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Review

Antimicrobial properties of lactoferrin

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Abstract

Milk is a vital nutritional source for the offspring of all mammals, including humans. In addition to its nutritional value, it is a rich source of proteins including lactoferrin. Lactoferrin is a truly multifunctional protein that has been studied extensively over the past decades. It is best known for its ability to bind iron, which eventually led to the discovery of its antibacterial activity. In addition, lactoferrin has demonstrated potent antiviral, antifungal and antiparasitic activity, towards a broad spectrum of species. It is also considered to be an important host defense molecule during infant development. In this review, we focus on the antimicrobial activities of lactoferrin with particular emphasis on antibacterial and antiviral activities, although its antifungal and -parasitic activity are also discussed.

Keywords: Lactoferrin; Antibacterial; Antiviral; Antifungal; Antiparasitic

1. Introduction

Antimicrobial proteins and peptides are produced by a wide variety of organisms as their first line of defense [1], and are found in large quantities in all secretory fluids. The most abundant antimicrobial proteins include lysozyme, collectin [2,3] and lactoferrin (for a comprehensive review see [4] and Baker et al., (2009). The antimicrobial activity of these proteins is related to bacterial lysis or opsonization of the pathogen, for example, mannose-binding proteins' interaction with HIV [5] and neutralization of influenza A virus by surfactant protein A [6]. Lactoferrin is truly a multifunctional protein (for review see [7–10]) and it is known to work as an opsonin to promote bacterial clearance [11], but this activity has not been described for viruses. It seems likely that the main physiological function of lactoferrin is to bind iron, and this was initially identified as a feature of the protein that contributed to its antibacterial activity, by sequestering iron, a necessary nutritional requirement for most bacterial pathogens, and thus inhibiting growth of a broad spectrum of bacterial strains [12–15]. Lactoferrin can also inhibit viral infections (Table 1) [16–28] of both naked [26,29–31], and enveloped viruses [18,20,23–25,32–39], and the activity is primarily exerted during an early phase of the viral infection. Iron saturation does not appear to influence the antiviral activity [24,25,27] of lactoferrin, in contrast to its antibacterial activity. The interplay between lactoferrin and different cellular lactoferrin receptor molecules (for review see [40]), could be of great importance for the antimicrobial activity, but this is outside the scope of this review. In addition to antiviral and antibacterial activity, lactoferrin also inhibits fungal [41,42] and parasitic infections [43]. This review provides an overview of the direct antimicrobial functions of the milk protein lactoferrin, namely its antibacterial, antiviral, antifungal and antiparasitic activity.

2. Antibacterial activity

Sequestering of iron from bacterial pathogens, thus inhibiting bacterial growth, was one of the first antimicrobial properties discovered for lactoferrin (Table 1) [12,13]. This was believed to be the sole antimicrobial action of lactoferrin for a long time, and was supported by several studies demonstrating that only apo-lactoferrin possessed antibacterial activity, and that this activity was reduced upon iron saturation [44–46]. It

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Table 1
Biological activity of lactoferrin

Activity	Target	Mode of action	References
Gram-positive bacteria	*S. mutans*	Iron-independent interaction with bacterial cell surface	[47–49]
	S. epidermidis	Interaction with lipoteichoic acid on bacterial surface	[62]
	S. epidermidis	Prevents biofilm formation – probably through iron sequestering	[81]
Gram-negative bacteria	*E. coli*, *S. typhimurium*	Cation chelators, damaging the bacterial membrane, altering the outer membrane permeability, resulting in a release of LPS	[54,56]
	H. influenzae	Altering bacterial virulence – degrading IgA1 and Hap	[65]
	S. flexneri	Disrupt bacterial type III secretion system – degrading IpaB and IpaC	[72,73]
	E. coli	Disrupt bacterial type III secretion system – degrading EspA, EspB and EspC	[73–75]
	S. typhimurium	Interaction with the bacterial surface	[76]
	P. aeruginosa	Prevents biofilm formation – probably through iron sequestering	[79,82,83]
	B. cepacia	Prevents biofilm formation – probably through iron sequestering	[80]
	B. cenocepacia	Prevents biofilm formation – probably through iron sequestering	[83]
Enveloped viruses	HSV	Targets adsorption/entry – contradicting results whether there is a direct effect on the viral particle or not	[23,24,100]
	HCMV	Targets adsorption/entry – no effect on the viral particle	[20,32,34]
	VSV	Upregulation of machrophage interferon α/β expression	[147]
	Hepatitis B	Targets cellular molecules interfering with viral attachment/entry	[19]
	Hepatitis C	Targets viral envelope protein E1 and E2 – blocks entry	[21,35,39,140]
	Hepatitis G	Unknown	[21]
	HIV	Targets V3 loop in envelope protein gp120 – blocks CXCR4- or CCR5-attachment	[17,25,38,102]
	Feline herpes virus-1	Targets viral attachment/entry	[16]
	Sindbis virus	Targets adsorption/entry – no effect on the viral particle	[105]
	Semliki Forest virus	Targets adsorption/entry – no effect on the viral particle	[105]
	RS-virus	Unknown	[171]
	Hantavirus	Targets adsorption/entry (not heparan sulphate) – no effect on the viral particle	[36]
Naked viruses	Rotavirus	Viral interaction – prevents hemaglutination and attachment to cellular receptors	[103]
	Poliovirus	Targets viral adsorption/competes for viral receptor interaction	[30]
	Adenovirus	Targets viral adsorption/binds viral protein III and IIIa.	[29,104,141]
	Enterovirus (EV71 and Echovirus 6)	Targets viral adsorption – binds both cellular receptors and the viral surface protein VP1. Inhibits apoptosis	[22,143,144]
Yeast and fungi	*C. albicans*, *C. tropicalis*, *C. krusei*, *C. guilliermondii*, *C. parapsilosis*, *C. glabrat*	Cell wall perturbation	[150–153]
	A. fumigatus	Iron sequestering	[155]
Parasites and other eukaryotic microbes	*P. berghei*	Targets host cell entry	[167,168]
	P. carinii	Iron sequestration	[43]
	E. histolytica	Probably linked to iron sequestration	[160]
	B. caballi	Iron sequestration	[161]
	B. equi		