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Lactoferrin: major physiological functions and applications.

Hao L[1], Shan Q[1], Wei J[1], Ma F[1], Sun P[1].

Abstract

Lactoferrin (lactotransferrin; Lf) is an iron-binding glycoprotein and one of the most important bioactivators in milk and other external secretions. It has numerous biological roles, including the regulation of iron absorption and modulation of immune responses, and has anti-microbial, anti-viral, antioxidant, anti-cancer, and anti-inflammatory activities. Lf regulates the quantity of iron absorbed in the intestine via its role in iron transport and can also chelate iron, directly or indirectly. Notably, it has been used as an adjuvant therapy for some intestinal diseases. It is now used in nutraceutical-supplemented infant formula and other food products. This article reviews the content, distribution, physiologic functions and current applications of Lf, and aims to shed light on future prospects for additional applications of Lf.

KEYWORDS:
anti-cancer effect; anti-microbial effect; anti-viral effect; antioxidant effect; application.; immunomodulatory function; iron-binding activity; lactoferrin (Lf)
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Effects of exogenous lactoferrin on phenotypic profile and invasiveness of human prostate cancer cells (DU145 and LNCaP) in vitro.

Zadvornyi TV[1], Lukianova NY[1], Borikun TV[1], Chekhun VF[1].

Author information

Abstract

AIM:

To investigate the biological effects of exogenous lactoferrin (LF) on phenotypic profile and invasiveness of human prostate cancer (PC) cells in vitro.

MATERIALS AND METHODS:

Human PC cell lines (LNCaP, DU-145) were cultured with an exogenous LF at a dose corresponding to IC30. The expression levels of steroid hormone receptors (androgen receptor, estrogen receptor, progesterone receptor), Her2/neu, Ki-67, E- and N-cadherin, were monitored by immunohistochemical analysis. The levels of miRNAs were assessed using q-PCR. The invasive activity of the cells was examined in a standard invasion test.

RESULTS:

Exogenous LF reduced expression of steroid hormone receptors (ERα and PR) and Ki-67 in both PC cell lines. The expression of E-cadherin increased significantly in LF-treated DU-145 cells. Also, we established the decrease in invasive activity upon LF treatment by 40% and 30% in DU-145 and LNCaP cells, respectively. In DU-145 cells, incubation with exogenous LF resulted in an increase in the expression of oncosuppressive (miR-133a and miR-200b) miRNAs.

CONCLUSIONS:

Exogenous LF causes the changes in phenotypic characteristics of PC cells and levels of oncogenic and oncosuppressive miRNAs involved in the regulation of key cellular processes.

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Decorating protein nanospheres with lactoferrin enhances oral COX-2 inhibitor/herbal therapy of hepatocellular carcinoma.

Abdelmoneem MA[1,2], Mahmoud M[3], Zaky A[3], Helmy MW[1,4], Sallam M[2], Fang JY[5,6,7], Elkhodairy KA[1,2], Elzoghby AO[1,2,8,9].

Abstract

AIM:

Lactoferrin (LF)-targeted gliadin nanoparticles (GL-NPs) were developed for targeted oral therapy of hepatocellular carcinoma.

MATERIALS & METHODS:

Celecoxib and diosmin were incorporated in the hydrophobic matrix of GL-NPs whose surface was decorated with LF by electrostatic interaction for binding to asialoglycoprotein receptors overexpressed by liver cancer cells.

RESULTS:

Targeted GL-NPs showed enhanced cytotoxic activity and increased cellular uptake in liver tumor cells compared with nontargeted NPs. Moreover, they demonstrated superior in vivo antitumor effects including reduction in the expression levels of tumor biomarkers and induction of caspase-mediated apoptosis. Ex vivo imaging of isolated organs exhibited extensive accumulation of NPs in livers more than other organs.

CONCLUSION:

LF-targeted GL-NPs could be considered as an efficient nanoplatform for targeted oral drug delivery for liver cancer therapy.

KEYWORDS:

COX-2 inhibitors; diosmin; gliadin nanoparticles; hepatocellular carcinoma; lactoferrin-targeting; oral delivery

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Oncotarget. 2016 Sep 20;7(38):62144-62158. doi: 10.18632/oncotarget.11394.

