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Lactoferrin's Anticancer Properties: Mechanisms of Action and Emerging Directions in Cancer Treatment

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Abstract

Over the past 70 years, lactoferrin has been extensively researched, and the scientific world today recognizes and generally accepts its role in a variety of biological processes. A higher incidence of cancer is typically linked to changes in the lactoferrin gene in cells. Numerous studies indicate that lactoferrin and its derivatives can effectively suppress tumor growth and lower cancer susceptibility when administered exogenously. New methods to enhance the anticancer properties of the lactoferrin protein and/or its derivatives are suggested based on these pathways. There is also discussion of lactoferrin's potential in cancer research, particularly its use as a chemotherapeutic agent in cancer therapy.

Keywords: Lactoferrin, Cancer, Chemotherapeutic agent and Tumor

Introduction:

The majority of mammalian tissues synthesize lactoferrin, an 80 kDa protein with the potential to bind iron, but it was initially found in mammary secretions (Ashraf et al., 2024). It is found in human (1.0 to ≈3.2 mg/mL) and bovine milk (0.02 to ≈0.35 mg/mL) in high amounts, and in various secretions from epithelial cells and neutrophil second granules at lesser concentrations (Rodrigues et al., 2009; Masson and De Vasconcelos et al., 2024). Since lactoferrin is widely distributed, it may be involved in a number of significant physiological processes. Lactoferrin has been shown to have a wide range of biologically significant properties, such as immune-regulating, anti-inflammatory, antiviral, antifungal, anticancer, and antibacterial properties. According to some research, the variety of biological roles that lactoferrin has so far been shown to exhibit are caused by its capacity to bind iron and the way it interacts with particular receptors (Adlerova et al., 2008). Furthermore, it has been demonstrated that lactoferrin-derived peptides and hololactoferrin, the iron-saturated form of lactoferrin, are effective antibacterial and anticancer medications. Bovine lactoferricin B, a cationic antimicrobial peptide generated from the N-terminal of the protein lactoferrin, is the most researched lactoferrin-derived peptide (Zhou et al., 2004; Gruden and Poklar Ulrih, 2021).

Similar to the protein, this peptide has drawn more attention. It is still necessary to elucidate the intricate mechanisms that underlie the wide range of actions of lactoferrin and its derivatives. Published information on lactoferrin's anticancer mechanisms has given light on the protein's function in the initiation and spread of cancer. For instance, research has demonstrated that a rise in malignant tumors results from the downregulation or silence of lactoferrin or cytosolic lactoferrin (delta lactoferrin) genes in cells (Zhang et al., 2014; Hoedt et al., 2010). On the other hand, after the lactoferrin gene is restored, the growth of cancer cells is inhibited. Furthermore, a number of studies have demonstrated that lactoferrin and/or its derivatives can stop tumor growth in vivo as well as in vitro.The goal of this popular article is to give a general overview of their anti-cancer mechanisms of action and potential uses in cancer research.

Anticancer Activity and Mechanisms of Action:

Although the precise processes underlying lactoferrin's anticancer action are yet unknown, they can be broadly divided into three categories: immunostimulation, intracellular effects, and extracellular effects. (Yang et al., 2003; Fillebeen et al., 1991). The impacts outside of cells are mostly associated with lactoferrin's interaction with the cell membrane and membrane receptors, whereas the majority of studies' proposed intracellular effects are primarily associated with cell death and cell cycle arrest. The main way that lactoferrin stimulates the immune system is by causing immune cells to release cytotoxic effectors that kill tumors.

Table No 1: Mechanisms of Action Underlying the Cytotoxic Effects of Lactoferrin and its Peptide Derivatives Against Different Cancer Cells

Mechanism of action	Cell lines	Effective concentrations	Reference
		(μM)	
Membrane disruption	Human neuroblastoma cell lines: Kelly, SK-N-DZ, and IMR-32 Human leukemia HL-60 cells	Bovine lactoferricin B 12	Eliassen et al. (2006)
Cell cycle arrest	Canine mammary gland adenocarcinoma cell lines: CIPp and CHMp	Bovine lactoferrin 0.32-6.41	Onishi et al. (2008)
Apoptosis	Human stomach cancer cell line: SGC-7901	Bovine lactoferrin 50−100	Xu et al. (2010)

Immunostimulation and iron regulation:

It is believed that immunostimulation plays a major role in lactoferrin's in vivo anticancer actions. The immunoreaction brought on by lactoferrin or its derivatives involves both innate and adaptive immunity (Figure 1) (Wolf et al., 2007). Immunoglobulin (Ig) A and IgG, two secretory components, rise dramatically during proestrus in the uterus and fall during subsequent stages due to the cyclic variation in lactoferrin concentration (Kaushic et al., 1998). Lactoferrin primarily acts in cancer by triggering the release of anticancer killer cells and a robust Th1 response. When bovine lactoferrin is given orally to treated animals, the recruitment of lymphocytes, primarily CD4+ and CD8+, can rise by up to 20 times. Tumor-infiltrating lymphocytes have the ability to significantly slow the growth of malignancies (Wolf et al., 2007).

