Human Milk Proteins: Composition and Physiological Significance

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Human milk (HM) is the ideal food that ensures optimal growth and development of infants [1]. In addition, HM contains a wide variety of bioactive components, including lipids, oligosaccharides, and proteins. Over the past 30 years, infant formulas have undergone dramatic changes in nutritional composition to more closely mimic that of HM [2]. However, clinical and epidemiological studies show that differences in short- and long-term health outcomes still persist between breastfed and formula-fed infants, including growth patterns, nutritional status, gut microbiota composition, prevalence of infection, and health outcomes [1]. HM contains over 400 proteins that can be broadly classified into 3 categories: caseins, whey proteins, and mucins, which are present in the milk fat globule membrane (MFGM). HM is whey predominant, but the whey/casein ratio of HM changes during the course of lactation, being 90/10 in colostrum and changing to 60/40 in mature HM. The predominant caseins in HM are β and κ, whereas bovine milk contains α, β, γ, and κ caseins. The proteins present in significant quantities in the whey fraction are α-lactalbumin, lactoferrin, IgA, osteopontin (OPN), and lysozyme. The predominant whey protein in bovine milk is β-lactoglobulin, although low concentrations of α-lactalbumin, lactoferrin, and OPN in bovine milk have enabled their isolation and utilization in preclinical and clinical trials. Additionally, bioactive peptides are formed during the digestion of casein and whey, and glycans from glycoproteins are bifidogenic, adding further complexity to the functional properties of HM proteins. These functions include: serving as a source of amino acids; improving the bioavailability of micronutrients, including vitamins, minerals, and trace elements, providing stimulation of intestinal growth and maturation; supporting immunologic defense; shaping the microbiome; and enhancing learning and memory (Fig. 1) [2, 3]. Recent advances in dairy technology have enabled the isolation of bioactive milk proteins from bovine milk in sufficient quantities for clinical investigations and, in some cases, addition to commercially available infant formulas [2].
Herein, the current evidence on HM protein composition and bioactivity of HM proteins will be reviewed, with a focus on lactoferrin, OPN, and the MFGM [4]. Lactoferrin is a non-heme iron-binding protein that has been shown to beneficially impact iron absorption in the breastfed infant and exert bacteriostatic effects. In the piglet model, bovine lactoferrin stimulated intestinal cell proliferation. In randomized controlled clinical trials, bovine lactoferrin reduced diarrhea and respiratory illnesses in term infants and sepsis and necrotizing enterocolitis in preterm infants [5]. OPN is an acidic, glycosylated, and highly phosphorylated protein. It interacts with cell surface integrins and the CD44 receptor to influence biomineralization, tissue remodeling, and immune regulation. Bovine OPN supplemented to formula at the concentration present in HM changed intestinal gene expression in rhesus monkeys to be more similar to breastfed monkeys. In a randomized controlled clinical trial, bovine OPN reduced fever incidence and serum TNF-a concentrations [4]. Lastly, MFGM is the triple membrane system that encapsulates milk fat. It contains cellular components, including cholesterol, glycerol phospholipids, sphingolipids, and proteins, including mucin 1, butyrophilin, CD36, adipophilin, and lactadherin. These bioactive components contribute to the antiviral and antibacterial activities of MFGM. In randomized controlled clinical trials, MFGM from bovine milk reduced diarrhea, fever, and antipyretic use and increased IQ [4]. In summary, HM contains many bioactive proteins that act independently and synergistically to

![Diagram](image)

**Fig. 1.** Biological functions of human milk proteins.
provide multilayer defense against infection, as well as stimulate intestinal and cognitive development and shape the microbiome. Purification of bioactive proteins from bovine milk have allowed clinical trials in infants and will ultimately enable modifications in infant formula composition to narrow the differences in health outcomes between breastfed and formula-fed infants.

References