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Letter to the Editor

A Potential Mechanism for Lactoferrin to Prevent and Inhibit Organ Fibrosis

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Dear Editors,

Numerous reviews, including the one authored by Yu *et al*,[1] have synthesized evidence regarding the fibrosis-preventing activity of lactoferrin. The classical mechanisms through which lactoferrin prevents organ fibrosis encompass the inhibition of inflammatory responses, modulation of oxidative stress, and remodeling of the extracellular matrix. In contrast, emerging mechanisms involve the regulation of microbiota abundance and potential microRNA targeting. Additionally, lactoferrin affects the progression of organ fibrosis by modulating autophagy, mitochondrial function, and senescence (Fig. 1).[2] It is noteworthy that these integrative reviews were supported by original studies, thus lending credibility to the extracted conclusions. Overall, the current body of knowledge offers a valuable integration of the interplay between lactoferrin and organ fibrosis, providing important guidance for future research in this field.

This letter aims to propose potential refinements to the emerging mechanisms of lactoferrin in preventing organ fibrosis, which may enhance the value of the previously mentioned mechanisms. Specifically, we suggest that lactoferrin's ability to inhibit ferroptosis may contribute to its organ fibrosis-preventing properties. We will briefly clarify this assertion through a syllogistic approach,[3] a classic logical tool that has been employed for centuries. For clarity, we provide a simple example to demonstrate the logical progression in a syllogistic manner.

Example:

- Statement 1 (major premise): Protein molecules contain amide bonds (-NH-CO-).
- Statement 2 (minor premise): Lactoferrin is a protein.
- Statement 3 (inference): Lactoferrin molecules contain amide bonds.

This example illustrates how robust inferences can be drawn from existing knowledge. Following this logical structure, we propose the exploration of previously unconsidered mechanisms by which lactoferrin might prevent organ fibrosis. The detailed syllogistic analysis is outlined below:

Statement 1 (major premise): Ferroptosis inhibition alleviates organ fibrosis. Ferroptosis has been extensively implicated in the pathological processes of organ fibrosis.[4] Our focus, within the context of respiratory pharmacology, is on the relationship between ferroptosis and pulmonary fibrosis. The transferrin receptor (TFRC) in lung fibroblasts is upregulated, leading to iron accumulation.[5] The resulting elevated iron deposition,[6] coupled with the suppression of glutathione peroxidases 4 (GPX4) and ferroptosis suppressor protein-1,[7] induces ferroptosis in normal pulmonary cells, contributing to the pathogenesis of pulmonary fibrosis. In other words, ferroptosis induction promotes pulmonary fibrosis progression. Conversely, inhibiting ferroptosis can impede the advancement of pulmonary fibrosis, suggesting it as a potential therapeutic target.[8]

Statement 2 (minor premise): Lactoferrin is an inhibitor of ferroptosis. Previous studies have documented at least three mecha-

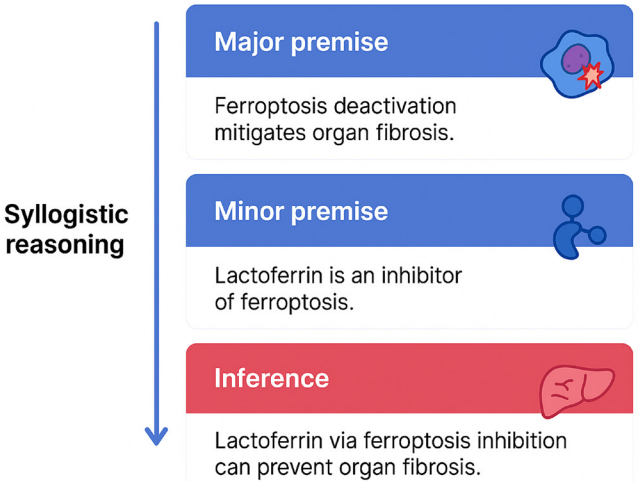

Fig. 1. Potential mechanisms through which lactoferrin affects organ fibrosis. miRNA, microRNA.

