Human Breast Milk and the Gastrointestinal Innate Immune System

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KEYWORDS

• Mucosal innate immune system • Human breast milk • Bioactive factors
• Lactoferrin • Antimicrobial peptides • Commensal bacteria • Intestinal microbiome

KEY POINTS

- Newborns infants are in a susceptible immunologic state after birth, with an immature adaptive immune system, making them reliant on their innate immune system for protection.
- The gastrointestinal innate immune system is comprised of many components. The acidic environment in the stomach and the mucus layer of the small intestine provide an initial barrier. The intestinal epithelial cells create a physical barrier and are involved in signaling to the underlying tissue. The lamina propria is rich in immune cells and contributes greatly to intestinal defense.
- In addition to providing optimal nutrition to infants, human breast milk has an abundance of bioactive factors that act as a part of the innate immune system of the gastrointestinal tract. Some factors have intrinsic properties that act as part of the defense system, whereas others enhance the ability of the gastrointestinal tract to defend the host.

INTRODUCTION

The epithelial layers and mucus secretions of the pulmonary, genitourinary, and gastrointestinal (GI) systems all provide a complex mechanical barrier and an inherent defense against pathogens that constantly threaten the human body. Evidence suggests that these systems do not work independently, but form what is referred to as the mucosal immunologic system, an integrated network of tissue, cells, and signaling molecules.[1] Of the 3 systems, the lining of the GI tract provides the largest interface with the external environment (200–300 m^2). Although it was long believed to exist solely for food digestion and nutrient absorption, it is now known that the responsibilities of the intestinal system are diverse and critical to host defense. This amazing organ has evolved an elaborate defense system to protect the human body from

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continuous threats of numerous disease-causing agents and commensal bacteria present at an impressive number (1×10^{14} CFU).[2] At no time in life is this function more important than shortly after birth. The infant's abrupt introduction to life outside the uterus and exposure to antigens forces the GI tract to adapt quickly and commence its crucial duties. But the neonate's adaptive immune system is naive, and the developmental immunologic immaturity leaves the newborn in a state of vulnerability and at increased risk for serious infection. Components of the intestinal innate immune system do not rely on memory and can act with a preformed, nonspecific response.

Feeding exclusively with human milk is recommended for the first 6 months of life[3] and provides unique components and nutrients, leading to optimal nutrition, growth, and development of the newborn infant.[4] The benefits of human breast milk and its association with healthier babies have been intermittently noted over the past few thousand years.[5] In 1934, Grulee and colleagues[6] showed that formula-fed infants had higher morbidity and mortality when compared with breastfed infants. More recently, breast milk has been associated with a decreased incidence of necrotizing enterocolitis (NEC),[7] gastroenteritis,[8] severe respiratory illness,[9] otitis media,[10–14] and urinary tract infections.[15] The unique and dynamic composition of human milk not only supplies optimal nutrients but also contributes an abundance of bioactive factors,[16] which support and enhance the deficient immunologic system of the newborn.

In this article, selected factors in breast milk and how they either act alone to provide innate protection or augment GI innate immune function are reviewed. First, a broad and brief overview of innate immunity within the intestinal system is provided. Then, individual constituents present in human breast milk and the variety of mechanisms by which they exert their effects and afford protection to the newborn infant are discussed.

THE INNATE IMMUNE SYSTEM OF THE GI TRACT

The complex immune system of the intestine can be divided into 2 broad categories: innate and adaptive immunity. Although the innate arm, as its name implies, is present from birth and capable of immediate protection at the local level, the adaptive immune system of the gut is initially naive and needs time to generate an appropriate response and memory. Although much of our focus is on the components of innate immunity in the gut, it is important to remember that this system does not work in isolation. The information it gathers communicates with the adaptive immune system, allowing the 2 to work in concert to provide optimal protection for the host. The innate defense system of the intestine can be broken down into 3 main components: the secreted mucus layer within the gut lumen, a single intestinal epithelial cell (IEC) layer, and the underlying lamina propria.

Mucus Layer

Large, highly glycosylated proteins called mucins are secreted by specialized goblet cells,[17,18] also known as mucin-secreting cells, and are the primary component of mucus. The mucus layer, which is present throughout the GI tract, provides protection, lubrication, and compartmentalization, minimizing contact between the epithelium and commensal bacteria. Mucins secreted by salivary glands coat food and assist with esophageal transit.[19] The mucus layer in the stomach plays a role in protecting the epithelium from the harsh acidic environment.[19] The gel-forming mucin, MUC2, is the most predominant mucin in both the small and large intestine.[20] There is 1 unattached layer of mucin in the small intestine, which acts as a physical and