Single microRNA fine-tunes innate immune response

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Over the last few years scientists have discovered hundreds of microRNAs—tiny RNAs that regulate the expression of protein-coding genes. However, the functions of these novel molecules in mammals are largely unknown.

Now, scientists in the lab of Whitehead Fellow Fernando Camargo have discovered the first microRNA shown to play a key role in the immune system's early warning system—the innate immune response. The research, published online on February 17 by *Nature*, reveals that microRNA-223 controls the production and activation of granulocytes, white blood cells essential for host defense against invading pathogens. The findings may have implications for the treatment of inflammatory conditions as well as leukemia.

"MicroRNA-223 is unique because its expression is entirely restricted to a specific branch of the immune system," says Camargo. "We found that microRNA-223 is crucial for the development and function of the innate branch of the immune system. Our work suggests that microRNA-223 physiologically fine-tunes both the generation and function of granulocytic cells, delimiting their production and dampening their activation."

The study indicated that microRNA-223 targets Mefc2, a transcription factor that promotes the expansion of granulocyte cell progenitors. (Transcription factors are proteins that regulate gene expression.) By knocking out Mefc2, the authors found that some of the effects caused

by microRNA-223 were eliminated.

The researchers demonstrated that mice modified to lack microRNA-223 expression had up to three times as many granulocytes in their bone marrow and blood. Moreover, the granulocytes matured more rapidly and then reacted more aggressively to stimuli. This increased activity caused tissue inflammation and damage within the lungs with age or, in an acute inflammation model, within the liver, muscle and kidneys.

“If you have an infection in the lungs, granulocytes will migrate to the site of the infection and attack,” says Jonathan Johnnidis, first author of the paper and a former technician in the Camargo lab, and now a graduate student in molecular biology at the University of Pennsylvania. “Once the infection is cleared granulocytes usually migrate away and settle down. However, in this case they didn’t stand down after they were done fighting. Instead they continued an inflammatory response that did more damage.”

“Like a hand grenade once you pop the trigger out, these granulocytes are going to explode, regardless of whether they are surrounded by healthy tissue or harmful bacteria,” adds Camargo. “Lack of microRNA-223 makes it much easier to activate the grenade.”

Camargo plans to further investigate the effect of this microRNA on disease. “Our work suggests that microRNA-223 physiologically fine-tunes both the generation and function of granulocytic cells, delimiting their production and preventing excessive activation,” he says. “Also, since many forms of leukemia express diminished levels of microRNA-223, we are investigating how silencing of this microRNA may contribute to the development of that disease.”

Source: Whitehead Institute for Biomedical Research