

Pluripotent Stem Cells: the Hidden Treasure of the Human Milk

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Editorial

For many decades, most of the milk compositional research has been centered on its bioactive molecules^[1]. In addition to its biochemical composition, milk contains maternal cells that are live in fresh milk, suggesting that they have specific functions in the milk-fed young^[2]. Nevertheless, very little is known about human milk cellular component, the origin, the properties and the factors influencing breast milk cells. Although, it has been over 170 years since the first observation of cells in milk, yet it is only in the last decade that research on human milk focused the existence of breast milk stem cells^[3]. At the beginning, milk cell research was based on studies of both bovine milk and on few studies on colostrums or early lactation breast, perpetuating the thought that the leukocyte is the predominant cell type in human milk. At that time, a major hurdle was the lack of knowledge about factors that influence the cellular composition of breast milk, such as the stage of lactation or the health status of the mother and infant, which may have contributed to the classification controversy between early investigators^[1]. However, recent analyses using state of the art techniques have resulted in a shift in the previously believed dogma that the dominant cell type in human milk is the immune cell^[4]. Leukocytes constitute only a small minority ($\leq 2\%$) of the cells in mature human milk when both the mother and infant are healthy^[4]. Indeed, in contrast to the milk of other mammalian species, such as the cow, after the first 1 - 2 weeks postpartum, human milk is dominated

by non-immune cells, which is what the infant receives for the majority of the breastfeeding period^[4]. This raises the question of the nature, the fate and the functions of the remaining $\geq 98\%$ of breast milk cells. The breast is a unique organ in that it fully matures during pregnancy and lactation, when it undergoes complete remodeling of its epithelium and stroma to support the synthesis and secretion of milk and its delivery to the infant^[5]. This ability for massive proliferation and self-renewal during pregnancy suggested the presence of stem cells in mammary tissue since 1970s^[6]. Since then, several evidences demonstrated the existence of mammary stem cells (MaSCs) in murine models. MaSCs are responsible for the changes that occur in the breast during this period because are able to produce both cell types of the mammary epithelium: myoepithelial cells and luminal cells^[6]. The identity and properties of intermediate steps along breast cellular hierarchy are still poorly understood, which is particularly so far for the human breast in its fully mature state, that is during lactation. This may be partly due to the scarcity of human lactating breast and the low numbers and quiescent state of MaSCs in the resting breast. Interestingly, in 2007, Cregan *et al* demonstrated, for the first time, the presence of cells with mammary stem/progenitor properties in human breast milk-derived cultures^[7]. This finding candidates breast milk as an excellent system to study the role of stem cells in normal development and carcinogenesis, since it represents a non-invasive and easily



accessible source of MaSCs. During this last decade, a growing body of evidence demonstrated that cellular composition of breast milk reflects the cellular composition hierarchy of the mammary lactating epithelium, including the presence of epithelial progenitors and cells with stem cell properties^[8]. MaSCs found in breast milk, called by Hassiotou human breast milk stem cells (hBSCs)^[3], displayed the two hallmark properties of “stemness”, since they were shown to be to multipotent *in vitro*, being able to both self-renew and differentiate into the two main mammary epithelial lineages: luminal cells and myoepithelial cells^[8]. Soon thereafter, a new discovery further revolutionized the field, due to the finding of hBSCs expressing the self-renewal core transcription factors network governing pluripotency and undifferentiated state in human embryonic stem cells (hESCs). Noteworthy, such cells were found almost absent in the normal breast. hBSCs have been shown to be extremely plastic and able to turn into cells from all three germ layers, including neurons and glia, hepatocytes that synthesise albumin and other liver-specific factors, pancreatic beta-like cells that synthesize insulin, osteoblasts, chondrocytes, adipocytes and cardiomyocytes^[8]. Interestingly, despite of hESCs or induced-pluripotent stem cells (iPSc), these somatic pluripotent stem cells are incapable of forming tumours in the teratoma assay, suggesting their safety for cell replacement therapies^[1]. Yet, in a mouse model it has been recently demonstrated that hBSC are able to survive in the gastrointestinal tract of the offspring, to transfer to the bloodstream and to integrate into different tissues *in vivo*^[9]. This phenomenon, called micro-chimerism, it was already known to occur in utero and it seems to continue via breastfeeding after birth. Consequently, it is even possible to think to the possibility to bank hBSC for their retrospective therapeutic usage, similar to cord blood stem cell banking. With these discoveries, the application of hBSCs extends far beyond the field of lactation and cancer. Regenerative medicine and stem cell biology may also benefit from utilizing these cells. In this last decade, it has become even more evident that breast milk is far more than just a nutrient supply and its benefits go even beyond the developmental programming and protection of neonate. In the infant, thousand to millions of viable hBSCs are ingested daily during breastfeeding. This implies a function, irreplaceable with artificial formulas. Replying to an old question raised in an Editorial of 1998 entitled: “The long-term effects of breastfeeding: a role for the cells in breast milk?”^[10] we can answer that even if, still today, we are only on the surface of the knowledge, most likely, the long-term effects of breastfeeding reside in breast milk cellular components. Starting from the need to standardize breast milk collection, advances in research on hBSC have become essential to clarify their physiological role and their possible applications in regenerative medicine, stem cell therapy and breast pathology.

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