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Long noncoding RNA found to quell inflammation

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A long non-coding RNA (lincRNA) - called lincRNA-EPS - responsible for regulating innate immunity has been identified by a team of scientists at the University of Massachusetts Medical School. Abundantly found in macrophages, lincRNA-EPS keeps the genes that trigger inflammation turned off until a pathogen is encountered. This discovery points to an unrecognized role for lincRNAs in the immune system and may lead to new insights into inflammatory diseases caused by uncontrolled immune responses such as lupus or inflammatory bowel disease.

"These findings suggest that there is an unexplored layer of regulation controlling inflammatory and immune responses," said Katherine A Fitzgerald, PhD, professor medicine and senior author of the study, which was published in *Cell*. "We've demonstrated an important functional role of a lincRNA in the immune system."

Long non-coding RNAs are non-protein coding transcripts arbitrarily defined as longer than 200 nucleotides (to help distinguish them from microRNA, short interfering RNAs, Piwi-interacting RNAs and other short RNAs). It is believed that lincRNA may account for the majority of RNA transcription in the human genome. "Despite their abundance, little is known about the functions of these long RNAs play in the immune system," said Fitzgerald. "In trying to understand the complex genetic circuitry that controls the immune system, immunologists have historically focused on the 2 percent of the genome that code for proteins."

Using a mouse model lacking lincRNA-EPS, Fitzgerald and colleagues showed that in their normal state, macrophages (a type of white blood cell that defends against infections) produce lincRNA-EPS to prevent the spontaneous activation of immune response genes. However, when macrophages detect a potential pathogen, lincRNA-EPS expression is suppressed to release this brake, and the pro-inflammatory response is initiated. Mice that were lacking lincRNA-EPS exhibited increased levels of cytokines and inflammatory responses that led to toxic shock.

Researchers found that lincRNA-EPS keeps the expression of immune genes in check by controlling the position of the nucleosome so they are inaccessible. When lincRNA-EPS is no longer expressed in the cells, the structure of the genome changes so critical immune-related genes are exposed for transcription. When researchers reintroduced lincRNA-EPS into the cell, expression of immune genes returned to normal levels.

"We have also found that the expression of lincRNA-EPS itself is very carefully regulated and is very sensitive to slight changes," said Maninjay K. Atianand, PhD, a postdoctoral fellow at UMMS and first author of the study. "This lincRNA is an important component in the molecular circuitry to prevent spontaneous activation of key immune genes. These findings have important implications for the potential role that lincRNAs may play in chronic inflammation and immune pathologies."

The next step for Fitzgerald and colleagues is to determine what role lincRNA-EPS plays in intestinal inflammation and its function in colon, where it is abundantly found.

More information: Maninjay K. Atianand et al, A Long Noncoding RNA lincRNA-EPS Acts as a Transcriptional Brake to Restrain Inflammation, *Cell* (2016). DOI: 10.1016/j.cell.2016.05.075