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Lactoferrin: the path from protein to gene

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Abstract This review focuses on the basic research that was performed on the lactoferrin protein and gene that was conducted in my laboratory over the past 25 years. This manuscript will outline how we discovered that lactoferrin is a target gene for estrogen, and how the first mouse lactoferrin cDNA, promoter and gene was cloned. Additionally, study was further extended to investigating the human lactoferrin protein and gene. Lastly the expression of lactoferrin in various tissues of both human and rodent under various physiological conditions were examined.

Keywords Gene · Estrogen regulation · Reproduction · Cancer · Methylation and SNPs · Promoter

Discovery of lactoferrin and the estrogen response

While searching for markers in which to study the molecular mechanism of estrogen action in the early 1980s, we found that the uterine fluid of estrogen treated immature mouse contains several estrogen-inducible proteins. Two of the more prominent proteins were detected at the 68–70 kDa regions on SDS-PAGE. Since albumin and transferrin, two major proteins in serum, were also detected around this region, we decided to use CM-Affi-gel blue column (BioRad #153-7340), which was routinely used in clinical laboratories to isolate albumin, as the first step to separating the uterine fluid proteins. Albumin, but not transferrin, binds this column tightly. At various concentrations of NaCl, we found that the 70 kDa protein was eluted at 0.5 M and was significantly increased after estrogen treatment. This protein was further purified by reverse-phase High Performance Liquid Chromatography (HPLC) to homogeneity and characterized as a highly basic glycoprotein. The purified protein was used to immunize three rabbits (8344, 8345, 8346) which produced specific polyclonal antibodies (Teng et al. 1986). Antibody (8345) was used to screen the estrogen-treated mouse uterine cDNA phage library generated in my laboratory and was used to identify several phage plaques that were specific to the antibody. After cloning and sequencing the cDNA of this estrogen responsive protein, we discovered that the protein was encoded by the lactoferrin gene. This marked the first cloning of lactoferrin cDNA from any species (Pentecost and Teng 1987; Teng et al. 1987a). Subsequently, we cloned the human lactoferrin cDNA (Panella et al. 1991) and produced

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a rabbit antibody (12683, 126484) against human lactoferrin protein isolated from human milk.

Due to the sensitivity to estrogen, the lactoferrin gene was used as a marker for estrogen action in basic research by many academic institutions and by us to screen for environmental chemicals that act as endocrine disruptors (Curtis et al. 1997; Jefferson et al. 1996; Liu and Teng 1994; McLachlan et al. 1988; McLachlan et al. 1992; Ranhotra and Teng 2005; Zhang and Teng 2002).

Lactoferrin expression

By combining the antibody and cDNA of lactoferrin with various molecular technology approaches, we were able to demonstrate that the lactoferrin mRNA and protein was induced by estrogen in the luminal and glandular epithelium of the uterus (Teng et al. 1989). Additionally both were found to be present in neutrophil granules and epithelial of various adult tissues (Shigeta et al. 1996; Teng et al. 2004; Teng et al. 1989) as well as in developing mouse embryos (Ward et al. 1999). Under physiological conditions such as pseudopregnancy and the estrus cycle (at the proesterous and estrus) of rodents (McMaster et al. 1992; Newbold et al. 1992; Teng et al. 2002a) or the menstrual cycle (proliferative phase) of monkey and human (Teng et al. 2002b), lactoferrin expression in the uterus fluctuates and correlates positively with the level of circulating estrogen. Estrogen regulation of lactoferrin expression was also demonstrated in the uterus and vaginal epithelium of the rat and hamster (Teng et al. 2002a). Patients with adenomatous hyperplasia of the uterus (chronically exposed to estrogen) persistently expressed lactoferrin in the endometrial epithelium (Teng et al. 1992) suggesting a link between estrogen exposure and lactoferrin expression. In the seminal vesicles of normal mice, lactoferrin expression is minimal, however, lactoferrin expression in developmentally estrogenized males was both constitutive and inducible by estrogen (Beckman et al. 1994; Newbold et al. 1989; Pentecost et al. 1988). It was interesting to find that the expression of lactoferrin in preimplantation mouse embryos (Ward et al. 1999) coincide with a high level of expression in preimplantation mouse uterine epithelium (McMaster et al. 1992) but decreased in a synchronous manner on day 3.5 of pregnancy. It is not clear whether the preovulatory estrogen surge induces lactoferrin expression in the embryo and the uterine epithelium. Nonetheless estrogen receptor (ER) was detected in the embryo at this stage of development raising the possibility that estrogen also plays a direct role in the regulation of lactoferrin expression of the embryo. The expression of lactoferrin in mouse embryo can be divided into three phases: (1) the preimplantation embryo from eight cell to blastocyst, (2) postimplantation neutrophils, and (3) epithelia cells of the developing digestive and respiratory tract (Ward et al. 1999). Lactoferrin in the mammary gland was found to be at its highest at the beginning of lactation and during involution of the gland (Teng et al. 1989). What regulates lactoferrin expression in non-reproductive tissue is unknown, however lipopolysaccharide (LPS) and dsRNA induce lactoferrin expression and secretion in normal mouse mammary gland cells (Li et al. 2009) whereas cell shape of the mammalian epithelia cultured on different surfaces could modulate lactoferrin expression (Close et al. 1997).

