

Lactoferrin Nanoparticles as Therapeutic Agent for Infectious Diseases

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Abstract

Lactoferrin (Lf) is a mammalian cationic iron-binding glycoprotein, present in many mammalian excretions and supporting newborn growth to food and pharmaceutical applications. It possesses antibacterial, antimicrobial, antiviral and antiparasitic activity thus, making it an important part of the host defense system. This review focusses on recent therapeutic advances of the natural bioactive protein Lf and its use as a potential treatment agent. Nanoparticles have been tremendously used for several clinical applications preferably as drug delivery system to improve the therapeutic efficacy. Effective conjugation of functionalized agents can improve the binding affinity of nanoparticles to specific areas of the body. Therefore, this property can ensure the protection of bioactive molecules from degradation and enabled prolonged sustainability without severe side-effects. In this study, significant advancements in Lf nanoparticle technology and their use in drug delivery arena have also been reviewed.

Keywords: Lactoferrin, nanoparticles, drug delivery, therapeutic

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INTRODUCTION

Diagnostics can implicate the onset of a disease and play an imperative role in uncovering the symptoms and signs shown by patients. Patients need to undergo several tests such as blood and urinary analysis, magnetic resonance imaging (MRI) and X-ray in order to establish accurate prognosis but these imaging systems fail to stipulate a definite diagnosis. Therefore, there should be an optimum treatment to satisfy the key requirements which can diagnose diseases at an early stage, be effective and safe even with long-term usage, be specific enough to discriminate between the diseased and healthy cells and image the accurate site of infections [1].

LACTOFERRIN

Lactoferrin is an 80 kDa cationic protein, having very high iron-binding affinity found in milk. It is an iron carrying protein and is produced in most mammalian external fluids. Recently, it has caused a significant uproar in the field of cancer research (Figure 1). Lf folds into globular lobes which further contain two major domains that are responsible to serve as the binding and glycosylation sites for iron molecules and carbonate ions. It is released

from neutrophils in the blood and inflamed tissues. Over the past few years, immense developments have been made for cancer potential alternative treatments. There are many downfalls associated with standard therapies for cancer and to overcome them, there is a need to switch to natural and alternative therapies [2, 3]. Recent study has reported the protective activities of Lf against tumorigenesis and metastatic cancers. Some of the remarkable features of Lf during regulation of cancer are that it increases the activation of natural killer (NK) cells and lymphokine-activated killer (LAK) cells, enhances the activation of apoptosis of cancer cells, up regulates neutrophil activity, inhibit angiogenesis and enhances macrophage cytotoxicity by increasing the production of cytokines and reactive oxygen species. Recent advancements in nanotechnology have paved the way for new possibilities in medical sciences, especially in the field of drug delivery.

APPLICATION OF NANOTECHNOLOGY

In recent decades, nanotechnology has evolved tremendously for the treatment of various chronic diseases. Nanomaterials have been

explored as drug delivery agents and are allowed for efficient delivery of bioactive agents to target organs. Nanoparticles range from about 10–100 nm and they have proved to be a promise as an efficient drug delivery system in order to achieve the site-specific action of drugs at a therapeutically optimal rate and dosage regimen [1, 2]. Some of the unique features associated with nanoparticles drug delivery system are that it can carry or deliver a variety of therapeutic and diagnostic agents such as small molecules, particle size of nanoparticles can be controlled, they can improve the solubility and stability of encapsulated drugs and site-specific drug delivery can be achieved using these nanoparticles. Utilizing lactoferrin by combining its multifunctional properties with nanotechnology can be a remarkable therapeutic agent.

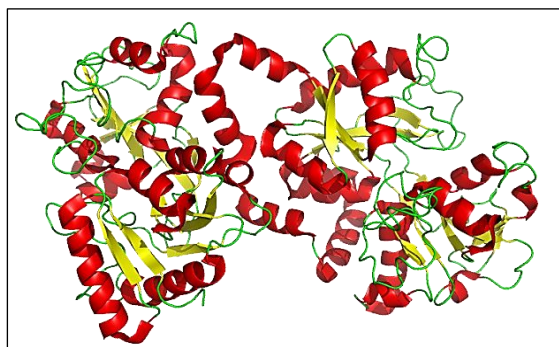


Fig. 1: Lactoferrin.

