Review Article

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Breast Milk Stem Cells and Maternal Microchimerism: Mechanisms and Clinical Implications

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ABSTRACT

Human breast milk is recognized as a living, cell-rich fluid that provides viable maternal cells along with supplementary nutrients and soluble immunomodulators. It contains heterogeneous populations of mesenchymal, hematopoietic, epithelial, and pluripotent-like stem/progenitor cells that can differentiate into derivatives of all three germ layers in vitro. Preclinical studies have shown that milk-derived cells can survive gastrointestinal passage, enter the neonatal circulation, and reside in multiple organs, such as the brain, liver, and immune tissues. These cells express organ-specific markers and contribute to maternal microchimerism. Studies on the neonatal gut and blood-brain barrier show that a narrow early-life window exists in which breast milk stem cells can access systemic and, in experimental models, central nervous system compartments. This window is established by immature intestinal barrier properties, age-dependent differences in neurovascular interfaces, and homing cues induced by injury or inflammation. It has been suggested that these cells may contribute to organ maturation and tissue repair. Maternal cell transfer during lactation has been associated with the expansion of regulatory T cells, tolerance to non-inherited maternal antigens, stronger vaccine-induced T-cell responses, and, in certain circumstances, improved infection control. These results collectively support the idea that maternal cellular transfer contributes to the development of infant immunity during the early stages of life. This review provides a concise summary of the phenotype and origin of breast milk stem cells, their trafficking and contribution to maternal microchimerism, neonatal immune development, and the clinical implications for the health of both infants and mothers.

Breastfeeding is strongly emphasized in clinical guidelines due to its beneficial effects on infection, necrotizing enterocolitis, and long-term metabolic outcomes, which are primarily due to its balanced nutrient content, bioactive molecules, and immune cells[1, 2]. Recent research has established a new dimension: breast milk stem cells (BMSCs), a heterogeneous population that includes mesenchymal, hematopoietic, and epithelial progenitors with documented multilineage differentiation potential in vitro across all three germ layers. This potential confirms that human milk may serve as a naturally delivered cellular therapy in early life[3, 4]. BMSCs are believed to be involved in the exchange of cells between the mother and the neonate during lactation[5]. The concept is based on the broader biology of maternal microchimerism (MMc), which refers to the presence of maternal cells in the organs of the neonate[6-8]. In this context, lactation is not merely a means of feeding; it is also a pathway for biological transmission that has the potential to impact the immune interactions between the mother and the infant, as well as the development of the infant.

The clinical significance of this field has increased due to the ability to collect BMSCs noninvasively, expand them in culture, and direct them toward multiple lineages using experimental conditions[1, 9]. This property makes them attractive for translational research in mammary biology, regenerative medicine, and neonatology. Meanwhile, the potential for milk-derived cells to integrate into neonatal tissues, such as the brain, raises significant questions about their physiological role in immune programming and organ maturation. MMc has emerged as a clinically pertinent phenomenon, rather than a biological curiosity. In the offspring, maternal cells that are transferred during lactation may contribute to immune tolerance, T-cell maturation, and potentially long-term health outcomes[6, 9]. This presents a novel perspective on lactation for clinicians: in addition to the well-established nutritional and immunologic advantages, human milk may also provide viable maternal cells with reparative and developmental potential.

This review aims to summarize the current evidence on BMSC phenotype and origin, describe the preclinical evidence for cell transfer and tissue integration, discuss microchimerism and neonatal immune development, review clinical and maternal health implications, and address future research considerations. The literature for this review was identified through searches of PubMed and Google Scholar; only peer-reviewed articles published in English were considered.

Phenotype and Origin of Breast Milk Stem Cells

Human milk is composed of rare stem/progenitor cells, leukocytes, myoepithelial cells, and epithelial cells, which are primarily derived from the mammary epithelium during lactation[10]. Stem cell populations identified in human breast milk include hematopoietic progenitors expressing CD34 and CD133, mesenchymal stem cells characterized by CD90, CD105, CD73, CD44, and CD29, mammary stem/progenitor cells marked by CK5 and CK14, and neuro-progenitor cells expressing nestin[11-13]. The pluripotency-associated transcription factors OCT4, SOX2, and NANOG, which are core components of the embryonic stem cell self-renewal network, are significantly upregulated in the lactating mammary epithelium relative to the non-pregnant breast, where their expression is minimal yet detectable[4, 14].

