

The Transfer of Immunity from Mother to Child

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ABSTRACT: The newborn's immune system grows fast from a small size at birth by exposure primarily to the intestinal microflora normally obtained from the mother at and after birth. While building up its immune system, the infant is supported by the transplacental IgG antibodies, which also contain anti-idiotypic antibodies, possibly also actively priming the offspring. The second mode of transfer of immunity occurs via the milk. Numerous major protective components, including secretory IgA (SIgA) antibodies and lactoferrin, are present.

The breastfed infant is better protected against numerous common infections than the non-breastfed. Breastfeeding also seems to actively stimulate the infant's immune system by anti-idiotypes, uptake of milk lymphocytes, cytokines, etc. Therefore, the breastfed child continues to be better protected against various infections for some years. Vaccine responses are also often enhanced in breastfed infants. Long-lasting protection against certain immunological diseases such as allergies and celiac disease is also noted.

KEYWORDS: anti-idiotypic; secretory IgA; lactoferrin; Bramwell receptor; immune system; breastfeeding

INTRODUCTION

The immune system develops in fetal life and is qualitatively quite complete at delivery, although certain cytokines are produced only at low levels. Also, many cells such as phagocytes and dendritic cells are not yet adequate in number and function.¹ The lymphocyte population is very limited, and the immune system of newborn mice is reported to be only a few percent of that of an adult.²

The major impetus for the expansion of the lymphoid population is the exposure to the microbial flora colonizing the gut from birth on. This is obvious from studies of germ-free animals, which quickly expand their limited immune system after in-

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testinal colonization.^{3,4} It takes time for the neonate to build up and develop its immune system and expand its range of specificities in this way.

The neonate clearly needs help from the mother for immediate protection, for colonization with the mother's gut flora, and for the long-term build up of its own immune system. This immunological support arrives via the placenta and the milk.

TRANSPLACENTAL SUPPORT OF HOST DEFENSE OF THE OFFSPRING

The well-known active transport of maternal IgG to the fetus in man usually results in about 90% of the maternal serum level of IgG antibodies in the full-term newborn at delivery. This transport takes place via an Fc γ receptor, called the Brambell receptor after its discoverer.⁵ Its binding to the Fc portion of the maternal IgG does not explain why IgG antibodies of certain specificities and of high avidity are more efficiently transferred than others.^{6,7}

It is quite clear that such IgG antibodies are important for the protection of the infant during the first several months of life. These antibodies meet microbes both on mucosal membranes and in the circulation and tissues. In the latter situation, complement activation and influx of neutrophils will follow resulting in an inflammatory reaction with production of pro-inflammatory cytokines. Thus, clinical symptoms, tissue damage, and considerable energy cost will ensue from this form of protection. For infants with frequent infections, this high energy cost may impair growth. This is especially striking in poor countries.⁸

The presence of an idiotypic network has been extensively studied and discussed.^{9,10} The significance of such a network in the relation between the immune systems of the mother and her offspring has been analyzed. Numerous studies give support to tolerogenic as well as immunogenic effects of maternal anti-idiotypic antibodies in the offspring.^{11,12} Injection of minute amounts of monoclonal anti-idiotypic or idiotypic antibodies against the *Escherichia coli* K13 polysaccharide capsular antigen into newborn mice primed them for protective responses after vaccination with killed *E. coli* K13.¹³ Neonates do not otherwise respond well to polysaccharide antigens. Several other studies have illustrated that neonatal exposure to monoclonal antibodies can induce selection and expansion as well as deletion of anti-idiotypic B cells and idiotypic antibody-specific regulatory or helper T cells given that the antibodies are specific for T cell dependent antigens.¹⁴⁻¹⁸

Secretory IgA (SIgA) and IgM antibodies against *E. coli* and poliovirus were found in Swedish newborns.¹⁹ Such antibodies are not transported from the mother to the fetus. The suggestion that they had been produced by the fetus was supported by the finding that such antibodies also occurred in newborns of mothers lacking IgA and/or IgM because they had hypogammaglobulinemia or selective IgA deficiency.²⁰ The possibility was considered that the poliovirus antibodies could have been induced by anti-idiotypic antibodies to poliovirus from the immunoglobulin given prophylactically to the deficient mothers. We did find such anti-idiotypes both in the immunoglobulin preparations used and in the cord sera from the studied neonates.^{20,21} It should be added that Sweden uses only inactivated poliovirus vaccine, which has successfully exterminated the wild virus. The vaccine virus does not exist in the country. Neither are any cross-reactive viruses known.

