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The pendulum swings
Tolerance versus priming to NIMA

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Fetal and/or perinatal exposure to noninherited maternal antigens (NIMA) has been reported to induce NIMA-specific tolerance. This tolerant state is highly beneficial in transplantation settings; enhanced graft acceptance has been observed when transplanted tissues express NIMA. Reduction in severe graft-vs-host disease has also been noted when bone marrow grafts originate from donors exposed to NIMA in early life. However, there is emerging evidence that exposure to NIMA can alternatively lead to specific priming. The processes regulating tolerance versus priming to NIMA are poorly understood and probably multifactorial. Based on studies in both humans and mice, we propose that both the quality and the quantity of NIMA exposure will be found to be key determinants of these opposing outcomes.

Recently, much attention has been paid to the beneficial, tolerizing effects of exposure of the developing offspring to non-inherited maternal antigens (NIMA). This beneficial effect is most evident in settings of solid organ transplantation, wherein grafts expressing NIMA are more readily accepted than non-NIMA-containing grafts.[1-4] An additional benefit is observed with bone marrow transplantation in which grafts from donors exposed to NIMA in early life cause a less severe graft-vs-host disease in sibling recipients expressing that NIMA.[5-7] Exposure to NIMA may be a relatively common event in fetal and neonatal life,[8-14] a developmental time period associated with susceptibility to tolerance induction. Factors that may contribute to this tolerizing NIMA effect include the development of regulatory T cell activity or clonal deletion in the offspring, the level and type of maternal microchimerism, the genetic backgrounds of mother and offspring and gender differences.[15,16]

In spite of the wealth of information pointing to a positive, tolerizing outcome to NIMA exposure, there are observations indicating that priming may be a rarer but alternate outcome. CTL[17] and antibody priming[18] to maternal antigens as well as acute rejection of NIMA-bearing grafts[1] have been described in humans. In the mouse, poorer graft survival and/or enhanced adaptive immune responses to NIMA have been demonstrated.[4,19-21] At first blush, the observation that early life exposure can lead to priming seems to fly in the face of the prevailing dogma that fetal and neonatal animals are highly susceptible to the induction of tolerance. However, one of the most striking findings in the recent past is that full-fledged priming of adaptive immune responses can occur in both human and murine neonates and even in utero.[22] Therefore, it is actually not surprising that robust priming to NIMA can occur during gestation and/or perinatally.

An important question that arises from these observations is why NIMA-specific tolerance develops in some individuals, while priming occurs in others. Although there are clearly many possible explanations, we propose that the quantity of NIMA exposure may influence whether tolerance or priming occurs. Tolerance may arise in response to relatively high doses of NIMA from persistent exposure throughout development. Breastmilk contains both immune cells and soluble HLA molecules;[23-25] therefore, high doses of NIMA could be attained through a combination of exposure to NIMA in utero and during breastfeeding after birth. Such chronic exposure may then lead to the development of tolerance-inducing processes. Several studies support this idea, demonstrating that chronic exposure to antigen can lead to the development of functional Tregs, both in vitro and in vivo.[26-28] On the other hand, priming to NIMA may occur in response to lower, more transient doses of NIMA, such as that occurring in utero only. The idea that low level NIMA exposure may lead to the absence of tolerance or even primed responses is supported by studies in both humans and mice. In humans, cord blood cells have been reported to develop NIMA-specific cytotoxic responses in vitro,[29,30] demonstrating a lack of tolerance after in utero exposure alone. Breastfeeding was found to be required, together with in utero NIMA exposure, to specifically downregulate CTL alloreactive responses to NIMA[29] as well as to improve the survival and function of kidney allografts from sibling[31] and maternal[32] donors. Similarly, although some level of tolerance was observed upon oral exposure only,[33] maximal tolerizing effects have been reported only with the combination of in utero and breast milk exposure to NIMA in mice.[3,33] In humans, priming to NIMA has been reported in newborns; Goulmy and colleagues[17] demonstrated the pre-existence of NIMA-specific cytotoxic cells in cord blood—i.e., priming following prenatal exposure only. Moreover, a recent study from van Rood et al.[34] indicated that cord cells may exhibit primed responses to NIMA in vivo; cord blood transplants in NIMA-matched versus non-NIMA matched recipients

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showed lower leukemia relapse rates, suggesting that the NIMA-matched transplanted cells mounted an anti-leukemic response. In addition, our studies in the mouse provide compelling evidence that low level NIMA exposure may lead to priming. Using an allogeneic transfer system that mimics the natural exposure to NIMA, we have found that, while large doses of NIMA-like antigens lead to CTL non-responsiveness, small doses induce specific CTL priming.[19,20] Small numbers of maternal cells may be insufficient for stable chimerism, thereby failing to support sustained Treg function and leading to priming instead. Indeed, as recently documented by McCune and colleagues,[8] human fetal cells can develop substantial anti-NIMA responses. Alternatively, small numbers of cells may lead to selective microchimerism, which, as discussed in the next section, may more likely induce priming rather than tolerance.

