LINK TO ORIGINAL ARTICLE
LINK TO AUTHOR'S REPLY

Breastfeeding-related maternal microchimerism

Jean-Pierre Molès, Edouard Tuaillon, Chipepo Kankasa, Anne-Sophie Bedin, Nicolas Nagot, Arnaud Marchant, Joann M. McDermid and Philippe Van de Perre

We were fascinated by the Review article by Jeremy M. Kinder *et al.* (Immunological implications of pregnancy-induced microchimerism. *Nat. Rev. Immunol.* **17**, 483–494 (2017))[1], which discusses the bidirectional exchange of maternal and fetal cells during pregnancy and the potential benefits and harmful effects of this microchimerism. These cells may persist for a long time, and circulating maternal cells have been detected for up to 62 years in the offspring, resulting in the so-called maternal microchimerism (MMc). It has been estimated that, due to MMc, up to 1 in 5,000 peripheral blood mononuclear cells are of maternal origin[2].

In addition to pregnancy-related MMc, compelling evidence points to the existence of a postnatal MMc present in the infant, which is related to breastfeeding. Experiments in rodents and non-human primates[3,4], and limited human-based observations, support the idea that cells from breast milk may traffic from the mother to the infant's tissues through the gut mucosae. This phenomenon is likely to occur mainly during the early stages of lactation, at a time when breast milk cells are abundant and the infant's gut permeability is highest. The precise nature of the maternal cells present in breast milk that are involved in microchimerism is presently unknown but may include stem cells and progenitor cells as well as mature immune cells.

Colostrum (the form of milk produced in the first 4 days of lactation) contains high numbers of maternal cells of various types including epithelial cells, T and B lymphocytes, natural killer (NK) cells, dendritic cells, macrophages and others. In the weeks after birth, the immune cell concentration of breast milk decreases rapidly[5]. Breast milk lymphocytes consist mainly of an extra-lymphoid memory cell population[6]. Most $CD4^+$ and $CD8^+$ T cells are effector memory cells[7,8]. Up to 6% of breast milk cells are progenitor or stem cells of haemopoietic, mesenchymal and neuroepithelial lineages[9,10]. Some of these cells express markers that suggest a mesenchymal stem cell phenotype (CD90, CD44, CD271 and CD146), some express markers of embryonic stem cells (TRA-1-60, octamer-binding protein 4 (OCT4), NANOG and SOX2) and some express markers of luminal mammary epithelial cells (cytokeratin 18)[11]. Given their potential, breast milk stem cells are good candidates for long-term MMc in the infant intestinal tissues. Indeed, it is likely that infants may become tolerant to stem cells of maternal origin as these cells do not express MHC antigens.

A recent study from the group of Sing Sing Way established the cross-generational reproductive benefit conferred by maternal microchimerism, which involved the persistence of non-inherited maternal antigen-specific regulatory T cells of fetal origin in the genital tract of female offspring[12]. In this study, there was a direct quantitative relationship between MMc and cross-generational reproductive fitness. We can therefore hypothesize that, if tolerance and reproductive fitness (and potentially other consequences such as tissue healing and immune modulation) are quantitative functions of pregnancy-related MMc, breastfeeding-related MMc may increase these beneficial functions in the child in an additive or synergistic fashion.

The transfer of viable maternal immune and stem cells from breast milk to an infant may contribute to optimizing neonatal and infant immune system maturation, tissue repair and immune tolerance and thereby complement pregnancy-related MMc.

There is a Reply associated with this Correspondence by Jeremy M. Kinder, Ina A. Stelzer, Petra C. Arck and Sing Sing Way, *Nat. Rev. Immunol.* http://dx.doi.org/10.1038/nri .2017.117(2017).

Jean-Pierre Molès and Anne-Sophie Bedin are at Pathogenesis and Control of Chronic Infections, INSERM, EFS, Université de Montpellier, 34394 Montpellier, France.

Edouard Tuaillon, Nicolas Nagot and Philippe Van de Perre are at Pathogenesis and Control of Chronic Infections, INSERM, EFS, Université de Montpellier, 34394 Montpellier, France; and at CHU Montpellier, Department of Bacteriology-Virology and Department of Medical Information, 34295 Montpellier, France.

Chipepo Kankasa is at the University of Zambia, School of Medicine, Department of Paediatrics and Child Health, University Teaching Hospital, 10101 Lusaka, Zambia.

Arnaud Marchant is at the Institute for Medical Immunology, Université Libre de Bruxelles, B - 6041 CHARLEROI, Belgium.

Joann M. McDermid is at Division of Infectious Diseases & International Health, Department of Medicine, School of Medicine, University of Virginia, Charlottesville, Virginia, USA 22908.

Correspondence to P.VdP.
p-van_de_perre@chu-montpellier.fr

doi:10.1038/nri.2017.115
Published online 3 Oct 2017

1. Kinder, J. M. *et al.* Immunological implications of pregnancy-induced microchimerism. *Nat. Rev. Immunol.* **17**, 483–494 (2017).
2. Loubière, L. S. *et al.* Maternal microchimerism in healthy adults in lymphocytes, monocyte/macrophages and NK cells. *Lab. Invest.* **86**, 1185–1192 (2006).
3. Ma, L. J. *et al.* Trans-epithelial immune cell transfer during suckling modulates delayed-type hypersensitivity in recipients as a function of gender. *PLoS ONE* **3**, e3562 (2008).
4. Jain, L. *et al. In vivo* distribution of human milk leucocytes after ingestion by newborn baboons. *Arch. Dis. Child.* **64**, 930–933 (1989).
5. Goldman, A. S. *et al.* Immunologic factors in human milk during the first year of lactation. *J. Pediatr.* **100**, 563–567 (1982).
6. Sabbaj, S. *et al.* Breast milk-derived antigen-specific $CD8^+$ T cells: an extralymphoid effector memory cell population in humans. *J. Immunol.* **174**, 2951–2956 (2005).
7. Wirt, D. P. *et al.* Activated and memory T lymphocytes in human milk. *Cytometry* **13**, 282–290 (1992).
8. Valea, D. *et al.* $CD4^+$ T cells spontaneously producing human immunodeficiency virus type I in breast milk from women with or without antiretroviral drugs. *Retrovirology* **8**, 34 (2011).
9. Cregan, M. D. *et al.* Identification of nestin-positive putative mammary stem cells in human breastmilk. *Cell Tissue Res.* **329**, 129–136 (2007).
10. Fan, Y. *et al.* Unravelling the mystery of stem/progenitor cells in human breast milk. *PLoS ONE* **5**, e14421 (2010).
11. Sani, M. *et al.* Origins of the breast milk-derived cells; an endeavor to find the cell sources. *Cell Biol. Int.* **39**, 611–618 (2015).
12. Kinder, J. M. *et al.* Cross-generational reproductive fitness enforced by microchimeric maternal cells. *Cell* **162**, 505–515 (2015).

Author contributions
J.P.M., E.T. and P.VdP. participated in discussions and contributed to researching data related to this manuscript, and also the writing, review and editing of this manuscript. C.K., A.S.B., N.N., A.M. and J.M.M. participated in related discussions and contributed to the writing, review and editing of this manuscript.

Competing interests statement
The authors declare no competing interests.