

Recent advances in lactoferrin research and development during the past two years (2007–2009): in lieu of a preface of the special issue lactoferrin

Jianhua Wang · Zigang Tian

Published online: 18 February 2010
© Springer Science+Business Media, LLC. 2010

Abstract This is a short preface of this Special Issue Lactoferrin, it described the major points of key reporters in ‘The 9th International Conference on LF Structure, Function and Applications’ in Beijing in late Autumn 2009, and the major articles published in this issue. A panorama and the latest advances of lactoferrin R&D during past two years (2007–2009) was tried to extract.

Keywords Lactoferrin ·
Research and development · Advances

Lactoferrin (Lf) is an extracellular iron binding glycoprotein that was first identified in milk secretions and functions as a key component of the mammalian immune defense. ‘*The International Conference on Lf Structure, Function and Applications*’ is held biennially and allows scientists to introduce and discuss the latest research advances related to this fascinating glycoprotein and its

potential applications. This BioMetals special issue on Lactoferrin contains refereed papers from most of the speakers at the IXth International Lactoferrin Conference held during 18–22nd October 2009 at Beijing (China) and organized by the Feed Research Institute, the Chinese Academy of Agricultural Sciences. The co-organizers include the Chinese Academy of Agricultural Sciences, Friesland Foods Domo/DMV, the National Natural Science Foundation of China, the Natural Science Foundation of Beijing, Shanghai Genon Bio-engineering Co. Ltd./Shanghai Transgenic Research Center, and the State Key Laboratory for Agrobiotechnology of China Agricultural University.

In the most recent conference with a size of over 130 attendees from 23 countries and regions, scientists gave a total 45 oral presentations including the following topics: structure–function relationships, ligands/receptors, regulation of cell proliferation and differentiation, immunomodulating effects, Lf in pathologies, antimicrobial activity of Lf and Lf-derivatives, molecular design and expression of Lf-derivatives, recombinant and transgenic Lfs and applications. In addition, safety evaluation, policy and legislation of transgenic Lf research, molecular design and expression of antimicrobial Lf-derived polypeptides, Lf evaluation and quality assays were also deeply discussed.

The sequence and structural features of Lf underpin its functional attributes. Professor Baker introduced the latest research on the three-dimensional

J. Wang · Z. Tian
Key Laboratory of Feed Biotechnology, The Ministry of Agriculture, 100081 Beijing, People’s Republic of China

J. Wang (✉) · Z. Tian
Gene Engineering Laboratory, Feed Research Institute, Chinese Academy of Agricultural Sciences, 100081 Beijing, People’s Republic of China
e-mail: jhwangfribio@yahoo.com.cn;
wangjianhua@mail.caas.net.cn

structure of Lf and the importance of surface features, discussed the iron binding sites and conformational transitions between iron-bound and iron-free forms. Professor Lonnerdal has recently found that the post-transcriptional expression of the Lf receptor is regulated by a specific microRNA miRNA-584. Lf was also found to stimulate cell proliferation with apo-Lf stimulating to a greater extent than holo-Lf. Professor Schryvers discussed the functional domains of the bacterial Lf binding proteins A and B (LbpA and LbpB), which enable Lf to be utilized as a source of iron for several Gram-negative bacterial pathogens of humans. Professor Pierce introduced delta-Lf, a 73 kDa cytoplasmic isoform of Lf, which is a transcription factor that regulates cell survival. Professor Choi demonstrated that a relatively low level of iron saturated Lf can elevate the level of cyclin D1 and stimulate S phase cell cycle entry.

There is a growing interest in the potential use of Lf for the improvement of bone health. Professor Cornish researched the mechanism and found that the mitogenic effect of Lf in osteoblasts is mediated mainly through a member of the low density lipoprotein receptor-related proteins (LRP1). Lf is a key component of the first line of host defenses. Professor Legrand reviewed the process and mechanism of iron-chelating anti-microbial activity and anti-inflammatory activity in fluids. Professor Valenti's research showed that oral administration of bovine Lf (bLf) resulted in beneficial effects including a mean increase of red blood cells, hemoglobin, total serum iron and serum ferritin that was significantly higher with respect to oral administration of ferrous sulfate. It was concluded that in hereditary *thrombophilia* affecting pregnant women, oral administration of bLf exerts a potent effect to cure iron deficiency and iron deficiency anemia and to decrease serum interleukin-6, one of the key factors in iron homeostasis and coagulation disorders. Professor Teng reviewed the basics of transcriptional regulation at different levels, Lf gene organization, methylation of the Lf gene and the signaling pathways that regulate the Lf gene expression.

