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Editorial

Milk Lactoferrin: A Nutraceutical Supplement Against Cancer

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Introduction

To fight cancer, multiple aspects of therapy are being considered involving suppression of side effects, adjunct and complementary treatments. Many epidemiological studies have revealed the importance of appropriate life style to prevent cancer. A diet containing the anti-cancer agents is proposed to be a suitable strategy to control the risk of cancer [1].

Dairy products especially milk contain many nutritional supplements including proteins, vitamins and bioactive peptides which are not only beneficial for human health but also reported for their anti-cancer potential. Lactoferrin has been derived from various sources but here the main focus in on lactoferrin derived from milk especially bovine milk [2].

Additionally, the peptides derived from lactoferrin especially bovine lactoferricin B and holo lactoferrin (iron-binding form of lactoferrin) have been reported as an anti-cancer agent. Multiple studies have reported the role of lactoferrin to stop cancer progression via various mechanisms. The silencing or downregulation of lactoferrin genes has been shown to be associated with cancer metastasis, while restoration of the expression of lactoferrin gene has inhibited the proliferation of cancer cells. Lactoferrin as an oral supplement with concentration of 0.2% to 2% showed the inhibition of carcinogenesis in animal models by 32.5 to 42.5% respectively [3]. Moreover, administration of bovine or milk lactoferrin showed preventive activity against multiple types of cancer. Finally, lactoferrin as a drug delivery system has been discussed for the targeted delivery of chemotherapeutic drugs.

Milk lactoferrin is effective on cancer

Modulation of cell cycle

Many anti-cancer agents are reported for their potential to arrest cell cycle and to induce cytotoxicity in cancer cells. The lactoferrin has been reported as a selective agent regarding to cancerous tissues because of exerting the inhibitory effect to only tumour cells while for the growth of normal cells, lactoferrin has shown to be its positive regulator. The molecular mechanism of both bovine and human lactoferrin to enhance the growth of normal cells is due to shorten the cell cycle by upregulation the expression of mRNA of proliferative cell nuclear antigen thus increases the number of cells in G2 and S phase of cycle [4].

Concerning tumour cells, both bovine and human lactoferrin has been reported to arrest the cell growth in different phases of the cell cycle. Its reported the selectivity of bovine lactoferrin in which bLF blocked the growth of tumour in four breast cancer cell lines but did not inhibit in normal cell lines. The authors revealed that the molecular mechanism of bovine lactoferrin for cell cycle arrest was associated with upregulation of phosphorylated AMPK and downregulation of mTOR, which is crucial for cell survival [5].

Induction of apoptosis

In cancer, beside higher proliferation rate and invasion characteristics, genetic changes accumulating in cells lead to dysregulation in extrinsic and intrinsic pathways and disrupt the balance between pro-apoptotic and anti-apoptotic proteins which confer the cell to evade apoptotic signalling [6].

Lactoferrin has been reported to activate the apoptotic signalling in various types of cancers. Bovine lactoferrin (bLf), when evaluated for its anti-cancer effect in stomach cancer cell line (SGC-7901) showed apoptosis induction through down regulation of AKT pathway. Finally, lactoferricin B, derivative of lactoferrin, has also shown to induce ROS-dependent apoptosis induction in human leukaemia cell line and in different cancer models [7].

Inhibition of metastasis

Lactoferrin has been reported to inhibit the cell invasion and migration in various models of cancer but exact molecular mechanism of its anti-invasive and anti-migratory activities is not cleared yet. Bovine lactoferrin showed reversal of EMT process in recent investigations on oral cancer cells and glioblastoma [6].

Besides anti-migration and anti-invasiveness effects, lactoferrin has been also reported to suppress metastasis of cancer. Particularly, when apo form of bovine lactoferrin was injected subcutaneously in mice with lymphoma and melanoma cells, it inhibits the liver, lung and spleen cancer metastasis along with inhibition of tumour induced angiogenesis. Moreover, the oral administration of bovine lactoferrin and lactoferricin B to mice having highly metastatic colon cancer, suppress the metastasis in lung and inhibit colony formation. A recent study demonstrated that deficiency of lactoferrin increased the cancer metastasis to lungs through recruiting myeloid suppressor cells in lactoferrin knockout mice. Hence, lactoferrin is an important agent to control the metastatic behaviour of cancer [8,9].