The lactoferrin gene becomes estrogen responsive at the neonatal age of 10-day-old mouse even though the ER is detected earlier (Shigeta et al. 1996). After birth, both lactoferrin mRNA and protein were present in many tissues (Shigeta et al. 1996), nonetheless it was restricted in a tissue and species specific manner. For example lactoferrin mRNA was abundant in the human kidney but undetectable in mouse kidney while the opposite was found in the lung (Shigeta et al. 1996; Teng et al. 2004). Regulation of lactoferrin expression has been previously reviewed (Teng 2002; Teng 2006).

Molecular characterization of lactoferrin gene promoters

A major project of my laboratory was to analyze and characterize the human and mouse lactoferrin promoters. After cloning the lactoferrin cDNA from mouse (Pentecost and Teng 1987; Teng et al. 1987a) and human (Panella et al. 1991), we mapped the lactoferrin gene to human chromosome 3p21.3 and mouse chromosome 9 (Llintworth et al. 1998; McCombs et al. 1988; Teng et al. 1987b). Subsequently, the promoter region of the human and mouse lactoferrin gene were isolated (Liu and Teng 1991; Teng et al. 1992) and the estrogen response element (ERE) which binds ER was

identified. After in-depth analysis of the mouse and human EREs, we found that they are located at a similar position upstream from the transcription start site, yet they were differentially organized into composite response elements and embedded with different transcription factor binding sites. In addition, we found unique and ubiquitous transcription factor binding elements surrounding the ERE in mouse and human lactoferrin gene promoters. These promoters have been described in more detail in several past review articles (Teng 1995; Teng et al. 1998; Teng 1994; Teng 1999; Teng 2002; Teng and Yang 1997).

Mouse ERE overlaps with a chicken ovalbumin upstream promoter- transcription factor (COUP-TF) element which modulates the estrogen responsiveness of the gene by direct competition between COUP-TF and ER for overlapping binding sites on the ERE (Liu and Teng 1992; Liu et al. 1993). There are two COUP-TF elements present in the human lactoferrin gene promoter, one overlaps with the ERE and the other, present within a composite response element adjacent to the ERE, suggests that COUP-TF is also involved in the fine tuning of estrogen regulation of lactoferrin gene expression (Yang and Teng 1994). We found unique response elements in mouse which is absent from the human and vice versa. The mitogen response unit (MRU) of the mouse lactoferrin is located closer to the initiation start site within the GC-rich region (Shi and Teng 1996; Shi and Teng 1994). This region contains CAAT/GT boxes, CREB transcription factor binding element (CRE) and epidermal growth factor binding element (EGFRE) and responds to epidermal growth factor (EGF), foskolin (FSK), 12-0-tetradecanoylphorbol-13-acetate (TPA) and transforming growth factor alpha (TGF-α) stimulation. Later, we identified and cloned a new transcription factor, Kruppel-like-factor 5 (IKLF/KLF5) as the CAAT/GT box binding protein (Shi et al. 1999; Teng et al. 2007; Zhang and Teng 2003). These response elements were not found in the human lactoferrin gene promoter at a similar location where binding sites for transcription factors such as SP1, C/EBP and Ets were found. Interestingly, mutation to the adjacent GATA element of the human lactoferrin ERE increases estrogen responsiveness (unpublished observation), suggesting a cross-talk of GATA and ER in the hematopoietic and hormonal signaling pathways, respectively. In contrast, mutation at the upstream estrogen-related receptor alpha (ERRα) binding element (ERRE) of the human lactoferrin gene promoter substantially decreased estrogen responsiveness (Stokes et al. 2004; Yang et al. 1996; Zhang and Teng 2000; Zhang and Teng 2001). Both GATA and ERRE were not found at the mouse promoter, however, we could not exclude the possibility that they are located in different regions of the mouse lactoferrin gene. Nonetheless, these studies demonstrated the similarity and dissimilarity of the molecular mechanisms that regulate the transcriptional activity of the human and mouse lactoferrin gene through various signaling pathways.

