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Penn researchers discover how key protein stops inflammation

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Researchers at the University of Pennsylvania School of Medicine recently identified how a regulatory protein called Bcl-3 helps to control the body's inflammation response to infection by interfering a critical biochemical process called ubiquitination. While previous studies suggested Bcl-3 plays a role in immunity, this is the first report that Bcl-3 regulates inflammation by blocking ubiquitination.

Their findings, published in Science, open new avenues of exploration for developing therapies to treat infectious or inflammatory diseases, such as sepsis, diabetes, and rheumatoid arthritis.

"The novelty of our study is the discovery that Bcl-3 acting on gene expression has a profound effect on inflammation," says Ruaidhri Carmody, PhD, Senior Research Investigator in the Department of Pathology and Laboratory Medicine and first author of the Science paper. "By mimicking Bcl-3 activity, we may be able to create an artificial way to block the inflammatory response."

In the laboratory of senior author Youhai Chen, PhD, Associate Professor of Pathology and Laboratory Medicine, Carmody and others searched for clues as to how Bcl-3 controls inflammation by examining how Bcl-3-deficient mouse cells respond to infection. Their studies revealed that Bcl-3 interacts with p50, a protein that inhibits gene transcription by binding to DNA.

"p50 turns off the DNA region coding for inflammation, halting the

response to infection," explains Chen. Without Bcl-3, Chen says p50 cannot stop the inflammation response, but instead will become degraded very fast, through ubiquintination.

Ubiquitination is an intracellular system of checks and balances, where cellular proteins are flagged for disposal. During exposure to infection, Bcl-3 appears to overrule the p50 ubiquitination, stabilizing the presence of p50 on DNA and halting inflammation.

"Our study identifies another layer of information that controls the inflammatory response," says Chen. "Bcl-3 appears to take in information from the body and, in response to infection, interferes with p50 degradation to decrease inflammatory response."

"Inflammation is natural," says Chen. "If we didn't respond to infectious agents, bacteria would kill us. However, the inflammatory response must be controlled or we could also die. Bcl-3 helps regulate inflammation."

"By using what we now know about Bcl-3 regulatory function, we hope to create new ways to control inflammation for therapeutic purposes with selective anti-inflammatory agents," says Carmody.

Although drugs to suppress inflammation currently exist, Chen and Carmody say they cause many undesirable side effects in patients with inflammatory diseases.

"Current drug treatments target inflammation signaling pathways. When you inhibit entire pathways, you can produce negative side effects," said Carmody. "Since Bcl-3 acts on specific genes, we should be able to target a subset of dangerous regulatory genes without disrupting other important immune responses." Such drugs could benefit patients with chronic inflammation and transplant recipients as well as those suffering with inflammatory diseases.

In the future, the scientists aim to determine the components of the cell responsible for flagging p50 for destruction and instructing Bcl-3 to perform its vital function.

Source: University of Pennsylvania School of Medicine