Breastmilk imparts the mother's stem cells to the infant: boosting early infant development?

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Breastmilk is a complex fluid containing a plethora of biochemical and cellular components that confer nutritional, immunological and developmental benefits to the infant. Although its biochemical composition has been extensively studied, breastmilk cells have received little attention. In the last decade, technological advancements in microscopy, flow cytometry and molecular biology have aided investigation of breastmilk cells, revealing some of their unique attributes and instigating potential applications. Contrary to previous belief, immune cells have been shown to constitute a minority in mature human milk when both the mother and infant are healthy. Periods of infection, however, stimulate a rapid increase in breastmilk immune cell numbers, returning to low baseline levels upon recovery. This observation highlighted that during healthy periods, the majority of cells in human milk are of non-immune origin. Flow cytometric analyses revealed that epithelial cells such as lactocytes, and to a lesser extent myoepithelial cells, comprise the majority of cells in mature human milk throughout lactation. In addition to those cells, stem and progenitor cells have been identified in breastmilk. Some of these stem cells display the known properties of mammary stem cells, being able to turn into functional lactocytes synthesising milk in culture. Interestingly, subpopulations of breastmilk stem cells appear to be extremely plastic, and able to turn into cells from all three germinal layers, including neurons, glia, hepatocytes, pancreatic cells, cardiomyocytes, osteoblasts, chondrocytes and adipocytes. They were also shown to express embryonic stem cell genes controlling self-renewal and differentiation, potentially facilitating the multi-lineage properties of these cells. Examination of the human resting and lactating mammary gland demonstrated that these cells exist in the lactating mammary epithelium, being scarce in the resting breast. Given that a term breastfed infant consumes 470–1300 mL of breastmilk daily and that the cellular content of human milk ranges from 10,000 to 13,000,000 cells/mL milk, it can be calculated that a breastfed infant ingests millions to billions of cells from mother's milk every day. What is the fate of these cells? To shed light into this, we used a mouse model to test tissue distribution and latency of milk stem cells in the neonate. Mothers that ubiquitously express TdTomato (TdT) cross-fostered wild type pups, which were imaged during the breastfeeding period, but also in adulthood. In the breastfed pups, milk-derived TdT+ cells were seen in the stomach and thymus. No TdT+ cell was found in wild-type controls nursed by their biological mothers. Flow cytometric analysis of blood collected from these pups revealed the presence of TdT+ milk cells in the blood, suggesting survival of some milk cells and migration into the blood circulation. Organs of these mice were extracted, fixed in formalin and embedded in paraffin, and were sectioned and immune-stained for confocal microscopy. TdT+ cells were seen in the stomach cavity as well attached to and penetrating the gastric lining. TdT+ cells were also noted in the thymus, liver, pancreas, spleen, and brain. Some of these TdT+ cells expressed stem cell markers OCT4, NANOG and CD49f. The thymus and to a lesser extent the liver and the other examined organs harbored clones of TdT+ milk-derived cells expressing the stem cell markers. In close proximity to the double positive population we observed TdT+ milk-derived cells with low or no expression of the stem cell markers, suggesting differentiation and assimilation with host tissue and/or homing of other types of TdT+ milk cells in these organs. Indeed, albumin+ TdT+ milk cells were found in the liver; insulin+ TdT+ milk cells were seen in the pancreas; and MAP2+ TdT+ milk cells were observed in the brain. These data suggest functional differentiation of milk stem cells in the organs of the neonate. Moreover, TdT+/CD45+ milk immune cells were also observed in many of the examined organs, particularly in the thymus. Blood of cross-fostered pups was also examined post-weaning into adulthood, revealing that some TdT+ milk-derived cells persisted in the blood even after breastfeeding stopped. These findings provide the first evidence of survival of milk stem cells in the neonate, and indicate migration and functional integration into organs, where they may provide developmental benefits to the offspring.

References

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