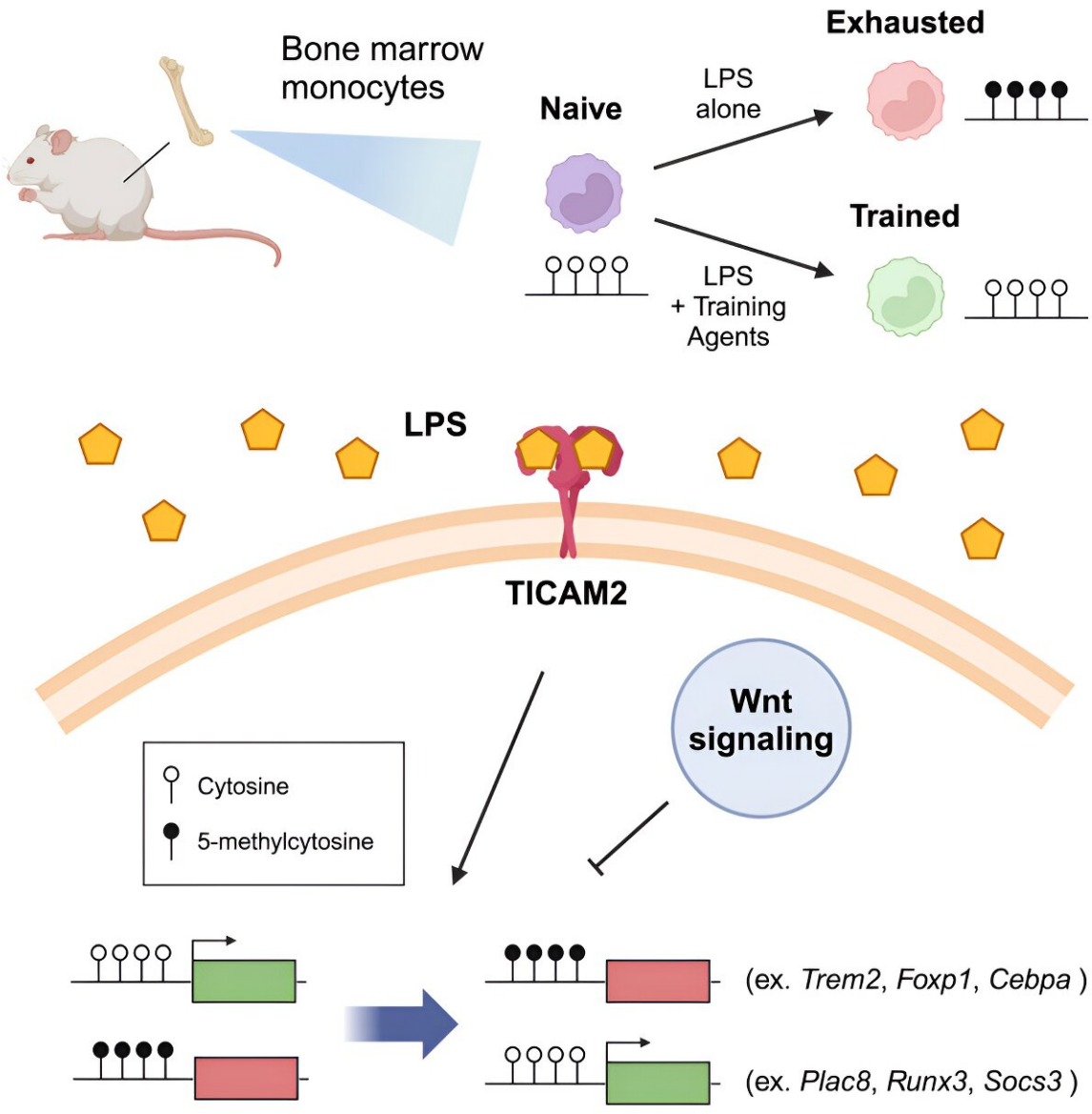
Novel DNA shift discovery may benefit severe immune conditions

March 12 2024, by Felicia Spencer



Credit: *Cell Reports* (2024). DOI: 10.1016/j.celrep.2024.113894

Discovery of a DNA shift in the innate immune memory of cells may aid in the fight against one of humans' most deadly foes—sepsis.

"Sepsis is a really horrible burden, not only in terms of mortality, but also money. It is the most expensive medical condition to treat in the U.S., like $20 billion a year, which is almost double the next highest," said Blake Caldwell, a Virginia Tech Presidential Postdoctoral Fellow.

The lead author of a study published in *Cell Reports*, Caldwell and his team demonstrated that changes to the structure and organization of DNA create an exhausted memory state in monocytes, the white blood cells that facilitate immune responses in the body.

"We found there's a critical involvement of DNA methylation in controlling innate immune memory," Caldwell said. DNA methylation is when a small molecule called a methyl group gets added to DNA, proteins or other molecules. "This impacts the capacity of monocytes to remember a past immune challenge and change their behavior in the future."

