal a previously unknown impact of breastfeeding on the outcome of allogeneic HSCT.

Key words: hematopoietic stem cell transplantation, graft-versus-host disease, regulatory T cells, noninherited maternal antigens, oral tolerance, cord blood transplantation

Abbreviations: NIMAs, noninherited maternal antigens; HSCT, hematopoietic stem cell transplantation; GVHD, graft-versus-host disease; BMT, bone marrow transplantation; IPAs, inherited paternal antigens

Submitted: 02/28/10

Revised: 04/06/10

Accepted: 04/07/10

Previously published online: http://www.landesbioscience.com/journals/chimerism/article/11996

DOI: 10.4161/chim.1.1.11996

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Addendum to: Aoyama K, Koyama M, Matsuoka K, Hashimoto D, Ichinohe T, Harada M, et al. Improved outcome of allogeneic bone marrow transplantation due to breastfeeding-induced tolerance to maternal antigens. Blood 2009; 113:1829–33; PMID: 19124834; DOI: 10.1182/blood-2008-05-155283.

Allogeneic hematopoietic stem cell transplantation (HSCT) is a potential curative therapy for various hematologic diseases; however, its widespread use is limited due to a lack of histocompatible donors for patients having rare HLA haplotypes. To further extend the donor availability in allogeneic HSCT, it would be beneficial to introduce the concept that some HLA mismatches are less immunogenic, or "permissive" to the recipients. Recently, high-risk HLA mismatch, that is, "nonpermissive mismatch" has been identified in a study analyzing a large-scale cohort in Japan Marrow Donor Program, while others are regarded as "permissive" mismatch.[1] Other promising lessons have been learned from renal transplantation. Graft survival in transplantation from a NIMA-mismatched sibling donor was better than non-NIMA mismatched sibling donors.[2] The clinical relevance of the NIMA effect finds further support in HLA-mismatched HSCT from a NIMA-mismatched donor.[3,4]

Mechanisms of the tolerogenic NIMA effect have been studied by using the F1 x P backcross breeding model of mice.[5,6] We previously reported that bone marrow transplantation (BMT) from H-2$^{b/b}$ offspring exposed to NIMA H-2^d during pregnancy and breastfeeding caused reduced graft-versus-host disease (GVHD).[7] However, the tolerogenic NIMA effects are not seen in "mother-to-child" BMT from a mother donor exposed to inherited paternal antigens (IPAs) from the fetus. These are in line with clinical observations showing that the incidence of severe acute GVHD may be lower in HSCT from a NIMA-mismatched donor than an IPA-mismatched donor.[3,4] Breast milk contains abundant maternal major histocompatibility complex antigens in both soluble and cellular forms.[8] To test a hypothesis that breastfeeding plays an important role in the buildup of the tolerogenic NIMA effect, H-2^b neonate mice were nursed by an H-2$^{b/d}$ foster mother to expose to NIMAs during lactation.[9] When these mice were used as donors for H-2^d mice at adulthood, GVHD was less severe in comparison with controls that were nursed by an H-2^b foster mother. We further presented that the tolerogenic NIMA effect mediated by breast-feeding was abrogated by depletion of CD25$^+$ T cells of donor innocula, as well as the in vivo depletion of CD25$^+$ cells in neonates during the lactation period, suggesting a CD4$^+$ CD25$^+$ regulatory T-cell dependent mechanism.[9] Although this tolerance to H-2^d did not extend to H-2^a in vivo, further studies are required to evaluate antigen-specificity of these regulatory T cells because we could not demonstrate antigen-specificity of regulatory T cells isolated

from NIMA-exposed mice in vitro. These results are consistent with a recent human study by Mold and colleagues demonstrating that substantial numbers of maternal cells cross the placenta to reside in fetal lymph nodes, inducing the development of FoxP3$^+$ regulatory T cells that suppress fetal antimaternal immunity and persist at least until early adulthood.[10] Recently, Dutta et al. showed in a mouse model that maternal microchimerism did not persist into adulthood in the absence of neonatal exposure through breastfeeding.[11]

Although accumulating evidence has suggested the presence of the tolerogenic NIMA effects, severe GVHD still occurs in many patients transplanted from a NIMA-mismatched sibling donor.[3,4] Further studies are needed to evaluate the association between the severity of GVHD and a history of breastfeeding, the presence or levels of fetal-maternal lymphohematopoietic microchimerism in the blood, type of NIMA haplotypes, and regimen for GVHD prophylaxis. Exposure to NIMAs may either downregulate or upregulate the allogeneic T-cell or B-cell responses depending on the NIMA haplotypes.[12-14] Calcineurin inhibitors may mask the tolerogenic NIMA effects by inhibiting activation and expansion of NIMA-specific regulatory T cells, as has been suggested in kidney transplantation.[2]

These findings have profound implications on the performance of clinical HSCT. NIMA matching might also be considered when selecting a cord blood donor.[16] A novel and individualized prevention strategy against GVHD may be achievable by administrating artificial and soluble host-specific HLA components orally to donors. A better understanding of the tolerogenic NIMA effects may lead us to reduced HLA limitations.

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