Lactoferrin-mediated targeting of oncogenic pathways for cancer chemoprevention and adjunct treatment: from mechanistic insights to clinical trials

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Abstract

Genetic, genomic and proteomic analyses of cells, tissues and body fluids have generated a wealth of precious information about the intricate mechanisms which underlie carcinogenesis and metastasis. Lactoferrin, a multifunctional cationic glycoprotein, has attracted widespread appreciation because of its characteristically novel properties for cancer chemoprevention. Tumor microenvironment is a highly complicated and sophisticated ecosystem, significantly reshaped by a wide variety of treatment regimes. Therefore, lactoferrin-mediated immunostimulatory role reshapes tumor microenvironment and inhibits cancer progression. There is sufficient experimental evidence related to immunostimulatory ability of lactoferrin in tumor microenvironment. Different clinical trials have been conducted for the evaluation of clinical efficacy of lactoferrin in different cancer patients. It is necessary to carefully interpret the clinical evidence and identify the major gaps in our understanding related to the selection of group of cancer patients likely to benefit the most from the combinatorial treatment regime comprised of lactoferrin and chemotherapeutic drugs. Moreover, lack of efficacy should be analyzed by a team of interdisciplinary researchers for a broader and comprehensive understanding of the mechanisms underlying treatment failure.

Key words: cancer, lactoferrin, metastasis, clinical trials, cell signaling

Introduction

The quest for biomolecules with remarkable biological activity has been ongoing for a long time. Medicinal chemistry and interdisciplinary research have revolutionized the field of drug discovery and we have witnessed the continuous upgrading of the list of natural products that have splendid preclinical and clinical efficacy (1-4). The discovery of lactoferrin has opened new horizons for the evaluation of its biological activities. Lactoferrin is a multifunctional glycoprotein widely distributed in milk and colostrum, as well as in other secretions, such as saliva and tears. It is released from neutrophils in inflamed tissues. Lactoferrin has a direct antimicrobial role, as it limits the adhesion and proliferation of microbes and/or kills them (5-8). The secretion of lactoferrin increases dramatically in neurodegenerative diseases (9, 10) and inflammation, which leads to the degranulation of neutrophils and activation of microglial cells. Lactoferrin efficiently reduces pollen antigen-mediated allergic inflammation of the airways (11). Lactoferrin has also been reported to demonstrate bactericidal effects (12-14).

In the era of precision oncology, the mechanistic understandings gathered from different cancers have highlighted the fundamental role of intra-tumoral heterogeneity, epithelial-to-mesenchymal transition (15-17), activation of oncogenic signaling cascades and immune escape mechanisms (18). The identification of bioactive molecules with extraordinary cancer chemopreventive effects has stirred research in multifaceted aspects of molecular oncology (19-24). Significant developments have been made in expounding the roles and functions of natural products in the pharmacological targeting of aberrantly regulated protein networks (25-30).

Lactoferrin, also known as lactotransferrin, is a nutrient produced by epithelial cells in mammalian species. Lactoferrin is an 80kDa single polypeptide chain containing 703 amino acids in one molecule, and it has a higher affinity to binding the ferric iron in the body. Conversely, lactoferricin is a shorter peptide of 49 amino acids produced by the breaking down of lactoferrin through pepsin digestion in the stomach.

There has always been a keen interest in searching for anticancer agents with minimum off-target effects and remarkable clinical efficiency (31-34). Different reviews have analyzed the role of lactoferrin in the inhibition of different cancers (35-38). In this mini-review, we have presented an overview of lactoferrin-mediated targeting of oncogenic pathways. We have browsed lactoferrin-mediated anticancer effects by using different keywords. We used "lactoferrin", "cancer", "metastasis", and "mice". We have also browsed clinicaltrials.gov for clinical trials related to lactoferrin in cancer prevention.

Lactoferrin-mediated regulation of protein networks in cancer inhibition

In this section, we have provided a brief summary of lactoferrin-mediated targeting of oncogenic proteins in different cancers. We have also provided a tabular form of effective doses of lactoferrin in different cancer cell lines (Table I).

