Lactoferrin secretion into milk: Comparison between ruminant, murine, and human milk

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ABSTRACT: Lactoferrin is an iron-binding protein found in external secretions such as tears, saliva, and milk and the secondary granules of granulocytes. As part of the innate nonspecific immune system it seems to play a wide variety of roles in infection and inflammation. The functions of milk lactoferrin have been postulated to include iron transfer to the neonate, iron scavenging from the neonatal gut, stimulation of intestinal growth, and defense against infection. The concentration of lactoferrin in milk varies widely from one species to another. It is highest in human milk (2 g/L, 25 × 10⁻⁶ M), moderate in murine milk (0.28 mg/L, 3.5 × 10⁻⁶ M), and very low in ruminant milk (~0.01 mg/L in bovine milk, 12 × 10⁻⁶ M). Unlike other milk proteins, lactoferrin has been found at high levels in the preparations secretions of the cow and human and at very high levels in postweaning mammary secretions from the cow, sheep, guinea pig, mouse, and human. It is also elevated in mastitic mammary glands. Data accumulated over the past three decades suggest that the protein may play an important role in defending the mammary gland against infection, particularly during periods of milk stasis.

Key Words: Milk, Lactoferrin, Mammary Gland, Species Comparison


Introduction

Lactoferrin belongs to a class of proteins that bind iron at neutral and alkaline pH and release it at low pH. It has a much higher affinity for iron than the closely related molecule transferrin and often acts as an iron scavenger rather than performing the reversible carrier function played by transferrin. Lactoferrin is present in external secretions (Masson, 1970; Inoue et al., 1993) and the secondary granules of neutrophils and has a wide variety of biological activities, including participation in host defense reactions, regulation of cell growth, and differentiation and prevention of microbial growth (Nuijens et al., 1996). Human milk is particularly rich in lactoferrin, with concentrations ranging from 5 to 10 g/L in colostrum to 1 to 2 g/L in mature milk (Lewis-Jones et al., 1985; Hennart et al., 1991). The concentration of lactoferrin in bovine milk is very low, 0.01 g/L in mature milk (Sanchez et al., 1988). Masson (1970) gave the concentration of lactoferrin in mouse milk between 0.2 and 2 mg/mL. In this article we review the current literature on the structure and function of lactoferrin and the potential receptors through which it acts followed by a comparison of the developmental regulation of lactoferrin in the mammary glands of the cow, human, and mouse, including some new data from this laboratory. A number of comprehensive reviews of lactoferrin secretion and action are available (Masson, 1970; Brock, 1980; Crichton, 1990; Schanbacher et al., 1993; Brock, 1995; Nuijens et al., 1996). The reader is referred to these and the recent book Advances in Lactoferrin Research (Spik et al., 1997) for additional information.

The Structure of Lactoferrin

The three-dimensional structure of human lactoferrin (Anderson et al., 1988; Baker et al., 1994) was one of the first proteins to be elucidated by x-ray crystallography. The molecule is composed of two major lobes, the N-lobe and C-lobe, each of which binds a molecule of iron in a complex with an anion, usually bicarbonate. At neutral pH two molecules of iron can be bound to lactoferrin with a dissociation constant of 10⁻¹⁵ M; they can be dissociated by decreasing the pH to 2.0 (Crichton, 1990). Lactoferrin is a basic molecule that binds heparin with an affinity that is highly species-dependent (Van Berkel et al., 1997). Depending on the species, lactoferrin contains two to four glycan chains (Spik et al., 1988), thought to provide some stability against proteolysis (Van Berkel et al., 1995).