LITERATURE REVIEW

Zhang et al., 2013 used LF nanoparticles as carriers of gambogic acid (GA) to enhance oral absorption and anti-cancer activity further reducing the related toxicity. They prepared GA-Lf nanoparticles (GL-NPs) by the nanoparticle albumin-bound (NAB) technology. They further investigated *in vivo* and *in vitro* anti-tumor activities of GL-NPs and these nanoparticles were characterized by transmission electron microscopy. Their results showed that NAB technology can be feasible for industrial production of Lf nanoparticles and they can prove to be a promise for the oral delivery of GA [4]. Kumar et al., 2015 encapsulate antiretroviral drug AZT (zidovudine) in Lf nanoparticles (AZT-lactonano) to improve its oral delivery in HIV induced rats. They demonstrated that these nanoparticles were stable in simulated

gastric and intestinal fluids. They reported that AZT-lactonano can be used for the target specific drug delivery as it shows higher efficacy, improved pharmacokinetics parameter and low organs related toxicities while keeping its antiretroviral activity intact [5]. Khan et al., 2015 prepared docetaxel (DTX)-loaded solid lipid nanoparticles (SLN) using emulsification and solvent evaporation method for effective brain targeting. Lf was conjugated on SLN surface through carbodiimide chemistry and these nanoformulations were analyzed by atomic force microscopy and X-ray diffraction techniques. They concluded conjugating Lf on SLN surface (C-SLN) increased the targeting potential for brain tumor [6]. Kondapi et al., 2017 entrapped 5-fluorouracil (5-FU) in Lf nanoparticles to enhance their therapeutic efficiency. These nanoparticles were prepared by sol-oil method and they exhibit high encapsulation efficiency. They concluded that LfNPs can represent a superior nano-carrier for the targeted delivery of 5-FU in melanoma cells [7]. Nalam et al. (2017) reported photosensitizer (Chlorine e6) delivery system with Lf protein nanoparticles. Lf was used as sole matrix and Chlorine e6 (Ce6) as FDA approved photosensitizer. They prepared these nanoparticles by the water-in-oil emulsion method and further their spectral and physical properties were analyzed. They reported that these nanoparticle formulations are non-toxic to the cells and they can be efficiently loaded into the cells (Figure 2) [8].

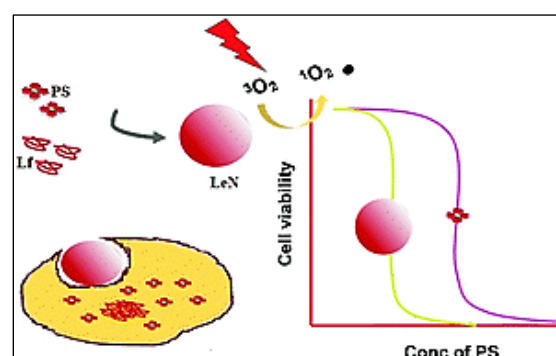


Fig. 2: Photosensitizer (Chlorine e6) Delivery System.

Kondapi et al. (2017) prepared Lf nanoparticles (LfNPs) to deliver temozolomide (TMZ) through blood-brain barrier (BBB) in glioma bearing mice.

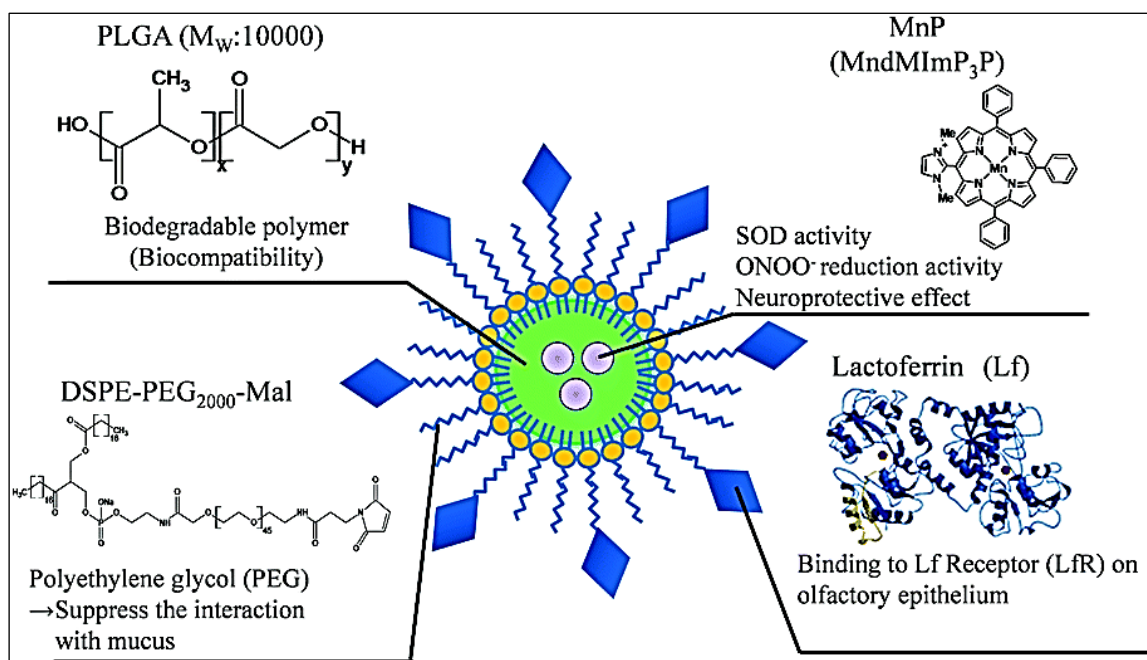


Fig. 3: Lf-NP-MnP.

