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REPLY

# Reply: Breastfeeding-related maternal microchimerism

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We recently reviewed pregnancy-imprinted immunological shifts in mothers and offspring from the perspective of genetically foreign cells that establish microchimerism in both individuals after parturition (Immunological implications of pregnancy-induced microchimerism. *Nat. Rev. Immunol.* **17**, 483–494 (2017))[1]. Expanded tolerance between mothers and their offspring is widely conserved across mammalian species[2], suggesting that the bidirectional transfer and long-term persistence of microchimeric cells are purposeful, with beneficial properties that outweigh any potential harmful immunological consequences[3]. Immunological acceptance of non-inherited maternal antigens (NIMAs) in offspring reinforces tolerance to matched antigens expressed by the developing fetus during next-generation pregnancies[4,5]. However, these cross-generational benefits require the overlap of antigenic traits between maternal grandmothers and their fetal grandchildren and can be diluted with increased polymorphism among individuals within a population. A more universal benefit of microchimeric maternal cells could involve their multilineage potential in replacing malfunctioning cells in a variety of infant and childhood autoimmune and autoinflammatory disorders[6–9]. In addition, a recent study reported detectable microchimeric maternal cells in the cord blood of human infants that decreased the risk of symptomatic malaria infection, but which were associated with increased parasitaemia risk[10]. Thus, regardless of commonality in polymorphic antigenic traits, microchimeric maternal cells likely instil in offspring important protective benefits with regard to optimal regeneration of vital tissues and dampened pathological inflammatory responses to microbial invaders.

In their Correspondence (Breastfeeding-related maternal microchimerism. *Nat. Rev. Immunol.* http://dx.doi.org/10.1038/nri .2017.115(2017))[11], Moles and colleagues highlight the importance of maternal cells in breast milk and breast feeding for maintaining NIMA-specific tolerance. Along with the aforementioned cross-generational reproductive benefits[4,5], another classic example of NIMA-specific tolerance is the improved long-term survival of human donor allograft tissue if it is matched for the recipient's non-inherited maternal HLA haplotypes[12]. Interestingly, the improved survival of NIMA-matched tissue allografts is overturned among individuals that were not breast fed[13]. A similar requirement for postnatal ingestion of maternal antigen occurs in animal cross-fostering studies, in which elimination of the offspring's exposure to maternal breast milk overrides tolerance to NIMA-expressing donor allograft tissue[14] and reduces the accumulation of immunosuppressive forkhead box protein P3-positive ($FOXP3^+$) regulatory $CD4^+$ T cells ($T_{reg}$ cells) with NIMA specificity[4,15]. Importantly, however, postnatal ingestion of maternal antigens through breastfeeding alone does not confer immunological tolerance as cross-fostered mice neither accept NIMA-matched allografts nor have expanded levels of NIMA-specific $FOXP3^+$ $T_{reg}$ cells[4,14]. Thus, breastfeeding functionally potentiates, but does not bypass, the necessity for prenatal exposure to maternal cells and tissues in priming NIMA-specific tolerance.

Nonetheless, this apparent requirement for postnatal ingestion of maternal antigens through breastfeeding opens up an instructive experimental window for probing how NIMA-specific tolerance is sustained in offspring. In turn, the potent immunomodulatory effects of maternal cells in breast milk suggest that it may be possible to therapeutically optimize their beneficial properties in offspring. As pointed out by Moles and colleagues in their Correspondence[11], breast milk and colostrum contain different immune cell populations, including memory lymphocytes, professional antigen-presenting cells, along with embryonic and mesenchymal stem cells. Given this diversity, further dissecting the unique immunological and non-immunological benefits of each cell subset will shed important new light on how microchimeric cells influence health and disease.

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**Competing interests statement**
The authors declare no competing interests.