Table I   Doses of lactoferrin used in different cell culture studies

Tabela I   Doze laktoferina korišćene u različitim ispitivanjima na ćelijskim kulturama

Lactoferrin/derivative	Cell line	Dose
Recombinant Lactoferrin	Head and neck squamous cell carcinoma cells	250 μM [39]
Recombinant Lactoferrin	Non-metastatic MDA-MB-231	109.46μg/ml [40]
Recombinant Lactoferrin	Metastatic MDA-MB-231	91.4μg/ml [40]
LfcinB9	SK-OV-3	60μg/ml [41]
Lactoferrin	Colon cancer cells	20mg/mL [53]
Lactoferrin	Oral squamous cell carcinoma	50μg/ml [46]
Recombinant Lactoferrin	Oral squamous cell carcinoma	25μg, 50μg, 100μg and 250μg [47]
Lactoferrin	T47D, MCF-7, MDA-MB-231, MDA-MB-468	10μg/ml [48]

250 μM of recombinant lactoferrin inhibits the growth and proliferation of head and neck squamous cell carcinoma cells. Oral lactoferrin stimulates the release of intestinal IL-18 and potently enhances splenic production of NK cells and serum CD8+ cells. Lactoferrin induces an increment in the number of circulating and splenic CD4+ and CD8+ cells. The depletion of mature lymphocytes with anti-CD3+ antibody severely impaired lactoferrin-mediated shrinkage of tumors (39).

Recombinant human lactoferrin demonstrates CC_{50} of 109.46μg/ml on non-metastatic and 91.4μg/ml on metastatic MDA-MB-231 cancer cells (40).

LfcinB9, a peptide derived from lactoferricin B, has been demonstrated to be effective against ovarian cancer. LfcinB9 (60μg/ml) increases the generation of ROS in SK-OV-3 cells. Intra-tumoral injections of LfcinB9 (60mg/kg) effectively impaired the tumor growth in mice inoculated with SK-OV-3 cells. It is non-toxic even at the highest tested concentrations of 640μg/ml. Hemolytic activity of LfcinB9 was very low in red blood cells (41).

LfcinB induces ~80% cell death in SKBR3 and MDA-MB-231 cells at a dose of 100 and 200 μg/ml. Intratumorally injected LfcinB induces the apoptotic death of the tumor cells, causing the shrinkage of the tumors (42).

Adenovirus carrying lactoferrin (Ad-hLF) inhibits the growth of cervical cancer cells. Ad-hLF increases natural killer cell activity and the number of CD4+ and CD8+ T lymphocyte cells in the peripheral blood of mice inoculated with cervical cancer cells (43). Ad-hLF has also been found to be effective against breast cancer (44, 45).

Lactoferrin (50μg/ml) works effectively with human neutrophil peptide-1(10μg/ml) against oral squamous cell carcinoma (OSCC) cells (46). Human recombinant lactoferrin (25μg, 50μg, 100μg and 250μg) has also been tested against OSCC cells (47).

IC30 dose for T47D and MCF-7 cells was 10μg/ml. However, at same dose, lactoferrin induced apoptosis in MDA-MB-231 (45%) and MDA-MB-468 (40%) cells (48).

Diabetes is more likely to increase the vulnerability of colon tumors in xenografted mice. HT29 tumors developed at a fast rate under a high glucose environment. Tumors formed by the colon cancer cells (HCT116 and HT29) in diabetic mice were found to be markedly different from those in non-diabetic animal models. HKDC1 (Hexokinase domain component 1) overexpression may contribute to carcinogenesis. However, NT5DC3 (5'-Nucleotidase Domain Containing 3) suppresses cancer progression. Lactoferrin upregulates the levels of m6A eraser genes and downregulates m6A writer and reader genes under high glucose concentrations. Lactoferrin was used at a dosage of 250 mg·kg−1 body weight (b.w.) (as 3.1 μM·kg−1 b.w.). Collectively, lactoferrin significantly reduced the levels of m6A modifications at 2309th site of NT5DC3 (49). Moreover, lactoferrin also inhibited DNA-methyltransferase-1 (DNMT)-mediated epigenetic repression of NT5DC3. These findings are highly intriguing and suggest that lactoferrin effectively inhibits colon cancer progression in a hyperglycemic environment.

In another exciting study, it was shown that lactoferrin interacted with NT5DC3 and activated its phosphorylation at Threonine-6 and Serine-11 sites. Lactoferrin suppressed the cancer development from T2D to colon cancer by activating the phosphorylation of NT5DC3 (50).

