Press Release

Keio University

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Keio University School of Medicine

# Discovery of a mechanism that regulates inflammation by the multifunctional exogenous protein, lactoferrin. A potential new anti-inflammatory drug alternative to steroids and immunosuppressants.

A team of Keio University researchers led by Junichi Hirahashi MD, PhD, Assistant Professor of the Department of General Medicine, School of Medicine, Keio University, has identified a new mechanism by which lactoferrin, a multifunctional exogenous protein, regulates inflammation. They discovered the basic mechanism of inflammation in collaboration with a team of researchers from The University of Tokyo, led by Yasuteru Urano PhD, a Professor of the Graduate School of Pharmaceutical Sciences, The University of Tokyo, who are well known for developing a new strategy for cancer-selective imaging.

Neutrophils are the most abundant (40% to 75%) type of white blood cells in humans and are the first responders of the immune system. They are endowed with microbicidal functions including phagocytosis, degranulation, and neutrophil extracellular traps (NETs) that have recently been identified as having a web-like structure composed of chromatin fibers and serine proteases that protect against invading pathogens. On the other hand, NETs are also associated with the development of autoimmune and/or inflammatory diseases such as sepsis, systemic lupus erythematosus (SLE), *anti*-neutrophil cytoplasmic antibody (ANCA)–associated vasculitis, atherosclerosis, and deep vein thrombosis. Therefore, a treatment that properly regulates NETs is regarded as one of the ideal therapeutic strategies combatting various inflammatory diseases. By utilizing novel live-cell imaging techniques developed in Prof. Urano's laboratory, the research team determined that lactoferrin, with its strong positive charge, regulates NETs release in inflammation by shrinking its nuclear-derived chromatin structure. The current standard treatment involved in immunosuppressive therapy is often associated with fatal infections and cardiovascular disease, leading to therapy-related mortality and morbidity. Several anti-inflammatory functions of lactoferrin have previously been reported, but these new insights will open the possibility of future drug development against inflammatory diseases.

Lactoferrin (Lf) is a multifunctional protein contained in various secretory fluids, such as milk, saliva, tears, and nasal secretions of mammals. It is also present in secondary granules of neutrophils. By focusing on the positive charge of lactoferrin, the team has found that charge-charge interactions between lactoferrin and NETs were required for this function. These observations suggest that Lf serves as an intrinsic inhibitor of NETs and prevents

subsequent DNA release into the circulation. The data indicated that Lf may represent a therapeutic lead for controlling NET release in autoimmune and/or inflammatory diseases.

The team's research was also published in the July 13 edition of ***EBioMedicine***, which is an Elsevier journal published with editorial support from ***Cell Press*** and ***The Lancet***, focusing on creating dialogue and collaborations to effectively translate insights gained from biomedical research that improves human health.

Article title
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