Exploiting the evolution of lactation: a new paradigm for intervention strategies to improve health outcomes of preterm babies

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Significantly preterm babies have diminished lung, gut and brain development, generally fail to thrive, have increased mortality and higher frequency of mature-onset disease presumably resulting from the disruption to timing of developmental clocks. The latter condition can be exacerbated if the growth rate of the baby is accelerated too rapidly during treatment. However, mothers often cannot breastfeed, and babies receive either formula or pasteurized human donor milk. The bioactivity of the donor milk is potentially compromised due to processing and both breast-fed and donor milk fed preterm babies require an additional milk fortifier to meet their nutritional requirements for optimal growth. New innovative approaches are required to manage the early stages of neonatal treatment that provide both appropriate nutrition and signaling for tissue development without an accompanying large increment in growth.

Exploiting comparative approaches to better understand the evolution of lactation is providing new insights into the role of milk in acute and chronic development of the baby. For example, the tammar wallaby (an Australian marsupial) evolved about 140 million years ago with a very different reproductive strategy to eutherians (eg humans). The tammar has a short 26 day gestation, a simple placenta and gives birth to an altricial young equivalent to a final trimester, preterm human embryo. Both the tammar newborn and the preterm human baby will receive milk to sustain their development. The tammar neonate will receive milk that is appropriate for growth and development of a healthy juvenile. However, the preterm baby will continue to face serious acute and chronic health challenges that may limit recovery. This poses an interesting question; can understanding the temporal delivery of milk bioactives to the tammar neonate provide new options for intervention strategies to better manage preterm babies?

The tammar neonate remains in the pouch and permanently attached to the teat for 100 days postpartum and a large component of organ development and function occurs postnatally. During this time the mother slows growth of the young and progressively changes the composition of the milk to deliver signals for organ development, including the lung and gut, and potentially the brain. Therefore, examining timed delivery of bioactives in marsupial milk in the early phase of lactation may provide a better understanding of the continuum of the signalling program of the placenta, amniotic fluid, colostrum and milk required for normal eutherian development. A good example is the correlation between temporal delivery of milk bioactives in the tammar and early postnal development of the lung. The lung is so immature at birth the neonate respirates through the skin for the first 2 weeks. Studies using *in vitro* models have shown that milk collected from marsupials during early lactation (day 20-100), but not late lactation (day 100-300) stimulated

proliferation and differentiation of cultured whole lung from mouse embryos, and these signalling molecules were directed to differentiation of both lung epithelial and mesenchymal cells. This temporal delivery of bioactivity provides a window to search for the specific signalling molecules in the milk and to use comparative approaches to examine human colostrum and milk for homologues of these putative signals.
A second more expansive approach has exploited the comparison of data sets of differentially expressed genes in the tammar mammary gland during the first 100 days of lactation, cells from human milk and colostrum, placenta and the amniotic fluid. A focus only on genes coding for secreted proteins has allowed for a comparison of potential protein signalling molecules secreted by these tissues. This analysis has identified a number of proteins of interest in placenta and amniotic fluid, and unexpectedly identified a large dataset of signalling candidates in colostrum prompting the need to re-examine the role of colostrum for development of both term and preterm babies.

Exploiting these new approaches provides options to understand the role of milk in acute and chronic development of the baby. Studies using the tammar wallaby may lead to a new range of human milk fortifiers that include bioactives to specifically target tissue development in the human neonate to improve outcomes for preterm and babies with application in the developed and developing world.