The development of transgenic animals was considered to be the approach with the greatest potential for large scale production of Lf for industrial purposes. Ms Gros-Van Hest discussed the safety evaluation of recombinant human Lf (rhLf) and rhLF

products with different purities by transgenic cows. Professor Li described four transgenic cows that secreted rhLf at a level of 3.4 g/l. In the milk, Lf provides protection against bacterial contamination. Professor Perraudin stated that during the production of the Lf, the process of elimination of lipopolysaccharide bound to Lf is crucial before it reaches the market.

The peptides lactoferricin (LFcin), LFB15 (W4, 10) and lactoferrampin (LFampin), derived from the Lf N-lobe, have higher antimicrobial activity than the intact Lf. Dr Yang presented research about the molecular design of the novel antimicrobial peptide LH28, derived from peptide LFB15 (W4, 10). Both LH28 and LFampin were heterologously expressed and characterized in the *Escherichia coli* system. Research by Dr Nidia found that the Lf chimera, Lf, LFcin and LFampin have potential as bactericidal agents against antibiotic-resistant *Staphylococcus aureus* and *Escherichia coli*. Moreover, the Lf chimera, LFcin and LFampin exhibited a microbicidal effect against the parasite *Entamoeba histolytica*.

Finally, Professor Shimazaki described a preliminary approach to creating an overview of Lf multifunctionality utilizing a text mining method. Such information visualization analysis will be very useful in determining novel relationships among a multitude of Lf functions and mechanisms.

The Spik Award was instituted in recognition of one of the pioneers in the Lf field, Professor Genevieve Spik of the University of Lille, France. This award recognizes young scientists with outstanding achievements. Stephan Hardiville was selected for the award this year from a group of eight excellent student candidates. There is an increasing interest by companies in the in-depth exploration of the functions and applications of Lf presented at the conference. We sincerely appreciate the financial support provided by the sponsors: Shanghai Genon Bio-engineering Co. Ltd. (Shanghai Transgenic Research Center), Friesland Foods Domo/DMV, Morinaga Co. Ltd., Taradon Laboratory, Pharming Group N.V., TATUA Co-operative Dairy Co., Pall-Food and Beverage, Westland Milk Products, NRL Pharma Inc., Belgomilk, Favea, and New Baili International Industry & Trade Co. Ltd. Their financial support was invaluable for organizing the meeting and supporting the attendance of participating students and scientists.

This special issue consists of over 20 reviews and research papers, from which the readers can browse a different panorama of lactoferrin research and development during past two years with more detail information than the oral talk or poster presentations at the conference. For example, Pietrantonio et al. observed an inhibition of bovine lactoferrin against programmed cell death in vitro induced by influenza A virus. A possible interaction between bovine lactoferrin and cable pili of *Burkholderia cenocepacia* was revealed (Ammendolia et al.). The liposomalization was considered to enhance anti-tumoral effects of lactoferrin on melanoma cells (Roseanua et al.). A potential contribution of bovine lactoferrin inter-lobe region to iron binding stability and anti-microbial activity against *Staphylococcus aureus* was deduced (Bai et al.). Takayama et al. put forward that lactoferrin regulates chondrogenic differentiation by up-regulating the Smad2/3-Sox9 signaling pathway of mouse ATDC5 chondroprogenitor cells. Hoedt et al. for the first time developed an assay using *TaqMan* real time PCR to discriminate and evaluate gene expression levels of lactoferrin and delta-lactoferrin in cancer cells and cells under inflammatory stimuli. A study about probiotic *Lactobacillus*

casei expressing human lactoferrin for the purpose of higher antibacterial activity in host gastrointestinal tract would attract more attention (Chen et al.). van der Does et al. reported that a human lactoferrin-derived peptide (hLF1-11) primes monocytes of human and murine so that upon encountering microbial stimuli the cells produce enhanced levels of proinflammatory and anti-inflammatory cytokines and chemokines. In addition, some papers (Wakabayashi et al., Evrard et al., Héctor et al., and Tian et al.) focusing on application in the field of food and pharmaceutical industry related to lactoferrin would also attract your attentions. As for those their papers with a similar subject as their oral reports mentioned in above paragraphs will not be repeated here.

We are very happy that the IXth International Lactoferrin Conference was successfully implemented according to the original plans. We sincerely thank all our colleagues who have made a contribution to this special issue for Lf and especially to the editorial staff of *BioMetals*.

The Xth Lf conference will be held in Sinaloa, Mexico in 2011. We wish the organizers great success in the next meeting and hope that more colleagues can gather in sunny and beautiful Mexico.