Pulmonary metastatic nodules were found to be remarkably enhanced in LF knockout (Lf $^{−/−}$) mice injected with B16-F10 melanoma cells. Myeloid-derived suppressor cells (MDSCs) are pathologically activated monocytes and neutrophils with strong immunosuppressive functions. There was a considerable increase in polymorphonuclear MDSCs in LF knockout mice. The apoptotic death of MDSCs was significantly reduced in cells derived from naive Lf$^{−/−}$ mice. However, the addition of LF increases the apoptotic percentage of MDSCs from Lf$^{−/−}$ mice. LF promotes the differentiation of MDSCs into DCs and macrophages. Lactoferrin deficiency facilitates a pro-metastatic microenvironment in lung tissues, which is facilitated by PMN-MDSCs. TLR9 (Toll-like receptor-9) is downregulated significantly in the lung tissues of tumor-bearing Lf $^{−/−}$ mice. TLR9 agonist not only inhibited the immunosuppressive activity of PMN-MDSCs, but also suppressed pulmonary metastatic nodules in tumor-bearing Lf$^{−/−}$ animal models (51). Lactoferrin was used as (200 mg/kg body-weight) in animal models.

Lactoferrin overexpression in 5-8F cells significantly suppressed tumor growth in xenografted mice. However, tumor growth was found to be enhanced in mice inoculated with lactoferrin- knockdown HONE1 cells. PDK1 (Phosphoinositide dependent Protein kinase-1) phosphorylates AKT at 308th threonine and increases AKT activity. Resultantly, AKT phosphorylates SIN1 and enhances mTORC2 kinase activity, which

leads to phosphorylation at serine residue-473 (AKT) by mTORC2, thus catalyzing the fullest activation of AKT. Lactoferrin not only inhibits c-Jun mediated transcriptional activation of PDK1, but also reduces PDK1-mediated phosphorylation of AKT (52).

Lactoferrin inhibits the migration and invasion of colon cancer cells at 20mg/ml. Vascular endothelial growth factor (VEGF)/VEGFR signaling contributes to the key aspects of tumorigenesis. Lactoferrin was found to effectively downregulate the levels of VEGFA, VEGFR2, p-PI3K, p-AKT and p-ERK1/2 in HCT8 and HT29 cancer cells (53).

Moreover, lactoferrin inhibited tumor xenografts in mice implanted with U87MG cells into the left caudate nucleus (54).

Recombinant adenovirus expressing human lactoferrin induced an increase in the levels of Fas and Bax in cervical cancer cells. Furthermore, caspase-3 was activated, but the levels of anti-apoptotic BCL-2 were noticed to be suppressed in cervical cancer cells (55).

Lactoferrin considerably reduced the levels of cyclin D1 and Rb phosphorylation in nasopharyngeal carcinoma cells. p21 blocks CDK2-cyclin E and inhibits CDK2-dependent phosphorylation of RB. The levels of p21 and p27 have been found to be enhanced in lactoferrin-treated cancer cells. Extracellular signal-regulated kinase-1/2 (ERK1/2) are the downstream constituents of a phosphorelay pathway that conveys mitogenic and growth signals. Lactoferrin also reduced phosphorylated ERK1/2 in nasopharyngeal carcinoma cells (56). Overall, Lactoferrin interferes with NPC proliferation through the induction of cell cycle arrest and modulation of MAPK signaling cascade.

Recombinant lactoferrin and epirubicin inhibited tumor growth in mice bearing solid Ehrlich carcinoma. Co-administration of recombinant lactoferrin and epirubicin effectively enhanced the levels of activated JNKs and p53 in tumor tissues (57).

M860 is a mouse antihuman lactoferrin monoclonal antibody having the unique ability to form a stable immunocomplex (IC) with lactoferrin. LTF-IC induced repolarization of human TAMs to M1-like phenotype. It is well-known that CD163 and CD206 are specifically expressed on M2 macrophages. Research has shown that LTF-IC significantly suppressed CD163 and CD206 and caused the stimulation of M1 markers CD86 in MDA-MB-231-TAMs (58). MDA-MB-231-TAMs expressed FcγRIIa/CD32a and FcγRI/CD64. LTF-IC exerted extraordinarily robust effects on TAMs by the induction of cross-signaling between FcγRIIa (CD32a) and lactoferrin receptor (TLR4, CD14). Blockade of mAbs against CD32a almost completely impaired LTF-IC-mediated secretion of TNFα by MDA-MB-231-TAMs. TAMs interacted with MDSCs and regulatory T cells (Tregs) for the formation of an immunosuppressive microenvironment, which played an important role in promoting the growth of tumors. Intraperitoneally administered LTF-IC caused the inhibition of tumor formation in hCD32a-transgenic mice implanted with B16 melanoma cells. LTF-IC considerably reduced the number of CD4$^+$Foxp3$^+$ Tregs and CD11b$^+$Gr-1^{hi} MDSCs within B16 tumor tissues from hCD32a-transgenic mice. Directly injected LTF-IC-pretreated viable hCD32a-TG-B16-TAMs

