Enigmatic molecules maintain equilibrium between fighting infection, inflammatory havoc

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Special RNA molecules called long non-coding RNAs (lncRNAs) are key controllers for maintaining immune health when fighting infection or preventing inflammatory disorders, according to research led by Jorge Henao-Mejia, MD, PhD, an assistant professor of Pathology and Laboratory Medicine in the Perelman School of Medicine at the University of Pennsylvania. The discovery offers a potential drug target for several inflammatory disorders characterized by an abnormal lifespan in a group of white blood cells, which can lead to organ damage.

The gene for a lncRNA called Morrbid was identified in 2013 by Henao-Mejia when he was a postdoctoral fellow in the lab of the present study's coauthor, Richard Flavell, PhD, FRS, at Yale University in collaboration with another coauthor, Adam Williams, of The Jackson Laboratory for Genomic Medicine, Bar Harbor, Maine. After Henao-Mejia established his lab at Penn in 2014, he and his students led the team that eventually identified the immune cells in which Morrbid is expressed and illuminated its role and mechanism by which it regulates immune cell lifespan. This current study appears as an advance online publication in *Nature* this month.

Long non-coding RNAs are transcribed from genes and are often abundant in cells, yet they do not code for proteins. The human genome contains about 20,000 protein-coding genes - less than 2 percent of the total genome - but 70 percent of the human genome actively produces

about 10,000 lncRNAs and the function of the majority of them is unknown.

The team found that Morrbid controls the life span of circulating myeloid cells, which are key to maintaining the proper balance between fighting infection and inflammation. The gene for Morrbid is conserved across species, including mice and humans, and is specific to certain immune cells—neutrophils, eosinophils, and monocytes.

These cell types comprise 70 percent of all circulating white blood cells, however, they are very potent in their reaction and sometimes so strong that they can cause much damage to surrounding, healthy tissue. The active system is akin to the first responders to a crisis or an invader of all immune cells.

But, how does the body keep this initial over-zealous-guard-dog response in check? How does the body know when and how to tell the cells to back off?

"These cells are extremely short-lived - less than one day—and their life span is tightly regulated to meet the demands of an organism," Henao-Mejia said. "If we understand the molecular mechanisms by which their life span is tightly regulated, perhaps we could correct it when the control goes awry or power it up, when needed."

Morrbid regulates cell lifespan by controlling the expression of Bim, a nearby gene that in turn controls programmed cell death in response to the abundance of pro-survival cytokines and metabolites in the surrounding environment outside cells. Morrbid essentially overrides a signaling mechanism that prevents premature immune cell death.

By deleting Morrbid in mice, the team instigated a drastic reduction in the frequency of immune cells that normally express Morrbid.

Therefore, the mice had less ability to fight infection but gained protection against inflammation.

The expression of the human version of the gene, MORRBID, is impaired in patients with hypereosinophilic syndrome, in which the lifespan of some immune cells is not kept in check, causing inflammation and organ damage. "Knowing this, Morrbid might be a good drug target for this uncommon disease and maybe even has a potential role for chronic diseases like asthma, inflammatory bowel disease, obesity, or cancer, all of which have an errant inflammatory component to their symptoms," Henao-Mejia said. "In the near future, we would like to concentrate our efforts to develop strategies to modulate the function of MORRBID in human cells as an effective therapeutic tool against inflammatory disease."

More information: Jonathan J. Kotzin et al, The long non-coding RNA Morrbid regulates Bim and short-lived myeloid cell lifespan, *Nature* (2016). DOI: 10.1038/nature19346

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