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Chloroquine finding may lead to treatments for arthritis, cancer and other diseases

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In a study published recently in the journal *Science Signaling* Van Andel Research Institute (VARI) scientists demonstrate on the molecular level how the anti-malaria drug chloroquine represses inflammation, which may provide a blueprint for new strategies for treating inflammation and a multitude of autoimmune diseases such as arthritis, multiple sclerosis, and certain cancers.

Chloroquine is a widely used anti-malaria drug that inhibits the growth of parasites. For decades, chloroquine and its derivative amodiaquine have also been used as anti-inflammation drugs to treat diseases such as rheumatoid arthritis, though the exact mechanism of how chloroquine affects the immune system has remained unclear.

By providing an understanding of these basic functions, researchers may now have the necessary tools to develop improved treatments for a myriad of common autoimmune disorders.

"The implications of this study are significant," said Henry F. McFarland, Ph.D., former Chief of the Neuroimmunology Branch of the National Institute of Neurological Disorders and Stroke (NINDS). "These results provide a mechanistic basis for therapeutic strategies for treating inflammation and autoimmune diseases and should provide exciting new approaches which can be tested in clinical trials."

Autoimmune diseases arise when the body's immune system mistakes otherwise healthy cells, tissues, and organs for pathogens and attacks

them. These diseases can afflict any part of the body, but one symptom common to most autoimmune diseases is that of inflammation.

The National Institutes of Health (NIH) lists more than 80 common autoimmune diseases including asthma, Crohn's disease, Guillain-Barré syndrome, multiple sclerosis, myasthenia gravis, psoriasis, rheumatoid arthritis, and some types of cancers among many others.

Dr. H. Eric Xu, Head of the VARI Center for Structural Biology and Drug Discovery, and his colleagues showed that chloroquine represses inflammation through synergistic activation of glucocorticoid signaling. Glucocorticoids are a class of steroid hormones that bind to the glucocorticoid receptor present in almost every vertebrate animal cell. They are among the most potent and effective agents for treating inflammation and autoimmune diseases.

Synthetic glucocorticoids are used for treating asthma, allergies, and rheumatoid arthritis. Since glucocorticoids also interfere with some of the abnormal mechanisms in cancer cells, they are also used in high doses to treat certain cancers such as leukemia and lymphoma. However, at therapeutic dosages, glucocorticoids can cause a range of debilitating side effects including diabetes, osteoporosis, skin atrophy, and growth retardation.

"The discovery and development of novel uses of glucocorticoids that retain their beneficial therapeutic effects but reduce undesired adverse side effects remains a major medical challenge," said VARI Research Scientist Yuanzheng He, Ph.D., lead author of the study.

The VARI research revealed an unexpected regulation of glucocorticoid signaling by lysosomal functioning. Lysosomes are organelles found in animal cells that use enzymes to break down waste materials and cellular debris.

Researchers found that they could mimic the effect of chloroquine by inhibiting lysosomes in the cell. They believe that the development of new therapies for treating inflammation and autoimmune disease will involve strategies that combine both glucocorticoid and lysosomal inhibitors.

"We have known for some time that both steroids and lysosomes affect the immune system, but we didn't know that they worked together," said VARI President and Research Director Jeffrey Trent, Ph.D. "Researchers now have a clear path forward for undertaking projects to develop glucocorticoid and lysosomal inhibitors, and to improve the efficacy and potency of chloroquine as a therapeutic agent."

Provided by Van Andel Research Institute