into solid tumors led to a momentous reduction in the percentage of Tregs and MDSCs in the tumor tissues (58).

Lactoferrin-mediated regulation of non-coding RNAs has also garnered scientific interest. Lactoferrin has been shown to trigger the expression of miRNAs in prostate cancer cells (59). However, these aspects have to be tested in detail, using experimental mice inoculated with prostate cancer cells. Expression profiling of miRNAs in the tumor tissues derived from prostate cancer cells will be helpful in the evaluation of anticancer effects of lactoferrin.

There has been a significant increase in the number of macroscopic pulmonary metastases in mice injected with miR-214 overexpressing 6-10B cells. miR-214 acts as an oncogenic miRNA and directly targets lactoferrin. miR-214 promoted AKT signaling in nasopharyngeal carcinoma cells. Therefore, lactoferrin inhibited tumor progression by the inhibition of miR-214 and AKT signaling in nasopharyngeal carcinoma cells (60).

The available evidence suggests lactoferrin-mediated regulation of different non-coding RNAs, but the information is limited and needs comprehensive validation in animal model studies.

Clinical trials

Talactoferrin (TLF), a recombinant form of human lactoferrin, was well-tolerated. No significant hematologic, hepatic, or renal toxicities were reported. Research has provided important information about the clinical efficacy of Talactoferrin. Progressive advanced or metastatic renal cell carcinoma patients were enrolled in the clinical trial for evaluation of lactoferrin (Table II) (61).

After the transportation of talactoferrin into the small intestinal Peyer's patches, it promotes the recruitment of circulating tumor antigen-loaded dendritic cells to GALT (gut-associated lymphoid tissues) and promotes their maturation. These signals trigger the induction of robust systemic innate and adaptive immune responses mediated by Natural Killer cells, $CD8^+$ lymphocytes and NK-T cells.

Phase II clinical trial was conducted by a combination of talactoferrin with paclitaxel and carboplatin as a treatment regime of metastatic NSCLC. Combinatorial treatment consisting of talactoferrin and carboplatin/paclitaxel demonstrated an increase in response rates compared to paclitaxel and carboplatin alone (62). In view of the clinically relevant evidence, clinicians initiated another correlative study to further characterize and interpret the immunostimulatory mechanisms induced by talactoferrin in patients suffering from metastatic NSCLC. However, the trials failed to generate significant evidence to substantiate the efficacy of talactoferrin in increasing the progression free survival and overall survival (63).

Furthermore, the promising results of phase II trials also paved the way for two randomized, phase III trials, including a trial of single agent talactoferrin versus placebo in patients with refractory/relapsed NSCLC, and a trial of carboplatin/paclitaxel/talactoferrin versus carboplatin/paclitaxel alone as frontline therapy (64).

However, the trials were unfortunately reported to be negative for progression free survival, as well as overall survival.

In another clinical trial, talactoferrin was used as a monotherapy. There was no evidence of grade 3 or grade 4 toxicities. Importantly, the immunological systems of enrolled patients were found to be compromised, and thus least expected to generate significant immunological responses. It was also noticed that heavily pretreated NSCLC patients with a heavy disease burden also failed to generate effective immunological responses (65). Importantly, immunological responses are inversely related to the number of previous chemotherapy regimes. Two patients with the lowest number of prior anticancer regimens remained in the trial the longest, and demonstrated an increase in the number and functional activity of NK cells.

