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Study reveals surprising cause of immune challenges in people with Down syndrome

Researchers identify an unexpected genetic pathway behind excess hydrogen sulfide — offering fresh insight into infection risk, inflammation and potential new therapies

TEXAS A&M UNIVERSITY

image:

Dr. Larry Suva, a professor in the Texas A&M College of Veterinary Medicine and Biomedical Sciences, collaborated on research identifying a previously unknown pathway that may contribute to immune dysfunction and increased infection risks in people with Down syndrome.

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Credit: Texas A&M University

Getting sick can look very different for people with Down syndrome (DS); illnesses that are mild for most people may lead to serious complications, including pneumonia, hospitalization or intensive care.

Scientists have long known that excess hydrogen sulfide — a naturally occurring gas that becomes harmful when it accumulates in cells — has been a contributing factor for susceptibility to infections for people with DS. For years, researchers have believed that a chromosome 21 gene called CBS was largely responsible for this overproduction.

But now, researchers at the Texas A&M University College of Veterinary Medicine and Biomedical Sciences (VMBS) and the Texas A&M Health Institute of Biosciences and Technology (IBT) have identified evidence for a previously unknown pathway that may help explain those immune challenges.

The study, published in Science Advances, suggests that a different chromosome 21 gene, SOD1, may play a much larger role than previously recognized by driving an alternative pathway associated with hydrogen sulfide overproduction.

The research — led by Dr. Thomas Kent, a nanomedicine expert and neurologist at the Institute of Biosciences and Technology, in collaboration with Dr. Larry Suva, a professor in the VMBS Department of Veterinary Physiology and Pharmacology — suggests this pathway may help explain the chronic inflammation, increased infection susceptibility, and premature aging often associated with DS.

The findings shift how researchers think about the biological mechanisms behind DS's immune dysfunction.

"This is what's called non-canonical. Canonical means what the original discovery was in relation to the actions of a certain gene," Kent said. "Here is a non-canonical action of superoxide dismutase 1, which is involved in this whole other pathway of hydrogen sulfide."

The findings also suggest there may be another important biological pathway contributing to immune dysfunction in people with DS.

"It points to possible therapeutic strategies," Suva said. "If we could normalize the metabolism and production of hydrogen sulfide, it would have significant health benefits."

A new finding pointing to a potential hydrogen sulfide pathway

Because immune cells in people with DS are overactive and age quickly, Kent and Suva analyzed blood samples from 270 individuals with DS and 146 without the disease, examining gene activity and immune-related proteins.

They found that most consistently elevated gene in individuals with DS was superoxide dismutase 1 (SOD1), which helps cells break down harmful oxygen molecules and acts like part of the body's built-in cleanup system.

"Other people have reported higher levels of CBS — the enzyme that's one of the main producers of hydrogen sulfide — in Down syndrome, but we didn't see that at the protein level," Kent said. "In this study, we didn't find elevated CBS in immune cells either."

This prompted the team to investigate why hydrogen sulfide remains increased in individuals with DS. By looking at genes that are related to hydrogen sulfide metabolism, Kent's team, with first author Karthik Mouli, a Texas A&M MD/Ph.D. student, found that SOD1 may be indirectly driving a "back door" route — called the MPST pathway — which is what produces additional hydrogen sulfide.

"Hydrogen sulfide appears to come from increased import of a precursor—cysteine, an amino acid that the body can turn into hydrogen sulfide. This increase was tied to higher SOD1 levels," Kent explained. "We think there may be an alternative pathway raising hydrogen sulfide in immune cells and that this

could help explain both the autoimmune problems and the early aging of the immune system seen in Down syndrome."

A serendipitous collaboration

The project came about when Kent and his team were studying nanozymes — tiny, carbon-based particles that act like artificial enzymes in the body. After discovering they could neutralize harmful oxygen radicals linked to tissue damage, his team wondered whether the particles might also regulate hydrogen sulfide.

Working with hydrogen sulfide expert Dr. Ken Olson, at the Indiana University School of Medicine, Kent tested the idea.

"They were very active at what's called oxidizing hydrogen sulfide, essentially turning it into beneficial products the body can use,' Kent said.

When Kent's team looked for conditions where hydrogen sulfide becomes toxic, DS came into focus, and they found Suva, who conducted some of the earliest work on bone health in adults with DS and was the first to show that their fractures may not heal normally.

Kent and Suva brought their distinct scientific backgrounds together to ask a shared question: What is driving the excess hydrogen sulfide and immune dysfunction in DS?

"Dr. Kent was interested in hydrogen sulfide, and I've long been interested in the immune system in people with Down syndrome," Suva said. "We began discussing whether his technologies could be used in our disease models."

Looking ahead

The new finding gave Kent's team confidence to continue testing their nanoparticles, which mimic SOD enzyme activity to help regulate hydrogen sulfide.

"We're encouraged because Dr. Suva tested our nanoparticles in bone studies using mice that carry Down syndrome genes, and they seem to be very effective at restoring the bone function he examined," Kent said. "We're optimistic about these results, but we need to continue the work."

The team is also working to move their nanoparticles through the regulatory system to allow testing in conditions seen in individuals with DS.

Ultimately, Kent and Suva hope their research will improve the health and quality of life of people with DS.

"We hope they take away that approaches are continuing to emerge—and that it's worth keeping a close watch on how the research is progressing," Kent said.

For Suva, that progress matters when it resonates with what patients want.

"Family members know their loved one isn't going to be the greatest student. What they want to know is whether their loved one can ride a bike, play soccer, or join the 5K run at Lick Creek Park," Suva said. "If they tell me they'd much rather we do something else, that's what we would try to do."

By Ye (Vivian) Chen, Texas A&M University College of Veterinary Medicine and Biomedical Sciences

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