MOTHER'S MILK: PASSIVE AND ACTIVE NON-INFLAMMATORY SUPPORT OF HOST DEFENSE IN THE OFFSPRING

Passive Transfer of Defense

SIgA is the predominant isotype in milk, occurring at levels of about 0.5–1.5 g/L. There is only little IgG and IgM.²² Because of the *enteromammary link*, lymphocytes home from the gut lymphoid tissues, primarily the Peyer's patches, to the lactating mammary glands. Therefore, the milk SIgA provides protection against all the microbes the mother has or has had in her gut. Thus, the neonatal colonization with the mother's gut flora does not pose a threat even if pathogens are transferred, provided that the child is breastfed.^{23–25}

The SIgA antibodies prevent microbes from attaching to mucosal surfaces, especially in the gut. In this way, tissue engagement, inflammation, and an energy-costly defense reaction are avoided. Such protection by milk SIgA antibodies has been proven against *Shigella*, *Vibrio cholerae*, *Campylobacter*, *ETEC*, and *Giardia lamblia*.^{26–30}

Lactoferrin (LF) is the major protein in mature milk at about 1–4 g/L. Like SIgA, it is relatively resistant to enzymatic degradation. It is striking that the SIgA and LF, both important for host defense, make up about 30% of the milk proteins although milk is to cover the needs of nutrients for the baby. This is totally different from the bovine, for instance, where these defense factors correspond to just 5% of the milk protein.³¹ LF carries a number of effects being microbicidal, immunostimulatory, and efficiently anti-inflammatory, by turning off the production of numerous pro-inflammatory cytokines such as IL-1 β , IL-6, TNF- α , and IL-8.^{32–36} Especially during neonatal colonization and the subsequent expansion of the intestinal microflora, it might be important to have considerable amounts in the gut of a protein such as LF, which is both bactericidal and prevents the induction of cytokines that cause clinical symptoms, energy consumption, and inflammation. It may also be important to prevent the appearance of such cytokines at each encounter with new colonizers, many of which carry lipopolysaccharides, which efficiently activate the innate immune reactivity characterized by production of pro-inflammatory cytokines. The cytokines induce increased production of leptin, which adds to a reduction in appetite.³⁷ This is one reason why repeated infections in infants often cause undernutrition.

The oligosaccharide fraction in milk contains analogues to various receptors for microbes on mucosal epithelium. Such milk oligosaccharides can prevent mucosal attachment of several pathogens, that is, pneumococci and *Haemophilus influenzae*.³⁸ In addition, milk contains numerous other components such as the anti-secretory lectins,³⁹ and lysozyme presumably supports the host defense of the offspring.

Active Stimulation of the Immune System of the Offspring via Milk

It is well evidenced that during lactation human milk protects against numerous infections such as otitis media, upper and lower respiratory tract infections, diarrhea, urinary tract infections, neonatal septicemia, and also necrotizing enterocolitis (for a review, see Ref. 40).

More recently, it has been recognized that breastfed children are also significantly better protected against a number of infections for several years compared to non-

breastfed children. This is true for otitis media, respiratory tract infections, diarrhea, infection-induced wheezing bronchitis, and invasive *H. influenzae* type b infections.⁴⁰

Furthermore, it has been noted that vaccination during or after breastfeeding often results in better antibody and T cell responses than in non-breastfed children.^{41–43} A few vaccine studies have not seen these effects. Some of these have used oral vaccines with live viruses, which may be neutralized by the milk antibodies in breastfed infants (for a review, see Ref. 40).

