



GLADSTONE INSTITUTE OF VIROLOGY AND IMMUNOLOGY NEWS

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INHIBITORY SWITCH FOUND FOR MASTER REGULATOR OF INFLAMMATION, GLADSTONE RESEARCHERS REPORT

Often called the “master regulator,” NF- κ B is a protein that controls a whole host of important bodily functions including the key inflammatory and immune responses. Researchers at the Gladstone Institute of Virology and Immunology have now discovered a new pathway by which the cell regulates the activity of NF- κ B, setting the stage for new therapeutic approaches.

Published in the August 31, 2001 issue of *Science*, the study unveils significant information about the much-studied NF- κ B, which is central to many biological processes. NF- κ B is known to be a transcription factor, a protein that jumpstarts the production of other proteins that go on to trigger inflammatory and immune responses. In order for NF- κ B to be active, it must enter the nucleus where the DNA, the genetic blueprint for proteins, is located.

“These findings reveal a previously unknown mechanism by which this powerful transcription factor is regulated,” said Warner C. Greene, MD, PhD, senior author of the paper and director of the Gladstone Institute of Virology and Immunology.

The Gladstone scientists have shown that a chemical reaction called acetylation, whereby an acetyl molecule is attached to NF- κ B, determines if NF- κ B is active or not. When acetylated, NF- κ B is active and resistant to the effects of an inhibitory protein called I κ B α . However, once an enzyme called HDAC3 deacetylates NF- κ B, I κ B α readily binds to NF- κ B and causes the transcription factor to move out of the nucleus into the cytoplasm.

HDAC3, then, becomes the “intranuclear molecular switch” that turns off the biological processes triggered by NF- κ B. With more study, developing drugs that selectively promote the deacetylation of NF- κ B could be useful in treating a myriad of diseases. These include rheumatoid arthritis and chronic inflammatory bowel disease.

“These agents could form an exciting new class of anti-inflammatory drugs,” Greene said.

The need for them is clear. Glucocorticoids, the most common anti-inflammatory drugs in clinical use today, are plagued with serious side effects, Greene said.

(more)

Immunosuppressive drugs, like cyclosporin A, have serious side effects too. Drugs based on the NF- κ B deacetylation could help give an alternative to patients who have undergone organ transplants or who are suffering from systemic lupus erythematosus.

“We clearly need better anti-inflammatory drugs and superior approaches to immune suppression in the clinic,” said Greene, who is also a UCSF professor of medicine, microbiology and immunology. Since, NF- κ B also plays a key role in the growth of many types of human cancer, these drugs might also exhibit anti-cancer activity.

Greene and his colleagues showed many years ago that when NF- κ B was activated I κ B α would degrade in the cytoplasm. However, more I κ B α would soon be produced as NF- κ B entered the nucleus and triggered the production of its own inhibitor, I κ B α . The current findings unveil how the cycle of acetylation and deacetylation controls the ability of these newly synthesized I κ B α molecules to inhibit NF- κ B. As an inhibitor, I κ B α then limits the time in which NF- κ B is able to act.

Other contributors to this study include Lin-feng Chen, PhD, postdoctoral fellow in Greene’s laboratory; Gladstone research associate Wolfgang Fischle, MS; and Gladstone senior investigator Eric Verdin, MD, UCSF professor of medicine. This study was funded by the Gladstone Institute of Virology and Immunology.

The Gladstone Institute of Virology and Immunology is one of three research institutes that comprise The J. David Gladstone Institutes, a private biomedical research institution affiliated with UCSF. The institution is named for a prominent real estate developer who died in 1971. His will created a testamentary trust that reflects his long-standing personal interest in medical education and research.

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