Human Milk MicroRNAs/Exosomes: Composition and Biological Effects

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Human milk provides many benefits to the breastfed infant resulting in significantly better short- and long-term outcomes compared to formula-fed infants. These benefits are likely achieved by a well-balanced supply of nutrients and wide variety of bioactive components in breast milk. These components include long-chain fatty acids (e.g., DHA), complex oligosaccharides, bioactive proteins (e.g. immunoglobulins, lactoferrin, and osteopontin), nucleotides, and lutein. By various mechanisms that have been extensively studied, they protect the infant against infections and stimulate brain development and visual function.

More recently, it was discovered that breast milk also contains exosomes, i.e., microvesicles consisting of microRNAs (miRNAs) with sizes of ~22 nucleotides [1]. Exosomes are small extracellular vesicles about 30–100 nm in size and are produced by a variety of cells, including macrophages, lymphocytes, dendritic cells, epithelial cells, and tumor cells. They are found in physiological fluids such as plasma, urine, and malignant effusions. It is well known that exosomes are important in cell-cell signaling, but their physiological significance in vivo is less known. Early studies suggested promising roles in immunotherapy and cancer therapy, but this is a rapidly advancing field, and many clinical trials are ongoing. It was shown that isolated milk exosomes could affect immune responses of PBMCs and T-regulatory cells [1]. A subsequent study on miRNA expression in breast milk found large numbers of miRNAs (281 of 723 human miRNAs known at that time) and, in particular, high levels of immune-related miRNAs during the first 6 months of lactation [2]. Several breast milk miRNAs have been shown to originate from the mammary gland [3], and many of them are involved in cellular development and immune function.

Exosome-mediated transfer of miRNAs is a novel mechanism of genetic exchange between cells. It is therefore possible that exosomes in milk may survive digestion and deliver miRNAs to intestinal cells, or, if transferred into the blood stream, to cells in other tissues. In vitro
digestion experiments mimicking conditions in the infant gut have shown that exosomes and their miRNA cargo can survive proteolytic digestion [4]. Further, when human intestinal epithelial cells in culture were exposed to exosomes isolated from breast milk that was undigested or subjected to in vitro digestion, it could be shown by confocal microscopy that the cells could take up exosomes from both untreated and in vitro digested breast milk and that they migrated to the nucleus [4]. Therefore, it is possible that breast milk exosomes may affect gene transcription in the small intestine. Research on human adults consuming cow milk in various amounts has shown that major bovine milk miRNAs are found in the circulation postprandially and in a dose-dependent manner, further suggesting that exosomes can resist conditions in the gastrointestinal tract and be delivered to the systematic circulation [5]. Thus, it is possible that milk miRNAs may transfer genetic material to the infant and thereby affect gene transcription and regulation of cellular events in several tissues.

References