Several mechanisms have been proposed to explain the active stimulation of the infant's immune response by breastfeeding. One is based on animal experiments showing that transfer of anti-idiotypic antibodies against a bacterial and a viral antigen via milk resulted in priming of the offspring.^{13,44} In a preliminary study in germ-free newborn piglets, either anti-polio or anti-polio anti-idiotypic monoclonals, or both, were given orally at birth. A poliovirus vaccination at two weeks of age showed that those piglets who had been given the mix of idiotype and anti-idiotypic antibodies had the highest number of IgM anti-poliovirus secreting cells, followed by those who had obtained the idiotype antibodies only.⁴⁵ Such oral transfer of idiotype and anti-idiotypic antibodies may take place in humans because human milk is known to contain anti-idiotypic antibodies.²¹ In experimental systems such anti-idiotypic antibodies delivered orally could induce active protection.⁴⁶ The possible effect of monoclonal anti-idiotypic antibodies from mouse against the *E. coli* K13 polysaccharide over two subsequent generations when given orally was studied in neonatal rats.⁴⁷ Two-day-old pups were tube-fed with either 1 or 10 µg of IgG1 anti-idiotypic anti-K13. Six weeks later they were colonized in the intestine with *E. coli* O6K13 bacteria genetically manipulated to produce ovalbumin (OVA). At 4 months of age, the female rats were mated with naive males. The offspring, being the second generation, were colonized with the OVA-producing *E. coli* O6K13 at birth by their mothers. Whereas the rats in the first generation had not shown any major differences in their immune response to the bacteria, quite profound differences were noted in the second generation. Thus, there was a greatly increased antibody response not only to the idiotypically connected antigen K13, but also to the O6 LPS and the OVA of the bacteria. At this time, the proliferative response of spleen cells to OVA and the wild-type bacteria was lowered. The higher dose of the anti-idiotypic antibodies gave greater effects. These observations suggest that exposure of the neonate perorally to idiotypically connected antibodies against one bacterial component can affect and direct the immune response to other antigens on the same bacterium. In the neonatal rat, the Brambell Fcγ receptor protects the IgG from catabolism and may be crucial for the above results.⁵

The reason for the enhanced effect in the second generation is not clear, but might relate to that the animals in the first generation were exposed to the anti-idiotypic antibodies on only one occasion, whereas the second generation was presumably exposed continuously by their mothers. Another factor of likely importance is that the first generation was colonized at six weeks of age, whereas the second generation was colonized already from birth. We have noticed that neonatal colonization with bacteria leads to tolerance, while colonization at a later time induces a more intense immune response.⁴⁸ Thus, it might have been easier to note modulations of the immune response by the bacteria in the second generation. Nevertheless, it is striking that a relatively small amount of anti-idiotypic antibodies given in the neonatal pe-

riod can influence the immune system in a manner so profound that the effects could last for two generations.

The IgG2 antibody response to *H. influenzae* type b infection in children was enhanced by previous long-term (compared to short-term) breastfeeding.⁴⁹ This might well be an effect of exposure to idiotypic and anti-idiotypic antibodies in the milk together with effects attributable to the IFN- γ in the milk on the switching to IgG2 during lactation.

Quite remarkably, it has been found that lymphocytes from the milk are taken up and found in the intestinal mucosa and local lymph glands in a number of experimental models (for a review, see Ref. 50). The offspring becomes tolerized to the maternal major histocompatibility antigens. It has been noted that a kidney transplant to a person from the mother does significantly better if that person had been breastfed by the mother as a child.^{51,52} Breastfed infants have fewer cytotoxic T cells directed against the maternal HLA than non-breastfed infants.⁵³ Such milk lymphocytes from a sheep vaccinated against tetanus transferred to her lamb's intestine resulted in priming the lamb against the vaccine.⁵⁴ Using B cell deficient mice, it could be shown the functional Ig-secreting B cells were transferred from the mother via the milk.⁵⁵ Partial reconstitution occurred with B cells populating spleen and bone marrow.

Our ongoing studies in rat dams have shown that tolerance against ovalbumin can be transferred to the pups via the milk.⁵⁶ However, this effect was abrogated by a high maternal intake of polyunsaturated fatty acids. The ratio of n-6/n-3 fatty acids in the diet of the dams seemed to be of importance.

Exclusively breastfed infants have a thymus twice the size of that in non-breastfed infants, as measured with ultrasound.⁵⁷ This observation has yet to be explained.

Does Breastfeeding Protect against Immunological Diseases?