Lactoferrin selectively triggers apoptosis in highly metastatic breast cancer cells through inhibition of plasmalemmal V-H+-ATPase.

Pereira CS[1,2], Guedes JP[1,2], Gonçalves M[1], Loureiro L[1], Castro L[1], Gerós H[1,3], Rodrigues LR[2], Côrte-Real M[1].

Abstract

Breast cancer is the most common type of cancer affecting women. Despite the good prognosis when detected early, significant challenges remain in the treatment of metastatic breast cancer. The recruitment of the vacuolar H+-ATPase (V-H+-ATPase) to the plasma membrane, where it mediates the acidification of the tumor microenvironment (TME), is a recognized feature involved in the acquisition of a metastatic phenotype in breast cancer. Therefore, inhibitors of this pump have emerged as promising anticancer drugs. Lactoferrin (Lf) is a natural pro-apoptotic iron-binding glycoprotein with strong anticancer activity whose mechanism of action is not fully understood. Here, we show that bovine Lf (bLf) preferentially induces apoptosis in the highly metastatic breast cancer cell lines Hs 578T and MDA-MB-231, which display a prominent localisation of V-H+-ATPase at the plasma membrane, but not in the lowly metastatic T-47D or in the non-tumorigenic MCF-10-2A cell lines. We also demonstrate that bLf decreases the extracellular acidification rate and causes intracellular acidification in metastatic breast cancer cells and, much like the well-known proton pump

inhibitors concanamycin A and bafilomycin A1, inhibits V-H+-ATPase in sub-cellular fractions. These data further support that bLf targets V-H+-ATPase and explain the selectivity of bLf for cancer cells, especially for highly metastatic breast cancer cells. Altogether, our results pave the way for more rational in vivo studies aiming to explore this natural non-toxic compound for metastatic breast cancer therapy.

KEYWORDS:
V-H+-ATPase; V-H+-ATPase inhibitor; breast cancer; extracellular acidification rate; lactoferrin
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Radioprotective effect of lactoferrin in mice exposed to sublethal X-ray irradiation.

Feng L[1], Li J[2], Qin L[1], Guo D[3], Ding H[1], Deng D[4].

Abstract

The radioprotective effect of lactoferrin (LF) was studied in mice subjected to sublethal X-ray irradiation. The mice were randomly divided into the Control (non-irradiated mice fed a standard diet without LF), IR (irradiated mice fed a standard diet) and IR+LF (irradiated mice fed LF) groups. The mice were fed daily for 7 days prior to irradiation and for 30 continuous days following irradiation. The survival ratio of the mice in the IR+LF group was significantly increased compared with the IR group between days 15 and 30 after irradiation. The body weight of the mice in the IR+LF group was increased compared with the IR group, and the difference was statistically significant. Blood was collected from the mice via the tail vein on days 2, 7, 14, 21 and 30 following irradiation. The laboratory indicators, including leukocyte, erythrocyte and platelet counts recovered more rapidly following irradiation in the IR+LF group compared with the IR group. Treatment of the irradiated mice with LF significantly reduced the DNA damage. In the hepatic tissue the level of superoxide dismutase in the IR+LF group was significantly increased, while malondialdehyde was significantly decreased compared with the IR group. These findings indicate that LF may prevent radiation damage and may have potential as a treatment for patients with cancer who receive radiotherapy.

KEYWORDS:
X-ray; irradiation; lactoferrin; mice; radioprotection
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Evaluation of Antiproliferative Activity, Safety and Biodistribution of Oxaliplatin and 5-Fluorouracil Loaded Lactoferrin Nanoparticles for the Management of Colon Adenocarcinoma: an In Vitro and an In Vivo Study.

Ahmed F[1], Kumari S[1], Kondapi AK[2].

Abstract

PURPOSE:

Colon adenocarcinoma is the most common form of gastro intestinal tract cancer, predominantly in ageing population. Chemotherapy with 5-Fluorouracil and oxaliplatin is an indispensable treatment regimen, nevertheless having limitation of systemic toxicity and lower therapeutic index. The present study is based on evaluation of anti-proliferative potential, pharmacokinetics parameters, safety profile,

biodistribution and efficacy of 5-FU/oxaliplatin loaded lactoferrin nanoparticles in cell lines and wistar rats in order to overcome the above limitation.