Following treatment with bovine

lactoferrin, the small intestine also exhibits a substantial rise in the production of IgM+ and IgA+ B cells, interleukin (IL)-18, caspase-1, tumor necrosis factor-α (TNF-α), and interferon-γ. In actuality, these proteins have a cascading effect. Pro-IL-18 is known to be cleaved by caspase-1 to produce mature IL-18 (Iigo et al., 2004). IL-18 is a cytokine that induces interferon (Cao et al., 1999). Furthermore, IL-18 functions as a stimulator of TNF-α and a number of other cytokines and has a significant role in the development of TNF-γ in T cells and natural killer cells. Additionally, IL-18 can produce CD8+ effector T cells and boost Th1 and natural killer cell responses. Intralesional and systemic IL-18 injection dramatically reduced tumor development. Lactoferrin can also boost the synthesis of nitric oxide, which has been shown to make tumors more sensitive to chemotherapy, and increase the effector functions of macrophages and natural killer cells at low concentrations. Furthermore, it was discovered that rats' VEGF165-mediated angiogenesis was systemically inhibited by oral bovine lactoferrin (Tung et al., 2013). Therefore, the combined impact of these components may result in tumor eradication and pathogen blocking. Additionally, a variety of metal-related cations, including Zn^{2+}, Fe^{3+}, Cu^{2+}, Mn^{3+}, and Ga^{3+}, can be flexibly bound and released by lactoferrin. In fact, lactoferrin is one of the primary iron regulators in the human body and is in charge of preserving iron homeostasis throughout the body. Enzyme activity and cell development depend on iron balance (Beard et al., 1996). Iron can become a potentially harmful element if it is out of balance, which can result in the production of free radicals.