A recent critical review of the literature on whether breastfeeding protects against allergic diseases gave a surprisingly positive answer.⁵⁸ A few studies have indicated that breastfeeding also protects against celiac disease, at least in childhood,⁵⁹ and also ulcerous colitis, Crohn's disease, diabetes mellitus type I, rheumatoid arthritis, and multiple sclerosis, but this needs more study.⁶⁰

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REFERENCES

1. SCHELONKA, R.L. & A.J. INFANTE. 1998. Neonatal immunology. *Semin. Perinatol.* **22**: 2–14.
2. ADKINS, B. 1999. T-cell function in newborn mice and humans. *Immunol. Today* **20**: 330–335.
3. CRABBE, P.A. *et al.* 1970. Immunohistochemical observations on lymphoid tissues from conventional and germ-free mice. *Lab. Invest.* **22**: 448–457.

4. HORSFALL, D.J., J.M. COOPER & D. ROWLEY. 1978. Changes in the immunoglobulin levels of the mouse gut and serum during conventionalisation and following administration of *Salmonella typhimurium*. *Aust. J. Exp. Biol. Med. Sci.* **56**: 727–735.
5. JUNGHANS, R.P. 1997. Finally! The Brambell receptor (FcRB). Mediator of transmission of immunity and protection from catabolism for IgG. *Immunol. Res.* **16**: 29–57.
6. SOTO, H. *et al.* 1979. Transfer of measles, mumps and rubella antibodies from mother to infant. *Am. J. Dis. Child.* **133**: 1240–1243.
7. AVANZINI, M.A. *et al.* 1998. Placental transfer favours high avidity IgG antibodies. *Acta Paediatr.* **87**: 180–185.
8. HANSON, L.Å. *et al.* 1998. Undernutrition, immunodeficiency, and mucosal infections. *In* *Mucosal Immunology*. P. Ogra *et al.*, Eds. Academic Press. New York.
9. VARELA, F.J. & A. COUTINHO. 1991. Second generation immune networks. *Immunol. Today* **12**: 159–166.
10. LUNDKVIST, I. *et al.* 1989. Evidence for a functional idiotypic network among natural antibodies in normal mice. *Proc. Natl. Acad. Sci. USA* **86**: 5074–5078.
11. WIKLER, C. *et al.* 1980. Immunoregulatory role of maternal idiotopes: ontogeny of immune networks. *J. Exp. Med.* **152**: 1024–1035.
12. SEEGER, M. *et al.* 1998. Antigen-independent suppression of the IgE immune response to bee venom phospholipase A2 by maternally derived monoclonal IgG antibodies. *Eur. J. Immunol.* **28**: 2124–2130.
13. STEIN, K.E. & T. SÖDERSTRÖM. 1984. Neonatal administration of idiotypic or anti-idiotypic primes for protection against *Escherichia coli* K13 infection in mice. *J. Exp. Med.* **160**: 1001–1011.
14. MARTINEZ, C. *et al.* 1985. Establishment of idiotypic helper T-cell repertoires early in life. *Nature* **317**: 721–723.
15. MARTINEZ, C. *et al.* 1987. A functional idiotypic network of T helper cells and antibodies, limited to the compartment of “naturally” activated lymphocytes in normal mice. *Eur. J. Immunol.* **17**: 821–825.
16. CERNY, J., R. CRONKHITE & C. HEUSSER. 1983. Antibody response of mice following neonatal treatment with a monoclonal anti-receptor antibody: evidence for B cell tolerance and T suppressor cells specific for different idiotypic determinants. *Eur. J. Immunol.* **13**: 244–248.
17. AUGUSTIN, A. & H. COSENZA. 1976. Expression of new idiotypes following neonatal idiotypic suppression of a dominant clone. *Eur. J. Immunol.* **6**: 497–501.
18. RETH, M., G. KELSOE & K. RAJEWSKY. 1981. Idiotypic regulation by isologous monoclonal anti-idiotypic antibodies. *Nature* **290**: 257–259.
19. MELLANDER, L., B. CARLSSON & L.Å. HANSON. 1986. Secretory IgA and IgM antibodies to *E. coli* O and poliovirus type I antigens occur in amniotic fluid, meconium and saliva from newborns. A neonatal immune response without antigenic exposure: a result of anti-idiotypic induction? *Clin. Exp. Immunol.* **63**: 555–561.
20. HAHN-ZORIC, M. *et al.* 1992. Presence of non-maternal antibodies in newborns of mothers with antibody deficiencies. *Pediatr. Res.* **32**: 150–154.
21. HAHN-ZORIC, M. *et al.* 1993. Anti-idiotypic antibodies to poliovirus antibodies in commercial immunoglobulin preparations, human serum, and milk. *Pediatr. Res.* **33**: 475–480.
22. GOLDBLUM, R., L.Å. HANSON & P. BRANDTZAEG. 1996. The mucosal defense system. *In* *Immunological Disorders in Infants and Children*. 3rd edit. E. Stiehm, Ed.: 159–199. Saunders. Philadelphia, PA.
23. MATA, L.J. *et al.* 1969. *Shigella* infection in breast-fed Guatemalan Indian neonates. *Am. J. Dis. Child.* **117**: 142–146.
24. ADLERBERTH, I. *et al.* 1991. Intestinal colonization with Enterobacteriaceae in Pakistani and Swedish hospital-delivered infants. *Acta Paediatr. Scand.* **80**: 602–610.
25. ADLERBERTH, I., L.Å. HANSON & A.E. WOLD. 1999. Ontogeny of the intestinal flora. *In* *Development of the Gastrointestinal Tract*. I.R. Sanderson & W.A. Walker, Eds.: 279–292. B.C. Decker. Hamilton, Ontario.
26. GLASS, R.I. *et al.* 1983. Protection against cholera in breast-fed children by antibodies in breast milk. *N. Engl. J. Med.* **308**: 1389–1392.