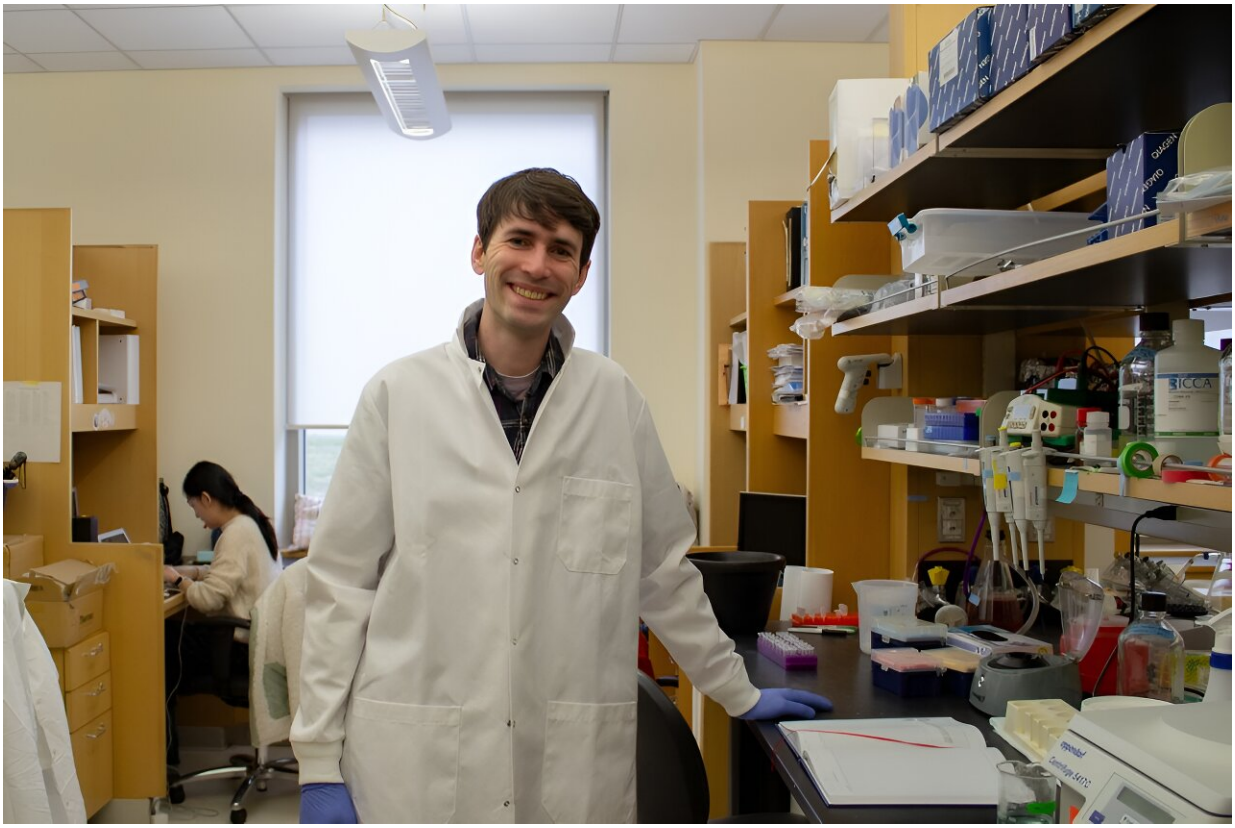
This exhausted state contributes to most sepsis patients' immune systems remaining critically disabled for months or years after the initial shock is treated.

"This is a very important work that sets a milestone marker for the novel phenomenon of innate immune memory," said Liwu Li, professor of biological sciences and Caldwell's mentor. Li is also an affiliated faculty in the Center for Emerging, Zoonotic, and Anthropod-Borne Pathogens in the Fralin Life Sciences Institute.

The research team also discovered that therapeutic interventions can prevent the DNA change and help the white cells stay in better fighting shape.

"By adding a drug that blocks the acquisition of DNA methylation, we can change the behavior of these monocytes. We can actually intervene and prevent those DNA methylation changes from occurring," said Caldwell. "We can restore normal monocyte activity, and I think that is what sets this study apart."

Caldwell credits the breakthrough in part to his previous studies and prior research experience.



Blake Caldwell, a Virginia Tech Presidential Postdoctoral Fellow, has been published in Cell Reports for his epigenetic research. Credit: Felicia Spencer for

A 2021 graduate of the University of Pennsylvania, Caldwell studied epigenetics, the study of stable cell function changes that happen without changes to the DNA sequence, with a focus on DNA methylation. When his current research team began studying the white blood cells' role in immune dysregulation during sepsis, his experience led him to look into the role of epigenetics.

"I just happened to be the right person with the right tool set to answer this question," Caldwell said. "It doesn't often work like that. I was very lucky."

Caldwell's team found that DNA methylation plays a large role in the long-term misbehavior of the white blood cells in sepsis and other severe immune conditions. And by blocking this change from occurring, researchers can right the behavior of the cells, which has implications beyond sepsis alone.

"The things we can cover using sepsis as a model for the innate immune system often apply more broadly because it's the same pathways that are being activated by COVID-19, coronary artery disease, and other severe immune events," Caldwell said. "It's a primitive but highly conserved biological system."

More information: Blake A. Caldwell et al, Altered DNA methylation underlies monocyte dysregulation and immune exhaustion memory in sepsis, *Cell Reports* (2024). DOI: 10.1016/j.celrep.2024.113894

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