In vitro, putative stem cells isolated from human breast milk can form spheroids or colonies and express markers such as nestin and a panel of pluripotency-associated transcription factors consistent with clonogenic behavior[12, 15]. Under appropriate culture conditions, these cells differentiate toward mesodermal, ectodermal, and endodermal lineages[4, 15]. BMSCs can be collected noninvasively, making them an attractive autologous source for future applications in regenerative medicine,

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mammary biology research, and lactation studies. Recent studies have revealed that the cellular composition of human milk undergoes substantial quantitative and qualitative changes throughout lactation. The proportion of hematopoietic stem/progenitor cells in mature milk is significantly higher than that in colostrum, and it is further influenced by the gestational age at delivery[16].

The biological features of BMSCs raise the question of their ability to survive and maintain functional potential following ingestion by the newborn and the possibility of reaching tissues outside the neonatal gut.

Evidence for Cell Transfer and Tissue Integration in Offspring

Animal models using labeled milk cells in mice and non-human primates demonstrate that milk-derived cells survive and integrate into neonatal tissues[17, 18]. In murine experiments, milk cells were observed to traverse the gut and engraft into neonatal tissues[19]. In a primate model, ingested human milk leukocytes were detected systemically in neonatal baboons, illustrating dissemination beyond the gastrointestinal tract[20]. Recent research has shown that labeled BMSCs can be monitored in suckling pups and are present in a variety of organs, such as the brain, spleen, liver, pancreas, thymus, and stomach[19, 21]. These cells express organ-specific proteins, which suggests functional integration. BMSCs located in the brain express NeuN and GFAP, indicating that they underwent differentiation into both neuronal and glial cell types[17]. These results confirm the concept that lactation provides viable maternal stem and immune cells that contribute to the establishment of postnatal MMc and may affect organ development and repair.

Crossing Mucosal and Neurovascular Barriers: Mechanistic Considerations

BMSCs must traverse the intestinal epithelium and, in some cases, cross the blood-brain barrier (BBB) in order to exert systemic and neurological effects[22]. The BBB is a specialized neurovascular interface formed by tightly connected brain microvascular endothelial cells, pericytes, and astrocytic end-feet that stringently regulates the entry of molecules and cells into the central nervous system (CNS)[23]. A plausible mechanism for central nervous system entry is the transmigration of mesenchymal stem cells across brain microvascular endothelial layers via transient inter-endothelial gaps. The developing BBB is functionally active but demonstrates distinct permeability characteristics in comparison to adults. These properties are influenced by the maturation of endothelial tight junctions and perivascular support cells. It should be noted that direct experimental evidence for BMSCs transmigration across the human neonatal BBB is not yet available.

The conditions that enable this trafficking are not merely passive. The neonatal intestinal epithelium demonstrates a higher paracellular permeability and immature tight junction organisation in early life, whereas the BBB is already functionally established but is still undergoing structural maturation. The BBB is characterized by evolving pericyte coverage and a greater susceptibility to permeability changes under inflammatory or hypoxic stress. Collectively, these attributes establish a biological window that is time-limited and coincides with the early lactation period. This window may facilitate the entry of maternal cells into the central nervous system and systemic access, at least in animal models. Stem cell recruitment is further enhanced by inflammatory and hypoxic signals via the HIF-1α/SDF-1/CXCR4 axis. This suggests that maternal cellular transfer is context-dependent and is likely to be more intense in injured or stressed neonatal tissues, where reparative signals are most potent[24-29]. Although BMSCs have not yet been assessed in hypoxic–ischemic encephalopathy (HIE) models, the shared mesenchymal-like phenotype and injury-directed homing properties between BMSCs and umbilical cord–derived MSCs indicate that milk-derived cells may be worth investigating in this context in the future,

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particularly due to their noninvasive availability and natural delivery during the neonatal period[29-31].

Microchimerism and Immune System Maturation

Maternal microchimerism has considerable immunological repercussions and extends beyond pregnancy through lactation. Maternal cells transferred during gestation and breastfeeding are closely linked to the induction of tolerance to non-inherited maternal antigens (NIMAs), the subset of maternal HLA alloantigens not present in the offspring's own genotype. Continuous exposure to these antigens in breast milk promotes the expansion of NIMA-specific FOXP3$^+$ regulatory T cells, which actively suppress anti-maternal immune responses and establish durable antigen-specific immune tolerance[6, 32]. Human data confirm this mechanism: exclusively breastfed neonates exhibit nearly twice the proportion of Tregs compared to formula-fed infants, and this Treg expansion is specifically associated with reduced proliferative responses to maternal, but not unrelated, antigens. This suggests that the tolerogenic effect is antigen-specific and cellular, rather than merely nutritional[33]. This tolerance mechanism may have long-term repercussions on the outcome of organ transplantation and the susceptibility to autoimmune disease.