27. CRUZ, J.R. *et al.* 1988. Breast milk anti-*Escherichia coli* heat-labile toxin IgA antibodies protect against toxin-induced infantile diarrhea. *Acta Paediatr. Scand.* **77**: 658–662.
28. RUIZ-PALACIOS, G.M. *et al.* 1990. Protection of breast-fed infants against *Campylobacter* diarrhea by antibodies in human milk. *J. Pediatr.* **116**: 707–713.
29. HAYANI, K.C. *et al.* 1992. Concentration of milk secretory immunoglobulin A against *Shigella* virulence plasmid-associated antigens as a predictor of symptom status in *Shigella*-infected breast-fed infants. *J. Pediatr.* **121**: 852–856.
30. WALTERSPIEL, J.N. *et al.* 1994. Secretory anti-*Giardia lamblia* antibodies in human milk: protective effect against diarrhea. *Pediatrics* **93**: 28–31.
31. LARSON, B.L. 1985. Determination of specific milk proteins. In *Human Lactation*. Vol. 1. R.G. Jensen & M.C. Neville, Eds.: 33–38. Plenum Press. London.
32. MATTSBY-BALTZER, I. *et al.* 1996. Lactoferrin or a fragment thereof inhibits the endotoxin-induced interleukin-6 response in human monocytic cells. *Pediatr. Res.* **40**: 257–262.
33. ELASS, E. *et al.* 2002. Lactoferrin inhibits the lipopolysaccharide-induced expression and proteoglycan-binding ability of interleukin-8 in human endothelial cells. *Infect. Immun.* **70**: 1860–1866.
34. HÅVERSEN, L.A. *et al.* 2000. Human lactoferrin and peptides derived from a surface-exposed helical region reduce experimental *Escherichia coli* urinary tract infection in mice. *Infect. Immun.* **68**: 5816–5823.
35. HÅVERSEN, L.A. *et al.* Anti-inflammatory activities of human lactoferrin and synthetic peptides thereof in experimental dextran-sulphate induced colitis in mice. Submitted for publication.
36. HÅVERSEN, L.A. *et al.* Lactoferrin inhibits the LPS-induced production of cytokines in THP-1 cells. In preparation.
37. BARBIER, M. *et al.* 1998. Elevated plasma leptin concentrations in early stages of experimental intestinal inflammation in rats. *Gut* **43**: 783–790.
38. ANDERSSON, B. *et al.* 1986. Inhibition of attachment of *Streptococcus pneumoniae* and *Haemophilus influenzae* by human milk and receptor oligosaccharides. *J. Infect. Dis.* **153**: 232–237.
39. HANSON, L.Å. *et al.* 2000. Nutrition resistance to viral propagation. *Nutr. Rev.* **58**: S31–S37.
40. HANSON, L.Å. 1998. Breastfeeding provides passive and likely long-lasting active immunity. *Ann. Allergy Asthma Immunol.* **81**: 523–533.
41. PABST, H.F. *et al.* 1989. Effect of breast-feeding on immune response to BCG vaccination. *Lancet* **1**: 295–297.
42. PABST, H.F. *et al.* 1997. Differential modulation of the immune response by breast- or formula-feeding of infants. *Acta Paediatr.* **86**: 1291–1297.
43. HAHN-ZORIC, M. *et al.* 1990. Antibody responses to parenteral and oral vaccines are impaired by conventional and low protein formulas as compared to breast-feeding. *Acta Paediatr. Scand.* **79**: 1137–1142.
44. OKAMOTO, Y. *et al.* 1989. Effect of breast feeding on the development of anti-idiotypic antibody response to F glycoprotein of respiratory syncytial virus in infant mice after post-partum maternal immunization. *J. Immunol.* **142**: 2507–2512.
45. LUNDIN, B.S. 1998. Regulation of the immune response to intestinal antigens. Ph.D. thesis, Göteborg University, Göteborg.
46. LUCAS, G.P., C.L. CAMBIASO & J.P. VAERMAN. 1991. Protection of rat intestine against cholera toxin challenge by monoclonal anti-idiotypic antibody immunization via enteral and parenteral route. *Infect. Immun.* **59**: 3651–3658.
47. LUNDIN, B.S. *et al.* 1999. Antibodies given orally in the neonatal period can affect the immune response for two generations: evidence for active maternal influence on the newborn's immune system. *Scand. J. Immunol.* **50**: 651–656.
48. KARLSSON, M.R. *et al.* 1999. Neonatal colonization of rats induces immunological tolerance to bacterial antigens. *Eur. J. Immunol.* **29**: 109–118.
49. SILFVERDAL, S.E. *et al.* 2002. Long-term enhancement of the IgG2 antibody response to *Haemophilus influenzae* type b by breastfeeding. *Pediatr. Inf. Dis. J.* **21**: 816–821.