METHODS:

Nanoparticles were prepared by Water-in-oil process. The anti-proliferative efficacy and mode of cellular entry was evaluated in COLO-205 cells. The pharmacokinetics and biodistribution analysis were performed in healthy rats while efficacy and safety assay were performed in ACF induced rats.

RESULTS:

5-FU and oxaliplatin loaded nanoparticles shows enhanced antiproliferative activity as compare to free drugs in COLO-205 cells. Lactoferrin nanoparticles also improve the pharmacokinetics profile, safety parameters and efficacy of 5-FU and Oxaliplatin.

CONCLUSION:

Lactoferrin nanoparticles demonstrated an attractive drug delivery module to manage the colon adenocarcinoma as it has improved the antiproliferative activity of 5-FU and Oxaliplatin against colon adenocarcinoma cells. Moreover, it also improves the pharmacokinetic profile and safety parameters of the same drug in wistar rat.

KEYWORDS:
5-fluorouracil; colon ACF; colon adenocarcinoma; lactoferrin nanoparticles; oxaliplatin; pharmacokinetic parameters
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Front Oncol. 2018 Jun 4;8:200. doi: 10.3389/fonc.2018.00200. eCollection 2018.

Bovine Milk Lactoferrin Selectively Kills Highly Metastatic Prostate Cancer PC-3 and Osteosarcoma MG-63 Cells *In Vitro*.

Guedes JP[1,2], Pereira CS[1,2], Rodrigues LR[2], Côrte-Real M[1].

Abstract

Prostate cancer and osteosarcoma are the second most common type of cancer affecting men and the fifth most common malignancy among adolescents, respectively. The use of non-toxic natural or natural-derived products has been one of the current strategies for cancer therapy, owing to the reduced risks of induced-chemoresistance development and the absence of secondary effects. In this perspective, lactoferrin (Lf), a natural protein derived from milk, emerges as a promising anticancer agent due to its well-recognized cytotoxicity and anti-metastatic activity. Here, we aimed to ascertain the potential activity of bovine Lf (bLf) against highly metastatic cancer cells. The bLf effect on prostate PC-3 and osteosarcoma MG-63 cell lines, both displaying plasmalemmal V-ATPase, was studied and compared with the breast cancer MDA-MB-231 and the non-tumorigenic BJ-5ta cell lines. Cell proliferation, cell death, intracellular pH, lysosomal acidification, and extracellular acidification rate were evaluated. Results show that bLf inhibits proliferation, induces apoptosis, intracellular acidification, and perturbs lysosomal acidification only in highly metastatic cancer cell lines. By contrast, BJ-5ta cells are insensitive to bLf. Overall, our results establish a common mechanism of action of bLf against highly metastatic cancer cells exhibiting plasmalemmal V-ATPase. This study opens promising perspectives for further research on the anticancer role of Lf, which ultimately will contribute to its safer and more rational application in the human therapy of these life-threatening cancers.

KEYWORDS:
V-ATPase; bovine lactoferrin; cancer therapy; highly metastatic cancer cells; intracellular pH; lysosomal dysfunction
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Biosci Biotechnol Biochem. 2016;80(2):257-63. doi: 10.1080/09168451.2015.1088376. Epub 2015 Sep 25.

Expression, purification, and breast cancer cell inhibiting effect of recombinant human lactoferrin C-lobe.

Hu L[1], Gao CH[1], Hong C[1], Zhong Q[1], Dong HL[1], Gao XM[1].

Author information

Abstract

Lactoferrin (LTF), a multifunctional glycoprotein of the transferrin family mainly found in exotic secretions in mammals, is an important defense molecule against not only microbial invasion but also tumors. It folds into two globular domains (N- and C-lobes) each containing an iron-binding site. The cationic antimicrobial peptide in N-lobe is known to exert anti-tumor effect via a non-receptor-mediated pathway. However, whether LTF C-lobe also contributes to its anti-tumor activity remains to be investigated. In this study, a human LTF fragment (amino acid residues 343-682) covering the C-lobe was expressed with a histidine tag in E. coli and the purified polypeptide refolded through a series of buffer changing procedure. The resultant recombinant protein caused significant growth arrest of breast carcinoma cells MDA-MB-231 in a dose- and time-dependent manner, evidently via induction of apoptosis of the cell. Our data suggest a positive role for the C-lobe of human LTF in controlling tumors in vitro.

