Fish genes hold key to repairing damaged hearts

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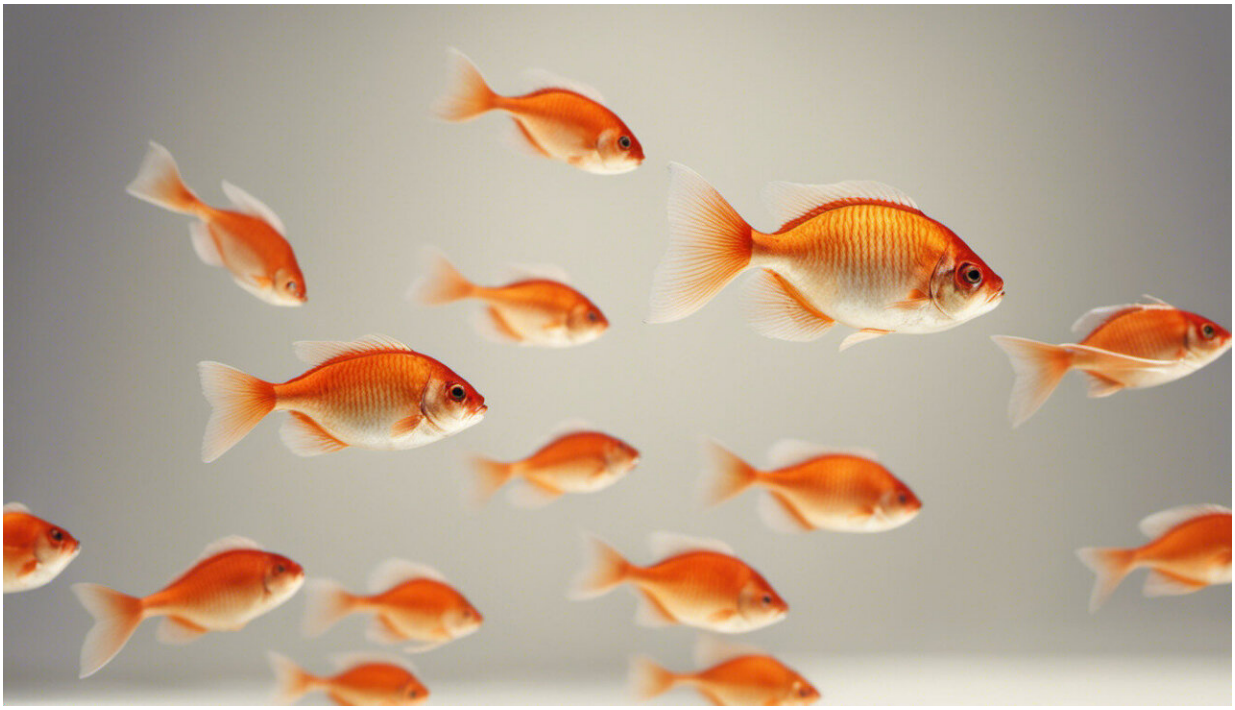

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The Mexican tetra fish can repair its heart after damage — something researchers have been striving to achieve in humans for years.

Now, new research funded by the British Heart Foundation (BHF) published in *Cell Reports* suggests that a gene called lrrc10 may hold the

key to this fish's remarkable ability.

Around 1.5 million years ago, the tetra fish (Astyanax Mexicanus) living in the rivers of Northern Mexico were periodically washed into caves by seasonal floodwaters. Over time, the floods became less frequent and eventually stopped. This created the perfect environment for different members of the same species to adapt and evolve to suit their different habitats — the river and the caves.

To this day, the surface fish still living in the rivers of Mexico have retained their ability to repair their heart tissue. However, the fish in one particular cave, called Pachón, lost this amazing ability. They also lost their colour and ability to see, with neither trait giving them any advantage in the perpetual darkness of their new home.

Dr. Mathilda Mommersteeg and her team at the University of Oxford compared the genetic code of the river fish to that of the blind cave fish to discover what special mechanisms are required for heart repair. They found three areas of the fish genome were implicated in the fish's ability to repair their hearts.

The researchers also compared the activity of genes in the river versus the cave fish in the period after heart injury. Two genes, lrrc10 and caveolin, were much more active in the river fish and could be key in allowing the river fish to repair their hearts.

Lrrc10 is already linked to a heart condition called dilated cardiomyopathy (DCM) in people. Studies in mice have previously shown that this gene is involved in the way that heart cells contract with every heartbeat.

The researchers went on to study the effect of this gene in the zebrafish, another fish which has the remarkable ability to heal its own heart.

When the team inactivated the lrrc10 gene in zebrafish they saw that the fish could no-longer fully repair their hearts.

Hundreds of thousands of people in the UK are living with debilitating heart failure, often as a result of a heart attack. During a heart attack, the heart is deprived of oxygen leading to the death of heart muscle cells and their replacement by scar tissue. This stops the heart muscle from contracting properly and reduces the heart's ability to pump blood around the body.

People suffering from heart failure can't regenerate their damaged hearts, and often the only cure is a heart transplant. Researchers hope that by unlocking the secrets of these remarkable fish, we will one day be able to heal human hearts in much the same way.

Professor Metin Avkiran, Associate Medical Director at the British Heart Foundation, said: "These remarkable findings show how much there is still to learn from the rich tapestry of the natural world. It's particularly interesting that the ability of the river fish to regenerate its heart may arise from an ability to suppress scar formation. We now need to determine if we can exploit similar mechanisms to repair damaged human hearts.

"Survival rates for heart failure have barely changed over the last 20 years, and life expectancy is worse than for many cancers. Breakthroughs are desperately needed to ease the devastation caused by this dreadful condition."

Dr. Mathilda Mommersteeg, Associate Professor of Developmental and Regenerative Medicine at the University of Oxford, who led the research, said: "A real challenge until now was comparing heart damage and repair in fish with what we see in humans. But by looking at river fish and cave fish side by side, we've been able to pick apart the genes

responsible for heart regeneration.

"Heart failure is a cruel and debilitating illness that more than half a million people across the UK are living with. It's early days but we're incredibly excited about these remarkable fish and the potential to change the lives of people with damaged hearts."

Provided by University of Oxford