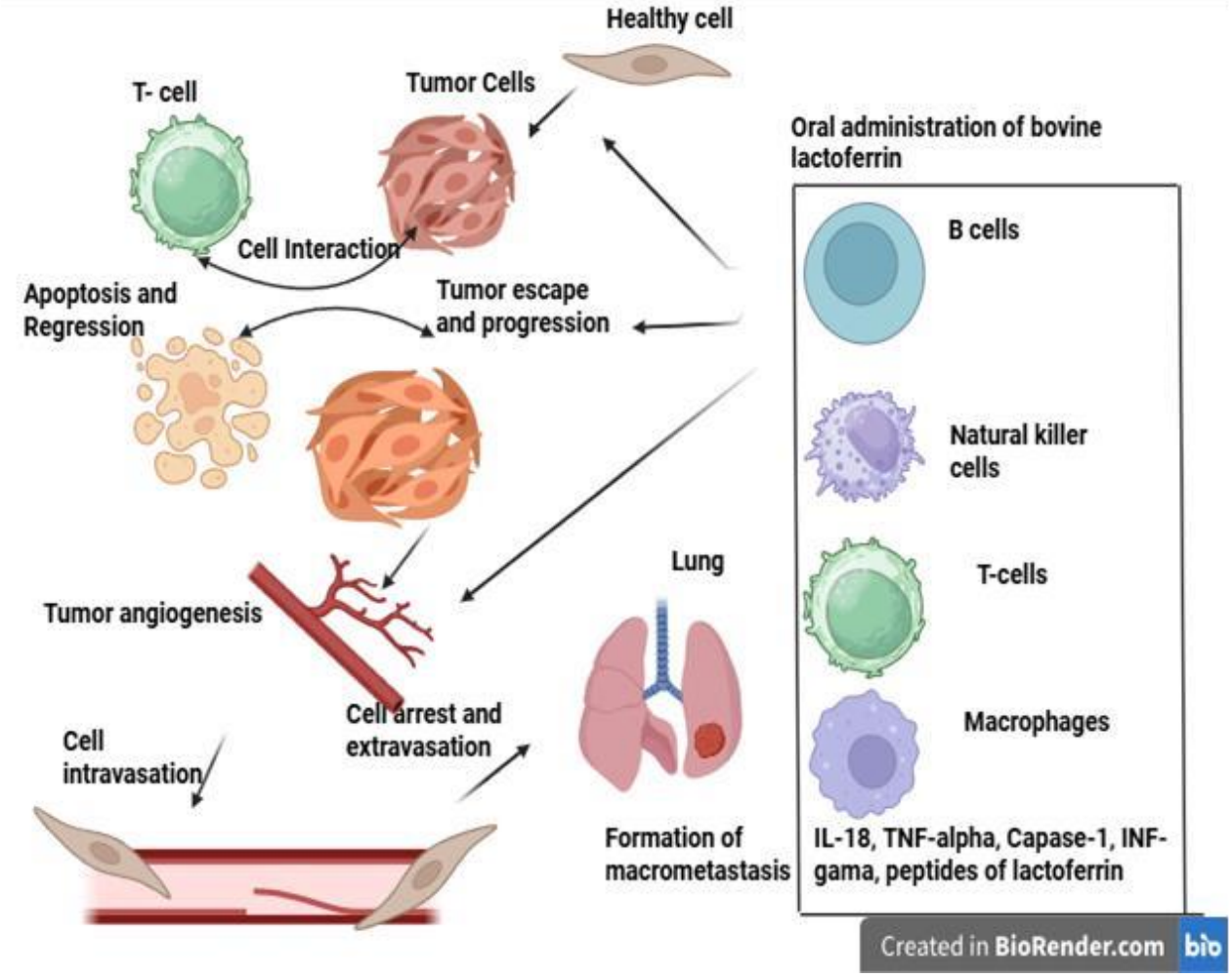

Figure No 1: In Vivo Anticancer Effects of Bovine Lactoferrin.

By causing oxidative stress, these radicals cause a cellular redox imbalance that could be linked to oncogenic activation (Valko et al., 1996). Lactoferrin may therefore be a useful chelator to preserve the iron balance in vivo.

Additionally, it has been demonstrated that iron chelators have antiproliferative properties in both in vitro and in vivo settings.

Clinical Applications and Future Trends for Lactoferrin in Cancer Therapy:

The majority of the information regarding lactoferrin's anticancer properties comes from in vitro research, where it was demonstrated that lactoferrin and its derivatives significantly reduced the growth of different types of cancer cells. This indicates that lactoferrin's direct interaction with cancer cells is most likely the cause of their cytotoxicity. Therefore, in order to get a stronger anticancer impact in vivo, lactoferrin's direct and indirect effects should be thoroughly investigated (Figure 1). Lactoferrin can be injected intravenously or intratumorally to produce its direct activity. Unfortunately, after being administered intravenously, lactoferrin can be rapidly eliminated.

At the moment, a number of carrier vectors that target both intracellularly and systemically, are accessible for the delivery of anticancer drugs. The popular liposomes and the newly developed nanoparticles have both demonstrated to be effective carriers, and their continued application in clinical practice is encouraged (Malam et al., 2009). They might be altered with certain ligands to target tumor cells or simply stay in circulation longer, releasing lactoferrin or its variations gradually and continuously stimulating the immune system. This strategy could improve the agent's ability to fight cancer and significantly lessen any potential side effects. Furthermore, it has been demonstrated that combining lactoferrin and its derivatives with proven anticancer drugs increases the death of cancer cells in vitro.

Lactoferrin's first clinical application as an adjuvant therapeutic agent in cancer patients is anticipated with this strategy. In addition to utilizing lactoferrin's immunotherapeutic benefits, this will have anticancer effects that are better than those of chemotherapy drugs alone.

Conclusion:

The majority of mammalian cells contain lactoferrin, a multipurpose protein. To preserve homeostasis, a number of variables regulate its expression. Certain illnesses, particularly carcinomas, are typically associated with the downregulation or silencing of the lactoferrin gene in cells. Restoring the expression of the lactoferrin gene can successfully stop cancer cells from proliferating. The crucial function that lactoferrin plays in preventing major diseases may be partially explained by the response elements of disease-related variables in the lactoferrin promoter and its surrounding areas. Additionally, cytotoxic experiments showed that lactoferrin and its derivatives inhibited the growth of several malignancies, indicating a possible involvement in cancer prevention. Nevertheless, the mechanisms behind the anti-cancer cytotoxicity of lactoferrin and its derivatives are based on in vitro studies and are not necessarily definitive. 11, 12, 16, 17, and 19 Thankfully, though, the findings from in vivo studies about the underlying mechanisms are comparable, namely that cancers are eradicated as a result of the growth of tumor-killer cells triggered by lactoferrin.

There are currently no reports about the use of lactoferrin in clinical practice, despite the fact that clinical trials evaluating its use in cancer therapy are ongoing. The paucity of information regarding the mechanisms of action and the comparatively low cytotoxicity of lactoferrin and its derivatives when compared to established anticancer medications are probably impeding the

practical application of lactoferrin in the treatment of cancer. But as was already indicated, lactoferrin and its derivatives may be a useful anticancer treatment option if taken in combination with other therapeutic agents or, with the right adjustments, encapsulated in carriers. Interestingly, some research has already started using these strategies to boost lactoferrin and its derivatives' cytotoxic effects.

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