KEYWORDS:
cancer; lactoferrin; recombinant protein
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BMC Cancer. 2015 May 22;15:425. doi: 10.1186/s12885-015-1441-4.

Iron-free and iron-saturated bovine lactoferrin inhibit survivin expression and differentially modulate apoptosis in breast cancer.

Gibbons JA[1], Kanwar JR[2], Kanwar RK[3].

Author information

Erratum in

- Correction to: Iron-free and iron-saturated bovine lactoferrin inhibit survivin expression and differentially modulate apoptosis in breast cancer. [BMC Cancer. 2018]

Abstract

BACKGROUND:

Iron binding, naturally occurring protein bovine lactoferrin (bLf) has attracted attention as a safe anti-cancer agent capable of inducing apoptosis. Naturally, bLf exists partially saturated (15-20%) with Fe(3+) however, it has been demonstrated that manipulating the saturation state can enhance bLf's anti-cancer activities.

METHODS:

Apo-bLf (Fe(3+) free) and Fe-bLf (>90% Fe(3+) Saturated) were therefore, tested in MDA-MB-231 and MCF-7 human breast cancer cells in terms of cytotoxicity, proliferation, migration and invasion. Annexin-V Fluos staining was also employed in addition to apoptotic protein arrays and Western blotting to determine the specific mechanism of bLf-induced apoptosis with a key focus on p53 and inhibitor of apoptosis proteins (IAP), specifically survivin.

RESULTS:

Apo-bLf induced significantly greater cytotoxicity and reduction in cell proliferation in both cancer cells showing a time and dose dependent effect. Importantly, no cytotoxicity was detected in normal MCF-10-2A cells. Both forms of bLf significantly reduced cell invasion in cancer cells. Key apoptotic

molecules including p53, Bcl-2 family proteins, IAP members and their inhibitors were significantly modulated by both forms of bLf, though differentially in each cell line. Most interestingly, both Apo-bLf and Fe-bLf completely inhibited the expression of survivin protein (key IAP), after 48 h at 30 and 40 nM in cancer cells.

CONCLUSIONS:

The capacity of these forms of bLf to target survivin expression and modulation of apoptosis demonstrates an exciting potential for bLf as an anti-cancer therapeutic in the existing void of survivin inhibitors, with a lack of successful inhibitors in the clinical management of cancer.

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Nutr Rev. 2014 Dec;72(12):763-73. doi: 10.1111/nure.12155. Epub 2014 Nov 18.

Anticancer effects of lactoferrin: underlying mechanisms and future trends in cancer therapy.

Zhang Y[1], Lima CF, Rodrigues LR.

Abstract

Lactoferrin has been widely studied over the last 70 years, and its role in diverse biological functions is now well known and generally accepted by the scientific community. Usually, alterations of the lactoferrin gene in cells are associated with an increased incidence of cancer. Several studies suggest that exogenous treatment with lactoferrin and its derivatives can efficiently inhibit the growth of tumors and reduce susceptibility to cancer. None of these studies, however, reported a consistent outcome with regard to the mechanisms underlying the anticancer effects of lactoferrin. In this review, the association of lactoferrin with cancer is thoroughly discussed, from lactoferrin gene expression to the potential use of lactoferrin in cancer therapy. Lactoferrin cytotoxicity against several cancers is reported to occur in distinct ways under different conditions, namely by cell membrane disruption, apoptosis induction, cell cycle arrest, and cell immunoreaction. Based on these mechanisms, new strategies to improve the anticancer effects of the lactoferrin protein and/or its derivatives are proposed. The potential for lactoferrin in the field of cancer research (including as a chemotherapeutic agent in cancer therapy) is also discussed.

KEYWORDS:

cancer therapy; cytotoxicity; gene; lactoferrin; mechanisms; protein

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