50. HANSON, L.Å. *et al.* 2002. Immune system modulation by human milk. *In* Research Agenda for the Millenium: Integrating Population Outcomes, Biological Mechanisms and Research Methods in the Study of Human Milk and Lactation. C. Isaacs *et al.*, Eds.: 99–106. Kluwer Academic/Plenum.
51. CAMPBELL, D.A., JR. *et al.* 1984. Breast feeding and maternal-donor renal allografts: possibly the original donor-specific transfusion. *Transplantation* **37**: 340–344.
52. KOIS, W.E. *et al.* 1984. Influence of breast feeding on subsequent reactivity to a related renal allograft. *J. Surg. Res.* **37**: 89–93.
53. ZHANG, L. *et al.* 1991. Influence of breast feeding on the cytotoxic T cell allorepertoire in man. *Transplantation* **52**: 914–916.
54. TUBOLY, S. *et al.* 1995. Intestinal absorption of colostral lymphocytes in newborn lambs and their role in the development of immune status. *Acta Vet. Hung.* **43**: 105–115.
55. ARVOLA, M. *et al.* 2000. Immunoglobulin-secreting cells of maternal origin can be detected in B cell-deficient mice. *Biol. Reprod.* **63**: 1817–1824.
56. KOROTKOVA, M. *et al.* Modulation of neonatal oral tolerance to ovalbumin by maternal essential fatty acids intake during lactation in rats. Submitted.
57. HASSELBALCH, H. *et al.* 1996. Decreased thymus size in formula-fed infants compared with breastfed infants. *Acta Paediatr.* **85**: 1029–1032.
58. VAN ODijk, J. *et al.* Breast feeding and allergy: a multidisciplinary review of the literature (1966–2001) on feeding mode in infancy and its implications on later allergic manifestations. Submitted.
59. IVARSSON, A. *et al.* 2002. Breast-feeding protects against celiac disease. *Am. J. Clin. Nutr.* **75**: 914–921.
60. DAVIS, M.K. 2001. Breastfeeding and chronic disease in childhood and adolescence. *Pediatr. Clin. North. Am.* **48**: 125–141.