Cave-dwelling fish could provide clues to staying healthy with diabetes

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The cave-dwelling form of *Astyanax mexicanus*, known as cavefish (bottom image), has lost traits such as vision and pigmentation and has acquired other traits that help them survive in dark caves with minimal food supply. Fish of the same species can also be found in surface rivers near the caves (top image). Credit: Nicolas Rohner of the Stowers Institute for Medical Research.

Cavefish that live in dark caves with only sporadic access to food show symptoms similar to diabetes, but don't appear to experience any health problems. New findings presented at The Allied Genetics Conference (TAGC) 2016, a meeting hosted by the Genetics Society of America, reveal the genetic basis of how cavefish have adapted to their extreme environment, information that might one day lead to new kinds of treatments for diabetes and other diseases.

"We found that cavefish have very high body fat levels, are very starvation resistant and have symptoms reminiscent of human diseases such as diabetes and nonalcoholic fatty liver disease," said lead author Nicolas Rohner, Ph.D., of the Stowers Institute for Medical Research. "However, the fish remain healthy and don't have any obvious health problems like we see in humans. Untangling the molecular mechanisms or genetics responsible for these adaptations could potentially lead to new insights into human diseases."

Rohner's research team is studying the fish species *Astyanax mexicanus* that is native to certain areas of Mexico. One form of these fish, known as cavefish, lives in completely dark limestone caves while another form of the same fish lives in surface rivers near the caves. Through evolution, the cavefish have lost traits they don't need in the dark such as vision and pigmentation and have acquired other traits that help them survive in these dark caves with little food supply.

Rohner's research focuses on changes in cavefish metabolism that let them survive extremely long periods without food. The researchers think that about once a year flooding brings food to the caves. When food is present, the cavefish eat a lot and greatly increase their fat levels. They then draw on these fat stores for energy until they can eat again.

The team previously showed that when cavefish and surface fish were fed the same amount every day in the laboratory, the cavefish accumulated 10 times as much body fat as their surface fish counterparts. The cavefish also retained more fat than the surface fish did during periods without food.

In their most recent study, the team discovered that the livers of cavefish contain high levels of fat, a condition similar to a human disease called non-alcoholic fatty liver disease. While in humans this condition can lead to tissue scarring, inflammation, cell death, and eventually liver failure, the cavefish with fatty livers didn't show any of these problems.

The researchers also found that the cavefish exhibit very high blood glucose levels just after eating and very low levels when food isn't available. These swings in blood glucose are similar to those experienced by people with untreated type 2 diabetes, though they appear to cause no negative effects in the cavefish.

"We think that like hibernating animals that acquire extra body fat in the fall to survive the winter, the cavefish become insulin resistant as part of their strategy to acquire high body fat levels," said Rohner. "Similarly they likely use higher body fat levels to be more starvation resistant during periods when food isn't available."

The researchers identified a genetic mutation as the source of the cavefish's insulin resistance. "It is not a regulatory or seasonal mechanism like in hibernating animals," said Rohner. "The cavefish are constantly insulin resistant, and that makes the argument even stronger that this is a strategy they are using to gain higher body fat levels. The fish must have also acquired compensatory mechanisms that allow them to stay healthy despite these high fat levels."

New approaches such as Rohner's could help yield new insights on diabetes, a complex disease that likely involves many genes and many biological pathways.

"Our approach, which is known as comparative physiology or evolutionary medicine, takes advantage of the fact that many organisms have adapted to very specific environments," said Rohner. "This is a new and emerging approach aimed at trying to use natural variation as an alternative way to discover novel molecular pathways that might be missed in other types of studies."

Rohner points out that this research is likely decades away from leading to a specific treatment for patients. "However, we can point towards candidate genes and pathways that cavefish use to stay healthy," he said. "This is a unique strategy that evolution has come up with and something that we couldn't invent. Once we identify the genes and pathways and understand them, then potentially researchers can develop drugs that might help patients."

Rohner will present "Cavefish evolution as a natural model for metabolic diseases" during The Allied Genetics Conference at 9:15 AM on Friday, July 15, in Grand Ballroom 7B at the Orlando World Center Marriott in Orlando, Florida.

Provided by Genetics Society of America