Zebrafish study leads to potential treatment for muscle disease

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Rob Bryson-Richardson and Avnika Ruparelia with zebrafish

The tiny zebrafish has been used by Monash University researchers to identify a potential approach to treating the progressive and devastating muscle disease, myofibrillar myopathy. The findings may also be useful for diseases such as Alzheimer's and Parkinson's disease, which also involve an accumulation of protein aggregates.

Myofibrillar myopathy is diagnosed by the presence of protein aggregates in the muscle cells, and the muscle structure is compromised so that when it contracts the fibres rip apart. The symptoms first appear

in teenagers but function continues to decline with age, resulting in severely debilitating muscle weakness and ultimately disruptions to breathing and cardiac function that can be fatal.

In the case of myofibrillar myopathy, the genetic variation that causes the disease changes a protein that forms part of the muscle structure, such that patients have a mixture of healthy and disease-causing versions of the protein.

The research team, led by Monash geneticist Dr Robert Bryson-Richardson, used zebrafish to model the disease and allow them to better understand how this mixture of proteins results in muscle weakness and to determine how it could be prevented. Zebrafish are an excellent model because they are transparent and so it is possible to see the muscle form inside the living animal.

Lead author Dr Avnika Ruparelia explained how the findings, published in the journal *Human Molecular Genetics*, were unexpected.

"Our research showed that while the disease-causing form of the protein created the characteristic aggregates in the muscle and disrupted the muscle structure, surprisingly, it did not result in muscle tearing, which instead occurred when the protein was removed. This was surprising as patients are known to have both healthy and disease forms of the protein, rather than loss of them."

"It appears that the diseased form of the protein triggers the formation of the aggregates and traps the protein away from the muscle, so although it isn't lost, it can't do its job of protecting the muscle." Dr Ruparelia said.

The team therefore turned their attention to the aggregates. Senior author Dr Bryson-Richardson explained how the cells of our bodies have

many ways to remove damaged components that should prevent aggregates such as these forming, but that this isn't the case with myofibrillar myopathy.

"We explored why these quality control pathways weren't removing the aggregates," Dr Bryson-Richardson said.

"We found that one of these pathways had started the process and then became stuck. Not only did this mean the aggregates were not removed but the other pathways were prevented from taking over. Crucially we found that if we turned off the blocked pathway or used drugs that triggered other quality control mechanisms, then the aggregates disappeared," Dr Bryson-Richardson said.

Dr Bryson-Richardson explained the significance of the findings and the next steps in the research.

"Achieving the same effect in humans may prevent their muscles from being torn and we are now testing this theory with zebrafish. We are optimistic that this could lead to a successful treatment for myofibrillar myopathy and has the potential to treat other aggregate diseases such as Parkinson's and Alzheimer's," Dr Bryson-Richardson said.

Provided by Monash University