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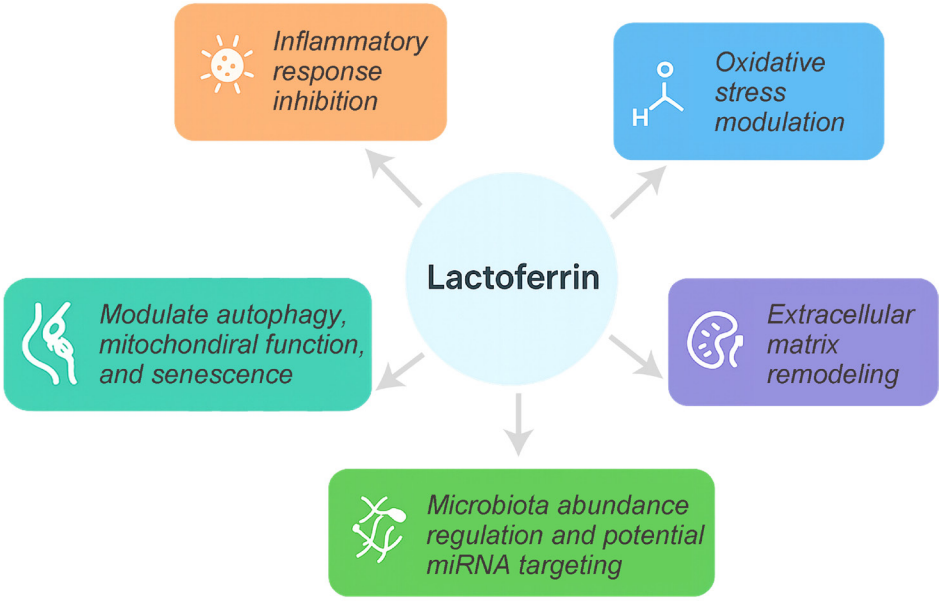

Fig. 2. Logical flow of the syllogistic argument.

nisms through which lactoferrin inhibits ferroptosis: iron chelation,[9] upregulation of GPX4,[10] and inhibition of the acyl-CoA synthetase long-chain family member 4 (ACSL4)/TFRC-1/nuclear receptor coactivator 4 pathway.[11] Iron chelation, upregulation of GPX4, and inhibition of ACSL4/TFR1/nuclear receptor coactivator 4 will suppress ferroptosis-inducing factors while promoting ferroptosis-inhibiting factors. These mechanisms may act synergistically to inactivate the ferroptosis pathway in fibrosis-related cells. Specifically, the molecular mechanisms by which lactoferrin intervenes in the three core pathways of ferroptosis are iron homeostasis regulation (TFRC/ferritin pathway), lipid peroxidation defense (GPX4/glutathione axis), and maintenance of cell membrane integrity (ACSL4-mediated polyunsaturated fatty acid metabolism). Additionally, lactoferrin can target the ferroptosis pathway through iron chelation and antioxidant synergy activated by GPX4, thereby achieving an innovative therapeutic paradigm of "multi-targeted intervention in ferroptosis in fibrosis-related cells."

Statement 3 (inference): Lactoferrin, through ferroptosis inhibition, can prevent organ fibrosis. This inference logically follows from the previous two premises, as demonstrated in the syllogistic example. Although this hypothesis reveals a new dimension of lactoferrin's anti-fibrotic action, the causal relationship of this hypothesis still needs to be further verified through targeted experiments (such as gene knockout or pathway inhibitors).

The logical flow of this reasoning is concisely illustrated in Figure 2.

Based on the above deduction, we infer that lactoferrin's ferroptosis-inhibitory capacity may provide an alternative pathway for preventing organ fibrosis. The potential targets for lactoferrin might include: TFRC/ferritin pathway, GPX4/glutathione axis, and ACSL4-mediated polyunsaturated fatty acid metabolism. As this mechanism has not been widely discussed, it offers a fresh perspective. Although we present this theory logically through syllogism, we recommend that researchers in this field further investigate the ferroptosis-related mechanisms of lactoferrin and gather solid evidence. Both *in vitro* and *in vivo* studies are anticipated to provide valuable insights. We are optimistic that, with continued investigation, lactoferrin-based therapeutic strategies for organ fibrosis treatment will be developed in the near future.

In conclusion, this letter proposes a compelling mechanism by which lactoferrin may prevent organ fibrosis, contributing to a better understanding of the mechanisms underlying lactoferrin-targeted therapies.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Formal analysis, manuscript writing (MG), investigation (YL, JC), supervision, proof-reading (CW), writing-review & editing, conceptualization, and funding acquisition (ZH). All authors have approved the final version and publication of the manuscript.

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