



SCIENCE FOR THE BENEFIT OF HUMANITY

Inhibiting Chronic Inflammation via Chemotaxis Regulation

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Technology Summary:

Millions of patients suffering from chronic inflammatory diseases have a diminished quality of life and an increased risk of mortality. While current treatment regimens are partially effective, they are often limited because of extensive immunosuppression. To find better solutions, scientists are researching crucial mechanisms and targets that play major roles in the inflammatory response for new drug development. This technology describes a novel mechanism of regulating immune cell chemotaxis by a humoral cofactor offering insight into new therapeutic development for controlling overactive immunity while minimizing immunosuppression.

Drs. Ponda and Breslow have identified a plasma cofactor that is activated at inflammation sites to stimulate the migration of lymphocytes, presenting a powerful mechanism coupling inflammation to adaptive immunity. C-C chemokine receptor 7 (CCR7) and its ligands, C-C chemokine ligand 19/C-C chemokine ligand 21 (CCL19/21) comprise a signal to stimulate the migration of T-cells, B-cells, and dendritic cells. The team observed *in vitro* that a factor present in serum enhanced migration of T-cells in response to CCL19/21. A proteolytic cleavage product of high-molecular-weight-kininogen (HK) - a plasma protein that plays role in inflammation as well as other biological functions - was responsible for the activity. Coagulation factor XII was also identified as a key enzyme required for HK cleavage. The Rockefeller team next tested the biological activity of the cofactor *in vivo*, in mice. When lymphocytes were exposed to the peptide *ex vivo* and then put back into mice, the cells showed an increase in homing of T-cells and B-cells to lymph nodes. The work therefore suggests that inhibiting the generation of the cofactor peptide by blocking factor XII could potentially decrease immune-mediated inflammation. Studies are underway to further develop compounds that could be used to treat patients with chronic inflammatory conditions.

Area of Application: Inflammatory diseases

Stage of Development: pre-clinical; animal work

Lead Inventors: Dr. Manish Ponda and Dr. Jan Breslow

Patent Information: Patents filed

Reference: Ponda M.P., Breslow J.L. (2016) Serum Stimulation of CCR7 chemotaxis due to coagulation factor XIIa-dependent production of high-molecular-weight kininogen domain 5. PNAS Vol.113, No.45 E7059-E-7068.

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