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PREFACE

Lactoferrin, all roads lead to Rome

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A picture taken of a statue in Rome showing how Romulus and Remus are being nursed back to health by la Lupa Capitolina. Milk is an excellent source of lactoferrin, a protein with many health benefits

Lactoferrin is an iron-binding cationic glycoprotein that is constitutively synthesized by exocrine glands and by neutrophils. Its biosynthesis can be markedly increased during infection and inflammation. This multifunctional protein also acts as a major player in host defense in bodily fluids while it simultaneously protects the human mucosa. Several functions of lactoferrin are dependent on its ability to avidly bind two ferric ions in two characteristic binding sites while other biological activities do not require this property and they are mediated by other parts of the protein. In particular, the highly basic N-terminal regions of human and bovine lactoferrin seem to play an important role in the antimicrobial and immuno-regulatory properties of the protein, which can be emulated to some extent by using synthetic peptide derivatives that resemble this region. From the 1960s onward, when the protein was first purified from milk, the number of scientific publications concerning its biochemical properties, the various biological functions and the potential therapeutic applications of lactoferrin and its bioactive peptides has significantly increased. This research area is regularly being reviewed and the reader may wish to consult some of these contributions to gain an entry into the field (Valenti et al. 2004; Lonnerdal 2009; Baker and Baker 2012; Vogel 2012). Currently a Pubmed search in the NCBI Medline database identifies almost 7,000 publications for this topic and this number increases by about 300 publications each year. In particular the potential for therapeutic or health-promoting applications of lactoferrin has led to a sustained research effort in this area.

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The XIth International Conference on Lactoferrin Structure, Function and Applications was held in Rome (Italy) from October 6th to 10th, 2013 and about 200 researchers from 28 different countries participated in this meeting. The biennial 'Lactoferrin Conference' provides an important forum for the dissemination and the promotion of research on this protein and for discussions about new insights into the benefits of lactoferrin as a mediator of general health and its potential therapeutic applications. Judging from the lectures and poster presentations all the conference participants were obviously inspired by the myth about the foundation of Rome, in which the two infants Romulus and Remus are nurtured to health by drinking milk from a female wolf (la Lupa Capitolina) (Garcia 2013). Some conference participants went as far as taking inspiration from Michelangelo, who has allegedly depicted several hidden scientific motifs into some of his paintings in the Sistine chapel (Meshberger 1990; Eknoyan 2000; Suk and Tamargo 2010). As before, the conference has been able to maintain a truly international flavor as evidenced by the fact that the Genevieve Spik Award for the best overall student presentation was chosen from among ten preselected submissions and presentations from graduate students coming from China Agricultural University, Beijing; National Polytechnic Institute, Mexico City; University of Tokyo, Tokyo; Institute for Research in Biomedicine, Bellinzona; Technion Israel Institute of Technology, Haifa; University of California, Davis; Università degli Studi di Padova, Padova; and the Universidad Autonoma de Sinaloa, Mexico.