The immunological effects of cell trafficking during breastfeeding are validated by human cohort studies that associate the extent of MMc with vaccine-induced T-cell responses. Molès et al. investigated animal and limited human data that support the notion that breastfeeding cell trafficking contributes to MMc and may facilitate immunological maturation in infants[6]. Balle and colleagues subsequently provided quantitative human data showing that higher levels of microchimerism at birth correlate with more robust polyfunctional CD4+ T-cell responses to BCG vaccination at 7 and 15 weeks of age[34], supporting the idea that microchimerism contributes to vaccine responsiveness and infection resistance in early life. This suggests that the infant's immune responses may be indirectly influenced by maternal health status and breastfeeding patterns through cellular components.

Clinical Evidence in Neonatal Disease

Although the majority of evidence on BMSCs is preclinical, there are emerging translational links to neonatal conditions. A recent review of BMSCs in neonatal disease discussed their potential effects on NEC, HIE, BPD, intraventricular hemorrhage, and sepsis, primarily through paracrine effects (anti-inflammatory, anti-apoptotic, pro-angiogenic) and potential direct tissue integration[5, 9, 35]. In human observational studies, neonates who receive mother's own milk, which contains a rich cellular fraction including exosomes and BMSCs, have demonstrated improved clinical outcomes[9]. However, the specific contribution of BMSCs and other cellular elements within this complex matrix has not yet been clearly defined. These findings are consistent with broader clinical data showing lower rates of NEC and improved neurodevelopmental outcomes in preterm infants with mother's own milk, as opposed to formula or donor milk. This suggests that the cellular fraction may contribute to the clinical benefits beyond macronutrients and antibodies.

Maternal Health Implications of BMSCs

BMSCs are most relevant to maternal health as a research and diagnostic resource, rather than as a disease risk to the mother. Given that BMSCs are derived from the mammary epithelium and are released into milk during lactation, they offer minimally intrusive access to mammary gland biology and potential applications in the early biomarker detection of breast cancer and the characterization of lactation problems[5, 11, 36]. Due to their accessibility, BMSCs have also been suggested as a potential autologous stem cell source for regenerative applications related to maternal health.

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BMSCs are distinct from fetal microchimerism, a separate, opposite-direction phenomenon that is more controversially linked to maternal autoimmune conditions such as systemic sclerosis and autoimmune thyroid disease[37]. Fetal microchimerism is the process by which fetal cells persist in maternal tissue after pregnancy. To date, no reliable evidence has been found that BMSCs themselves pose an autoimmune risk to the mother. The autoimmune associations that have been documented in the microchimerism literature are the consequence of fetal cells acting on maternal tissue, rather than BMSC transfer.

Limitations and Future Perspectives

The promise of BMSCs is accompanied by several limitations that also define priorities for future research. First, the full trafficking pathway from oral ingestion to organ integration has only been demonstrated in animal models and has not yet been observed in human neonates. Secondly, the specific contribution of the cellular fraction, compared with other bioactive components of milk has not been isolated in any trial, which means that clinical benefits cannot be attributed to BMSCs alone. Finally, the comparability of existing studies is still restricted by the absence of standardized, widely accepted protocols for BMSC isolation and characterization across lactation stages and maternal–infant contexts.

Conclusion

Breast milk is now more commonly recognized as a multifaceted bioactive fluid that not only provides nutrients but also viable maternal cells and extracellular vesicles. These cells may play a role in the organ development and neonatal immunity. The ability of milk-derived cells to survive gastrointestinal passage, disseminate systemically, and integrate into multiple organs, including the brain, has been shown in preclinical studies in rodents and nonhuman primates. Furthermore, human cohort data have established a correlation between MMc and vaccine-induced T-cell responses and early immune maturation. Collectively, these results support the hypothesis that BMSCs and other maternal cells transferred during lactation contribute to microchimerism, immune education, and potentially tissue protection. Additionally, they establish milk-derived cells as a distinctive, noninvasive window into mammary biology and maternal health. Any experimental or translational use of breast milk-derived cells should be conducted with meticulous attention to ethical and regulatory safeguards, including appropriate informed consent and long-term safety monitoring.

Conflict of Interest

None declared.

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Ethical Considerations

Not applicable. This manuscript is a review article and does not contain original data from human participants or animals.

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Author's Contribution

SS conceived the review, performed the literature search, drafted the manuscript and approved the final version.

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