Immunomodulation effects

Inflammatory cells make up the tumour microenvironment which is a very important factor in tumour metastasis and inhibition. These inflammatory cells that participate in tumour microenvironment are mainly leukocytes including macrophages, dendritic cells, lymphocytes and neutrophils. These cells secrete various inflammatory mediators, cytotoxic molecules and cell killing soluble mediators to regulate cancer progression. Tumour fate is usually decided by interplay between immunity and cancer regulation [10]. Therefore, immunomodulation has a great impact in cancer biology and in this case the molecules that boost cytotoxic components of immunity can be good candidates as an adjuvant to chemotherapeutic agents.

Lactoferrin has been proved to potentiate components of adaptive immunity and has anti-inflammatory activity. Both bovine and human lactoferrin are reported to enter in host cell nucleus and can bind with DNA to modulate gene expression thus, controlling inflammation and regulating carcinoma. In another study, bovine lactoferrin inhibited the tumour growth in human lung cancer cells and in murine models by regulating the levels of vascular endothelial growth factor. Finally, bLF is shown to provide shield against iron disorders that lead to cancer by immunomodulation and by decreasing levels of pro-inflammatory cytokines such as tumour necrosis factor and interleukin [11].

Lactoferrin and breast cancer

The potential of bovine lactoferrin has been assessed in various models of breast cancer. Duarte., *et al*. [12] studied the effect of bovine milk lactoferrin on two HS578T and T47D cancer cell lines of human breast cancer. The cells were given exposure or treated with different concentrations of lactoferrin ranging from 0.125 to 125 μM. Thus, milk lactoferrin is proved to be a suitable anti-cancerous agent against breast cancer [13].

Lactoferrin and colorectal cancer

Bovine Lactoferrin and its peptide derivative lactoferricin B (LFcinB) have been evaluated for their anti-cancer activity against colorectal cancer cells. It has been believed that bLF and LFcinB applied its anti-cancerous activity by regulation of multiple signalling pathways.

The oral administration of lactoferrin from bovine milk was known to have anti-cancer effects on colorectal cancer so, a randomized controlled trial study was directed to assess the effect of bovine lactoferrin on the growth of colorectal polyps when administered orally.

Camel's milk lactoferrin significantly reduced the proliferation of colorectal cancer cells and prevent DNA damage [14].

Lactoferrin and prostate cancer

Lactoferrin which possess anti-cancerous and anti-metastatic activity was evaluated for it potential to manage prostate cancer. The cells were treated with bLF and rate of cell proliferation, intracellular pH, apoptosis and extracellular acidification was analysed. These experiments showed that lactoferrin from milk source can be used to manage prostate cancer and its metastasis [15].

Lactoferrin as a carrier for drug delivery in cancer

Moreover, untargeted delivery of chemotherapeutic agents is one of main contributing factor for multi-drug resistance in cancer. Therefore, specific targeting of cancer cells in cancer therapy is highly desirable. Many ligands and particles have been evaluated for specific targeting of cancer cells including antibodies, organic molecules, nanoparticles and lactoferrin [16]. Lactoferrin has been shown to conjugate with nanoparticles loaded with anti-cancerous drugs for specific targeting of cancer cells and interestingly, Lactoferrin itself can act as a carrier for targeted delivery of anti-cancerous drugs.

Doxorubicin (Dox), an anti-cancerous drug used in chemotherapy, has been evaluated in conjugation with Bovine lactoferrin to enhance its working and internalization in prostate cancer cell line and then in mice models.

Lactoferrin has the ability to cross blood brain barrier and possess good safety profile. Lactoferrin derived nanoparticles loaded with different anti-cancer agents are shown to be safe, having increased permeation to blood brain barrier and efficient in delivery of chemotherapeutic agents to glioma cells [17].

Conclusion

Lactoferrin from bovine milk has been emerged as a suitable protein for cancer treatment because of its biological activities and provide more stable treatment. Bovine lactoferrin has known to exert its anti-cancerous potential in different types of cancers through its different extracellular and intracellular effects. Moreover, bLF has the ability to cross blood brain barrier which make it useable for tumours in brain. Lastly, bLF has been emerged as a potential carrier for targeted delivery of chemotherapeutic agents for specific killing of cancer cells.

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