J Pediatr (Rio J). 2015;91(1):4–5

Jornal de Pediatria
www.jped.com.br

EDITORIAL

Protective effects of human milk antimicrobial peptides against bacterial infection☆,☆☆

Efeitos de proteção dos peptídeos antimicrobianos do leite humano contra infecções bacterianas

Anders P. Hakansson[a,b]

[a] *Department of Microbiology and Immunology, University at Buffalo, State University of New York, Buffalo, United States*
[b] *The Witebsky Center for Microbial Pathogenesis and Immunology, University at Buffalo, State University of New York, Buffalo, United States*

Breast-feeding provides the nursing infant with a plethora of molecules evolved to optimally develop the infant's tissues and organs. Human milk contains numerous bioactive molecules that modulate the immune system as well as molecules with direct and indirect antimicrobial activities that avoid overgrowth of potentially pathogenic microorganisms. The combination of immunmodulatory and antimicrobial factors help the child to avoid the development of inflammatory diseases and childhood infection. Accordingly, the feeding of formula and other substitutes to infants is clearly correlated with an increased frequency of inflammatory diseases such as allergies, colitis, juvenile diabetes, and childhood cancer, as well as an increased frequency of infections. Although some of the mechanisms and molecules involved in human milk's protection against infection have been well studied, the complete picture of the very complex biology of the human milk anti-microbial protection is not yet clear.

In a study published in this issue of *Jornal de Pediatria*,[1] a group from Instituto Venezolano de Investigaciones Científicas (IVIC), Caracas, Venezuela, led by Dr. Luz Thomas, presents evidence for the potential role of human beta-defensin-2 (hBD-2) from human milk in anti-microbial protection against enteric infections and potentially other infections as well. The authors measured the concentration of hBD-2 in 100 human milk samples, 61 of which were from colostrum and the remaining from mature milk. Similar to what has been observed in one earlier study,[2] colostrum samples contained significantly higher concentrations of hBD-2 than mature milk samples; however, the concentrations observed here were considerably higher than the previously described, suggesting a possible contribution of milk-derived defensins to the antimicrobial defense of milk *in vivo*. The authors then produced recombinant hBD-2 and tested it against a broad range of potentially pathogenic enteric organisms, including *Salmonella spp*. and *Escherichia coli* strains, as well as strains of *Serratia marcescens*, *Pseudomonas aeruginosa*, and *Acinetobacter baumanii*, and observed a sensitivity of these organisms to hBD-2; the concentrations found in human milk are likely to have an effect on these organisms *in vivo*. The results represent the first report of defensin-levels in milk from Latin American women and suggest a role for hBD-2 in the defense against enteric infections in infants. This information will hopefully spur on future studies on milk antimicrobial peptides (AMPs) from this and

DOI of original article:
http://dx.doi.org/10.1016/j.jped.2014.05.006
☆ Please cite this article as: Hakansson AP. Protective effects of human milk antimicrobial peptides against bacterial infection. J Pediatr (Rio J). 2015;91:4–5.
☆☆ See paper by Baricelli et al. in pages 36–43.
E-mail: andersh@buffalo.edu

http://dx.doi.org/10.1016/j.jped.2014.10.001

other groups, increasing the understanding of the role of AMPs in both immune modulation and antimicrobial activity.

To put this work in perspective, there is strong epidemiologic data suggesting a detrimental association between formula-feeding and infection in infants.[3–5] When comparing formula-fed and breast-fed infants, breast-fed infants present lower incidences of gastrointestinal, respiratory, urinary tract, and other infections, as well as lower child mortality.[6] The main molecules associated with this protection are antimicrobial factors in human milk that act either indirectly to block adherence of bacteria to mucosal surfaces or to neutralize bacteria, such as oligosaccharides, glycoconjugates, and immunoglobulins, or directly killing microbes, such as lactoferrin, lysozyme, peroxidases, fatty acids, and other molecules.[7] Protection is further ameliorated by providing factors that modulate the immune system,[5,8,9] such as cytokines and growth factors. Additionally, recent studies have shown that human milk contains its own microbiome that, when provided to the infant, help establish a healthy microflora in the infant gut and other tissues, which also helps to optimally develop the infant immune system and to protect against overgrowth of pathogenic bacteria.[10,11]

The role of milk as a source of AMPs and the role of milk AMPs in the protection against infection has not been investigated in depth. Initial studies investigating the expression of defensins in mammary epithelium found expression of hBD-1, but no expression of hBD-2 was observed.[12] In fact, the major beta-defensin produced in milk appears to be hBD-1.[2,13] Yet, Armogida et al. identified expression of the *hbd-2* gene in 15% of the mammary epithelial cells they investigated,[14] and Wang et al. was recently the first group to show secretion of hBD-2 in milk.[2]