Bovine lactoferrin and recombinant or transgenic human lactoferrin can both be commercially produced on a large scale, and the purified proteins are used for several applications, such as a supplement to infant formula, as a health-promoting additive to various foods, as a nutraceutical, or as an immune-stimulating and bone-growth-promoting dietary supplement. Lactoferrin is also being tested as a potential biologic therapeutic protein for the treatment of diarrhea, inflammatory bowel diseases, anemia, wound healing, sepsis and certain forms of cancer. Moreover because the protein levels increase during inflammation it is also actively studied as a biomarker for disease. The lectures and poster presentations at the meeting covered many different aspects of lactoferrin (Lf) and its bioactive peptides. After the meeting many of the participants were invited to contribute an original research paper to this special issue. Together these contributions highlight the current status and ongoing research interests in this field. For example, Cutone et al. (2014) and Sokolov et al. (2014) were interested in the role of iron metabolism during inflammation and they discuss Lf interactions with ferroportin and ceruloplasmin, two proteins that play an important role in iron homeostasis. It is well known that Lf can spontaneously be taken up in many kinds of cultured eukaryotic cells and alter gene transcription. Several groups have taken advantage of this fact: specifically, Jiang and Lonnerdal (2014) performed extensive transcriptomic profiling using microarrays in intestinal epithelial cells, while Frioni et al. (2014) studied the inflammatory response and again found evidence for an important link to the iron transporter ferroportin. At the same time Blais and coworkers (2014) studied the Lf-dependent regulation of gene expression and cell proliferation in Caco-2 enterocyte cells, while Hardivillé et al. (2014) concentrated on a unique intracellular form of Lf, called delta-lactoferrin, which plays a role in regulating cell death. Many groups focused their efforts on the antibacterial activities of the intact proteins and some of its derived peptides. In particular Luna-Castro et al. (2014) studied the effects of Lf on the porcine pathogen *Actinobacillus pleuropneumonia*, while Chen et al. (2014b) and Oda et al. (2014) studied the effects on beneficial bifidobacteria, that are in use as probiotics. The potential role of bacterial surface lactoferrin-receptors in evading the host antimicrobial peptide response was studied by Morgenthau et al. (2014). A number of new synthetic antimicrobial peptides derived from and designed after various bioactive lactoferricins (Gifford et al. 2005) and lactoferrampins (Haney et al. 2012) were studied by Arias et al. (2014), Kanthawong et al. (2014), Xi et al. (2014) and Leon-Sicairos et al. (2014). These authors used different pathogenic Gram-negative and Gram-positive bacteria as their targets including *Escherichia coli*, *Burkholderia pseudomallei, Burkholderia thailandensis*, *Staphylococus aureus* and *Streptococcus pneumonia*. Various peptide chimeras and novel cyclic peptides were analyzed in these four studies. Furthermore, Riedl et al. (2014) focused on anticancer activities and they showed that several modified lactoferricin peptides could kill cancerous melanoma cells by binding specifically to phosphatidyl-serine headgroups of phospholipids.

Several reports during the conference concentrated on human studies, for example Paesano et al. (2014) showed that Lf can help combat anemia in pregnant women suffering from hereditary thrombophilia. Turin and coworkers (2014) reviewed studies indicating that Lf can help prevent sepsis in neonates. Also Iigo et al. (2014) reported on a human trail showing that oral ingestion of Lf suppressed the growth of precancerous intestinal polyps. Effects in several animal models of disease were also reported; Cooper et al. described the beneficial effects of Lf-enriched milk ingestion in piglets (Cooper et al. 2014); Shumake and coworkers (2014) studied potential behavioral effects in rats, while Chen et al. (2014a) showed that treatments with aerosolized Lf had beneficial effects on lung injuries in a mouse model.

Because lactoferrin is released from neutrophils at sites of infection, increases in Lf in stool samples is already being used as a clinical biomarker to distinguish between inflammatory bowel disease and irritable bowel syndrome (Zhou et al. 2014). Caccaro et al. (2014) describe in this special issue how detection of fecal Lf can be used during diagnostic work-up of chronic diarrhea as well. Also Mastromarino et al. (2014) provide novel insights into the correlations between lactoferrin levels and beneficial microbiota in breast milk and infant feces.

Taken together these contributions all highlight the broad interest in this protein. Indeed lactoferrin is one of the few (if not the only?) proteins that has its own dedicated scientific meeting. These papers also indicate the potential of lactoferrin for future diagnostic, health-promoting or clinical applications. Indeed several placebo-controlled human cohort studies and clinical trials have already been performed. While not all these trials have been successful, several of them have shown significant beneficial effects (Manzoni et al. 2009; Paesano et al. 2010; Parikh et al. 2011; Guntupalli et al. 2013; Manzoni et al. 2014), underscoring the need for continued research activity in this area. Typically in all these clinical studies the protein is very well tolerated, and clearly this bodes well for its future therapeutic use. We therefore expect that research in this area will continue unabated and we are already looking forward to hearing about these new advances during the upcoming XIIth Lactoferrin meeting in 2015 in Nagoya, Japan.

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