They prepared TMZ-loaded Lf nanoparticles (TMZ-LfNPs) by sol-oil method. Their result reported that TMZ-LfNPs treatment results in improved median survival of glioma bearing mice, higher tumor cell apoptosis and significant reduction of tumor volume. Furthermore, they demonstrated that LfNPs present an efficient TMZ delivery platform for an effective treatment of gliomas [9]. Kawakami et al., 2017 loaded amphiphilic Mn-porphyrin derivative, MndMImP₃P (MnP) with Lf-modified nanoparticles (Lf-NP-MnP) and demonstrated the antioxidative activity in an *in vitro* experiment. They confirmed their stability through intranasal brain delivery (Figure 3) [10].

CONCLUSION

It is a strong belief that the ability of the nanoformulation can target tumors with a high degree of specificity, may allow dose escalation and result in an improved response in diseased patients along with increasing the median life survival. Several promising pharmaceutical agents have entered the market as conventional drugs can exert detrimental effects on normal organs. Nanoparticles may provide opportunities as an effective agent that can be used for diagnostic applications in recent years. The present research therefore indicates the feasibility of using Lf as a potential nanoparticle carrier to enhance the

oral absorption of hydrophobic drugs and to reduce the related toxicity.

REFERENCES

1. Jagat R Kanwar, Rasika M Samarasinghe, Rakesh Sehgal, Rupinder K Kanwar. Nano-Lactoferrin in Diagnostic, Imaging and Targeted Delivery for Cancer and Infectious Diseases. *J Cancer Sci Ther.* 4: 031–042p. doi:10.4172/1948–5956.1000107
2. Warangkana Lohcharoenkal Liying Wang Yi Charlie Chen, Yon Rojanasakul. Protein Nanoparticles as Drug Delivery Carriers for Cancer Therapy. *BioMed Research International.* Volume 2014, Article ID 180549, 12 pages. <http://dx.doi.org/10.1155/2014/180549>
3. Prashant Agarwal, Ritika Gupta. A Review on Anticancer Property of Colostrum. *Research and Reviews Journal of Medical and Health Sciences.* September 2016; 5 (4).
4. Zhen-Hai Zhang, Wang Xiaopan, Ayman Waddad, Were LL Munyendo. Studies on lactoferrin nanoparticles of gambogic acid for oral delivery. *Drug Delivery.* March 2013; 20(1).
5. Prashant Kumar, Yeruva Samrajya Lakshmi, Bhaskar C, Kishore Golla, Anand K Kondapi. Improved safety, bioavailability and pharmacokinetics of

- zidovudine through lactoferrin nanoparticles during oral administration in rats. *PlosOne*. October 13, 2015. <https://doi.org/10.1371/journal.pone.0140399>
6. Indu Singh, Rajan Swami, Deep Pooja, Manish Kumar Jeengar, Wahid Khan, Ramakrishna Sistla. Lactoferrin bioconjugated solid lipid nanoparticles: a new drug delivery system for potential brain targeting. 2015; 212–223p.
 7. Sonali Kumari Anand, K Kondapi. Lactoferrin nanoparticle mediated targeted delivery of 5-fluorouracil for enhanced therapeutic efficacy. *International Journal of Biological Macromolecules*. February 2017; 95: 232–237p.
 8. Mahesh G Adimoolam, Vijayalakshmi A, Madhusudhana Rao Nalam, Manorama V. Sunkara. Chlorine 6 loaded lactoferrin nanoparticles for enhanced photodynamic therapy. *Journal of Materials Chemistry B*. 2017; (46).
 9. Sonali Kumari, Saad M Ahsan, Jerald M Kumar, Anand K Kondapi, Nalam M Rao. Overcoming blood brain barrier with a dual purpose Temozolomide loaded Lactoferrin nanoparticles for combating glioma (SERP-17–12433). *Scientific Reports*. 2017; 7: Article number: 6602.
 10. Motoyuki Matsuh, Riku Kubota, Shoichiro Asayama, Hiroyoshi Kawakami. Lactoferrin-modified nanoparticles loaded with potent antioxidant Mn-porphyrins exhibit enhanced antioxidative activity in vitro intranasal brain delivery model. *Journal of Materials Chemistry B*. 2017; (9).

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