In addition to the level, we propose that the type of NIMA exposure may also be instrumental in deciding the balance of tolerance versus priming. There are several ways that the quality of NIMA exposure may be important. First, the type of cell(s) that the fetus and/or neonate is initially exposed to may influence the direction of the resulting NIMA-specific response. Indeed, there are several studies that have shown that exposure to different cell subsets can induce the development of either tolerance or priming. Matzinger and colleagues[35] showed that whole spleen cells tolerized while mature dendritic cells (DC) primed neonatal animals. Further, in a model system that mimics early neonatal development, exposure to inoculum containing mature donor T cells induced tolerance to skin grafts, while grafts lacking T cells did not.[36] Most of the available evidence suggests that maternal immune cells of many types can be found in the offspring.[8,10,33] Therefore, exposure to maternal populations that contain mature DC may induce priming, while those that lack them may generate tolerance. Likewise, maternal populations that include T cells may tolerize, while their absence may lead to priming. Alternatively, the type of maternal chimerism that is stably maintained after the initial exposure may also influence whether tolerance or priming is achieved. In support of this, Anderson and colleagues[37] have shown that the presence of T cells alone may not be sufficient to induce tolerance; mice exhibiting persistent unilineage donor T-cell chimerism failed to develop tolerance whereas those with long-term multilineage chimerism were tolerant.

In summary, although tolerance to NIMA is the desired outcome in transplantation settings, the importance of priming against NIMA should not be overlooked. Overall, the challenge of exploiting NIMA exposure for successful transplantation relies on understanding how tolerance versus priming is achieved. We believe that both the quantity and quality of NIMA exposure will be found to play important roles in this outcome.