The lactoferrin gene is organized into 17 exons and the number of amino acids in each exon and exon/intron junction is highly conserved, however the intron sizes between human and mouse are variable (Teng 2002). Regulatory elements could reside in the introns thus providing another level of differential regulation of lactoferrin expression in different species. Discovering the alternative form of human lactoferrin mRNA (ΔLF) motivated us to search for the alternative promoter which regulates the expression of human ΔLF in various tissues (Liu et al. 2003). We identified an alternative promoter (P2) in the first intron of the human lactoferrin gene which encodes the untranslated region and the alternative exon 1 (1b) in the ΔLF mRNA. The P2 promoter was active in hematopoietic cell lines but showed little activity in uterine cell lines. Furthermore, we demonstrated that the Ets transcription factor is a strong regulator of the P2 promoter of the human lactoferrin gene in hematopoietic cell lines. When overexpressed, Ets also enhances the P2 promoter activity in uterine cell lines. The ΔLF protein is a truncated form of lactoferrin which lacks the leader peptide for a secreted protein and is missing the first 26 amino acids of the secreted lactoferrin. Therefore, it was not surprising that ΔLF could enter the nucleus in contrast to lactoferrin which stays in the cytoplasm (Goldberg et al. 2005; Liu et al. 2003). Based on the location of ΔLF in the nucleus, it could play a role in the regulation of gene expression.

Methylation and single nucleotide polymorphisms (SNPs) of the lactoferrin gene

Human lactoferrin has been found to be decreased or absent in most breast cancer and leukemia cells. The

decrease in lactoferrin associated with cancer is multifactorial and includes gene structural changes as well as altered regulation. Changes at the coding region of the lactoferrin gene may lead to abnormal protein structure and loss of normal function while changes at the promoter region such as mutation, deletions, or methylation could lead to altered regulation. Southern blot analyses with lactoferrin DNA probes indicated that the human lactoferrin gene is polymorphic with an alteration of the restriction enzyme sensitivity in cancer cells (Panella et al. 1991). By using the sodium bisulfate genomic DNA sequencing at three regions of the human lactoferrin gene, the −540/−190 which includes the ERE, the −282/−271 which contains the lactoferrin promoter and the +1087/+1476, a region within the first intron that has the P2 promoter, we found differential methylation between normal and cancer cells. In general, increased methylation at the CpG sites and presence of non-CpG methylation of the human lactoferrin gene were found to be present in cancer cell samples (Teng et al. 2004; Teng et al. 2000). In the uteri of mice neonatally treated with diethylstilbestrol (DES), the CpG/−464 site of the lactoferrin promoter was specifically demethylated indicating that this DES-elicted demethylation is under hormonal control (Li et al. 1997). The relationship between the methylation state of the mouse lactoferrin gene promoter and its expression in selected mouse tissues was explored (Grant et al. 1999). The results demonstrated a tissue-specific methylation pattern and an inverse correlation between methylation and expression of the lactoferrin gene in liver, lung, spleen and uteri.

There are enormous variations among DNA sequences from different individuals within the human population. Our study with restriction enzyme polymorphisms of the human lactoferrin gene indicated variations among individual and cancer cells. To extend the study, we first used non-radioactive polymerase chain reaction-single strand conformation polymorphism (PCR–SSCP) (Liu et al. 2002) and then re-sequenced the human genome in the Environmental Genome Project (EGP) of the National Institute of Environmental Health Sciences, which operates within the National Institutes of Health (Teng and Gladwell 2006). Ninety-one healthy donors of different ethnicities were used to establish common SNPs in the lactoferrin gene in the general population. The EGP detected 60 SNPs in the lactoferrin gene (promoter, exons and introns) with variations among the ethnic populations. Asians and Africans have a higher percent of homozygous variants at amino acids 11, 382 and 523. In addition, Asians also show higher percent homozygous variants at 346 and 398. It is not clear whether the amino acid variants in the lactoferrin protein in ethnic groups influence the protein structure and thus the function. A web search from NCBI Reference Assembly found more SNPs in human (33 SNPs) than in mouse (17 SNPs) exons. Interestingly, most abundant SNPs of the human lactoferrin gene occurs in exon 2 (9 SNPs) where antibacterial function lies while the mouse lactoferrin has only one SNP found in exon 2. In addition, many SNPs found in exon 5, 7 and 9 of human lactoferrin were missing from mouse lactoferrin. It will be interesting to know whether these SNPs have any effect on the expression and biological function of lactoferrin. Recent studies have linked SNPs to many diseases and it is possible lactoferrin polymorphism among the human population could influence immunity and variations of bacterial resistance.

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