Table II Clinical trials of talactoferrin

Tabela II Klinička ispitivanja talaktoferina

Selection Criteria	Number of Patients	Results
Progressive advanced or metastatic renal cell carcinoma. Treatment failure of prior systemic therapy.	44 adult patients	14-week progression-free survival rate of 59%. PFS was 6.4 months. Median OS was 21.1 months (61).
Stage IIIB/IV NSCLC having treatment failure for two or more prior regimens.	742 patients	Clinical trial failed to show a statistically significant difference between talactoferrin alfa and placebo (64).
Stage IV NSCLC patients previously treated with multiple chemotherapy regimens.	10 patients	Increase in immunologic activity in 2 patients (65).
Stages IIIB to IV NSCLC having treatment failure for one or two prior regimens.	100 patients	Increase in Median OS by 65% in oral talactoferrin group (66).
Progressive advanced or metastatic patients. Patients ineligible for standard chemotherapy.	36 patients	17 patients had stable disease (50% disease control rate). Median PFS in 12 NSCLC patients (4.2 months) Median PFS in 7 RCC patients (7.3 months) (67).

Concluding remarks

Lactoferrin-mediated anticancer and anti-metastatic effects have opened new horizons for the evaluation of clinical efficacy. It is pertinent to mention that clinical trials of lactoferrin give a unique perspective of translatability of lactoferrin as a promising clinical drug. Therefore, detailed analysis of lactoferrin-mediated effects in cell culture studies and tumor-bearing mice is compulsory. The highest concentrations of lactoferrins are present in bovine and human milk. Moreover, bone marrow cells, secondary granules of neutrophils, and the collecting tubules of kidneys also produce lactoferrin in the body. Emerging evidence has illuminated how lactoferrin inhibited AKT/mTOR and VEGF/VEGFR signaling for cancer inhibition.

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a highly efficient anticancer agent. There is a need to analyze how lactoferrin works with TRAIL-based therapeutics for durable cancer inhibition in animal model studies. How lactoferrin modulates different non-coding RNAs is another mystery that needs to be resolved. The identification of different long non-coding RNAs and circular RNAs likely to be regulated by lactoferrin will further refine our understanding about the combinatorial use of tumor suppressor non-coding RNAs and lactoferrin for cancer inhibition. Importantly, lactoferrin-mediated activation of immunological responses is also significant for the inhibition of cancer progression. Although researchers have started to explore the mechanisms and pathways modulated by lactoferrin for effective cancer chemoprevention, we still have to answer many outstanding questions.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

Iqra Mobeen Formal analysis, Writing - original draft; Uteuliyev Yerzhan Sabitaliyevich, Formal analysis, Writing - original draft; Aizat Moldagassimova Formal analysis, Writing - original draft; Rukset Attar Conceptualization, Supervision; Validation, Writing - review & editing.

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Ciljanje onkogenih puteva posredstvom laktoferina u hemioprevenciji raka i dopunskoj terapiji: od mehanističkih uvida do kliničkih ispitivanja

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Kratak sadržaj

Genetičke, genomske i proteomske analize ćelija, tkiva i telesnih tečnosti pružile su obilje dragocenih informacija o složenim mehanizmima koji leže u osnovi karcinogeneze i metastaza. Laktoferin, multifunkcionalni katjonski glikoprotein, predmet je velikog interesovanja zbog svojih karakteristično novih svojstava u hemioprevenciji karcinoma. Tumorsko mikrookruženje je veoma složen i sofisticiran ekosistem, koji u značajnoj meri mogu preoblikovati raznovrsni režimi lečenja. Stoga imunostimulativna uloga laktoferina preoblikuje tumorsko mikrookruženje i inhibira napredovanje kancera. Postoji dovoljno eksperimentalnih dokaza koji se odnose na imunostimulativnu sposobnost laktoferina u tumorskom mikrookruženju. Brojna klinička ispitivanja su sprovedena radi evaluacije kliničke efikasnosti laktoferina kod različitih pacijenata obolelih od kancera. Neophodno je pažljivo tumačiti kliničke dokaze i identifikovati ključne praznine u našim saznanjima vezanim za izbor grupe pacijenata obolelih od kancera za koje se očekuje da će imati najviše koristi od kombinovanog režima lečenja koji se sastoji od laktoferina i hemioterapijskih lekova. Pored toga, trebalo bi da nedostatak efikasnosti analizira tim interdisciplinarnih istraživača, zarad šireg i sveobuhvatnog razumevanja mehanizama koji leže u osnovi neuspeha u lečenju.

Ključne reči: kancer, laktoferin, metastaza, klinička ispitivanja, ćelijski signalni proces