AMPs are multifunctional defense molecules.[15] Besides their anti-microbial activity, they also modulate the immune system by activating immune cells against pathogenic organisms. Their importance in the defense against infections of mucosal linings such as the skin, respiratory tract, and gut, has been clearly demonstrated using animal models, where the genes for mouse defensins or cathelicidin have been removed or their expression has been reduced. Such studies have shown the importance of AMPs against various infections including those caused by *E. coli* O157:H7, *Streptococcus pyogenes*, and *Streptococcus* pneumoniae,[16–18] and defensins and defensin-like molecules are known to contribute to bacterial clearance in the gut and lung.[19] To conclude, the information provided by Baricelli et al.[1] in the current issue of this journal should stimulate future studies in the field for several reasons. Firstly, further studies will increase our understanding of the complex biology of human milk and its anti-microbial role in the gut and other mucosal tissues; secondly, the study of APMs, including defensins, are becoming more and more interesting as potential antibiotics in the era of antibiotic resistance.[20]

Conflicts of interest

The author declares no conflicts of interest.

References

1. Baricelli J, Rocafull MA, Vázquez D, Bastidas B, Báez-Ramirez E, Thomas LE. β-defensin-2 in breast milk displays a broad antimicrobial activity against pathogenic bacteria. J Pediatr (Rio J). 2015;91:36–43.
2. Wang XF, Cao RM, Li J, Wu J, Wu SM, Chen TX. Identification of sociodemographic and clinical factors associated with the levels of human β-defensin-1 and human β-defensin-2 in the human milk of Han Chinese. Br J Nutr. 2014;111:867–74.
3. Beaudry M, Dufour R, Marcoux S. Relation between infant feeding and infections during the first six months of life. J Pediatr. 1995;126:191–7.
4. Dewey KG, Heinig MJ, Nommsen-Rivers LA. Differences in morbidity between breast-fed and formula-fed infants. J Pediatr. 1995;126:696–702.
5. Hanson LA, Korotkova M. The role of breastfeeding in prevention of neonatal infection. Semin Neonatol. 2002;7:275–81.
6. Victora CG, Smith PG, Vaughan JP, Nobre LC, Lombardi C, Teixeira AM, et al. Evidence for protection by breast-feeding against infant deaths from infectious diseases in Brazil. Lancet. 1987;2:319–22.
7. Lönnerdal B. Bioactive proteins in breast milk. J Paediatr Child Health. 2013;49:1–7.
8. Newburg DS, Walker WA. Protection of the neonate by the innate immune system of developing gut and of human milk. Pediatr Res. 2007;61:2–8.
9. Kelly D, Coutts AG. Early nutrition and the development of immune function in the neonate. Proc Nutr Soc. 2000;59:177–85.
10. Civardi E, Garofoli F, Tzialla C, Paolillo P, Bollani L, Stronati M. Microorganisms in human milk: lights and shadows. J Matern Fetal Neonatal Med. 2013;26:30–4.
11. Hunt KM, Foster JA, Forney LJ, Schütte UM, Beck DL, Abdo Z, et al. Characterization of the diversity and temporal stability of bacterial communities in human milk. PLoS One. 2011;6:e21313.
12. Tunzi CR, Harper PA, Bar-Oz B, Valore EV, Semple JL, Watson-MacDonell J, et al. Beta-defensin expression in human mammary gland epithelia. Pediatr Res. 2000;48:30–5.
13. Jia HP, Starner T, Ackermann M, Kirby P, Tack BF, McCray PB Jr. Abundant human beta-defensin-1 expression in milk and mammary gland epithelium. J Pediatr. 2001;138:109–12.
14. Armogida SA, Yannaras NM, Melton AL, Srivastava MD. Identification and quantification of innate immune system mediators inhuman breast milk. Allergy Asthma Proc. 2004;25:297–304.
15. Metz-Boutigue MH, Shooshtarizadeh P, Prevost G, Haikel Y, Chich JF. Antimicrobial peptides present in mammalian skin and gut are multifunctional defence molecules. Curr Pharm Des. 2010;16:1024–39.
16. Chromek M, Arvidsson I, Karpman D. The antimicrobial peptide cathelicidin protects mice from Escherichia coli O157:H7-mediated disease. PLoS One. 2012;7:e46476.
17. Nizet V, Ohtake T, Lauth X, Trowbridge J, Rudisill J, Dorschner RA, et al. Innate antimicrobial peptide protects the skin from invasive bacterial infection. Nature. 2001;414:454–7.
18. Merres J, Höss J, Albrecht LJ, Kress E, Soehnlein O, Jansen S, et al. Role of the cathelicidin-related antimicrobial peptide in inflammation and mortality in a mouse model of bacterial meningitis. J Innate Immun. 2014;6:205–18.
19. Moser C, Weiner DJ, Lysenko E, Bals R, Weiser JN, Wilson JM. beta-defensin 1 contributes to pulmonary innate immunity in mice. Infect Immun. 2002;70:3068–72.
20. Steckbeck JD, Deslouches B, Montelaro RC. Antimicrobial peptides: new drugs for bad bugs? Expert Opin Biol Ther. 2014;14:11–4.