References

1. Burlingham WJ, Grailer AP, Heisey DM, Claas FH, Norman D, Mohanakumar T, et al. The effect of tolerance to noninherited maternal HLA antigens on the survival of renal transplants from sibling donors. The NEJM 1998; 339:1657-64.
2. Smits JM, Claas FH, van Houwelingen HC, Persijn GG. Do noninherited maternal antigens (NIMA) enhance renal graft survival? Transpl Int 1998; 11:82-8.
3. Andrassy J, Kusaka S, Jankowska-Gan E, Torrealba JR, Haynes LD, Marthaler BR, et al. Tolerance to noninherited maternal MHC antigens in mice. J Immunol 2003; 171:5554-61.
4. Molitor-Dart ML, Andrassy J, Haynes LD, Burlingham WJ. Tolerance induction or sensitization in mice exposed to noninherited maternal antigens (NIMA). Am J Transplant 2008; 8:2307-15.
5. Ichinohe T, Uchiyama T, Shimazaki C, Matsuo K, Tamaki S, Hino M, et al. Feasibility of HLA-haploidentical hematopoietic stem cell transplantation between noninherited maternal antigen (NIMA)-mismatched family members linked with long-term fetomaternal microchimerism. Blood 2004; 104:3821-8.
6. Shimazaki C, Ochiai N, Uchida R, Okano A, Fuchida S, Ashihara E, et al. Non-T-cell-depleted HLA haploidentical stem cell transplantation in advanced hematologic malignancies based on the feto-maternal michrochimerism. Blood 2003; 101:3334-6.
7. van Rood JJ, Loberiza FR Jr, Zhang MJ, Oudshoorn M, Claas F, Cairo MS, et al. Effect of tolerance to noninherited maternal antigens on the occurrence of graft-versus-host disease after bone marrow transplantation from a parent or an HLA-haploidentical sibling. Blood 2002; 99:1572-7.
8. Mold JE, Michaelsson J, Burt TD, Muench MO, Beckerman KP, Busch MP, et al. Maternal alloantigens promote the development of tolerogenic fetal regulatory T cells in utero. Science 2008; 322:1562-5.
9. Hall JM, Lingenfelter P, Adams SL, Lasser D, Hansen JA, Bean MA. Detection of maternal cells in human umbilical cord blood using fluorescence in situ hybridization. Blood 1995; 86:2829-32.
10. Loubiere LS, Lambert NC, Flinn LJ, Erickson TD, Yan Z, Guthrie KA, et al. Maternal microchimerism in healthy adults in lymphocytes, monocyte/macrophages and NK cells. Lab Invest 2006; 86:1185-92.
11. Lambert NC, Erickson TD, Yan Z, Pang JM, Guthrie KA, Furst DE, et al. Quantification of maternal microchimerism by HLA-specific real-time polymerase chain reaction: studies of healthy women and women with scleroderma. Arthritis Rheum 2004; 50:906-14.
12. Kaplan J, Land S. Influence of maternal-fetal histocompatibility and MHC zygosity on maternal microchimerism. J Immunol 2005; 174:7123-8.
13. Zhou L, Yoshimura Y, Huang Y, Suzuki R, Yokoyama M, Okabe M, et al. Two independent pathways of maternal cell transmission to offspring: through placenta during pregnancy and by breast-feeding after birth. Immunology 2000; 101:570-80.
14. Dutta P, Molitor-Dart M, Bobadilla JL, Roenneburg DA, Yan Z, Torrealba JR, et al. Microchimerism is strongly correlated with tolerance to noninherited maternal antigens in mice. Blood 2009; 114:3578-87.
15. Dutta P, Burlingham WJ. Tolerance to noninherited maternal antigens in mice and humans. Curr Opin Organ Transplant 2009; 14:439-47.
16. van den Boogaardt DE, van Rood JJ, Roelen DL, Claas FH. The influence of inherited and noninherited parental antigens on outcome after transplantation. Transpl Int 2006; 19:360-71.
17. Mommaas B, Stegehuis-Kamp JA, van Halteren AG, Kester M, Enczmann J, Wernet P, et al. Cord blood comprises antigen-experienced T cells specific for maternal minor histocompatibility antigen HA-1. Blood 2005; 105:1823-7.
18. Owen RD, Wood HR, Foord AG, Sturgeon P, Baldwin LG. Evidence for actively acquired tolerance to Rh antigens. Proc Natl Acad Sci USA 1954; 40:420-4.
19. Opiela SJ, Levy RB, Adkins B. Murine neonates develop vigorous in vivo cytotoxic and Th1/Th2 responses upon exposure to low doses of NIMA-like alloantigens. Blood 2008; 112:1530.
20. Adkins B, Jones M, Bu Y, Levy RB. Neonatal tolerance revisited again: specific CTL priming in mouse neonates exposed to small numbers of semi- or fully allogeneic spleen cells. Eur J Immunol 2004; 34:1901-9.
21. Warner NL, Herzenberg LA. Tolerance and immunity to maternally derived incompatible IgG 2a-globulin in mice. J Exp Med 1970; 132:440-7.
22. Adkins B, Marshall-Clarke S, Leclerc C. Neonatal adaptive immunity comes of age. Nat Rev Immunol 2004; 4:553-64.
23. Molitor ML, Haynes LD, Jankowska-Gan E, Mulder A, Burlingham WJ. HLA class I noninherited maternal antigens in cord blood and breast milk. Hum Immunol 2004; 65:231-9.
24. Weiler IJ, Hickler W, Sprenger R. Demonstration that milk cells invade the suckling neonatal mouse. Am J Reprod Immunol 1983; 4:95-8.
25. Goldman AS, Goldblum RM. Transfer of maternal leukocytes to the infant by human milk. Curr Top Microbiol Immunol 1997; 222:205-13.
26. Chen Y, Kuchroo VK, Inobe J, Hafler DA, Weiner HL. Regulatory T cell clones induced by oral tolerance: suppression of autoimmune encephalomyelitis. Science 1994; 265:1237-40.
27. Apostolou I, von Boehmer H. In vivo instruction of suppressor commitment in naive T cells. J Exp Med 2004; 199:1401-8.
28. Jonuleit H, Schmitt E, Schuler G, Knop J, Enk AH. Induction of interleukin 10-producing, nonproliferating $CD4^+$ T cells with regulatory properties by repetitive stimulation with allogeneic immature human dendritic cells. J Exp Med 2000; 192:1213-22.
29. Zhang L, van Bree S, van Rood JJ, Claas FH. Influence of breast feeding on the cytotoxic T cell allorepertoire in man. Transplantation 1991; 52:914-6.
30. Moretta A, Locatelli F, Mingrat G, Rondini G, Montagna D, Comoli P, et al. Characterisation of CTL directed towards non-inherited maternal alloantigens in human cord blood. Bone Marrow Transplant 1999; 24:1161-6.
31. Kois WE, Campbell DA Jr, Lorber MI, Sweeton JC, Dafoe DC. Influence of breast feeding on subsequent reactivity to a related renal allograft. J Surg Res 1984; 37:89-93.
32. Campbell DA Jr, Lorber MI, Sweeton JC, Turcotte JG, Niederhuber JE, Beer AE. Breast feeding and maternal-donor renal allografts. Possibly the original donor-specific transfusion. Transplantation 1984; 37:340-4.

33. 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.
34. van Rood JJ, Stevens CE, Smits J, Carrier C, Carpenter C, Scaradavou A. Reexposure of cord blood to non-inherited maternal HLA antigens improves transplant outcome in hematological malignancies. Proc Natl Acad Sci USA 2009; 106:19952-7.
35. Ridge JP, Fuchs EJ, Matzinger P. Neonatal tolerance revisited: Turning on newborn T cells with dendritic cells. Science 1996; 271:1723-6.
36. Anderson CC, Matzinger P. Immunity or tolerance: opposite outcomes of microchimerism from skin grafts. Nat Med 2001; 7:80-7.
37. Chan WF, Razavy H, Luo B, Shapiro AM, Anderson CC. Development of either split tolerance or robust tolerance along with humoral tolerance to donor and third-party alloantigens in nonmyeloablative mixed chimeras. J Immunol 2008; 180:5177-86.