Scientists discover gene controlling muscle fate

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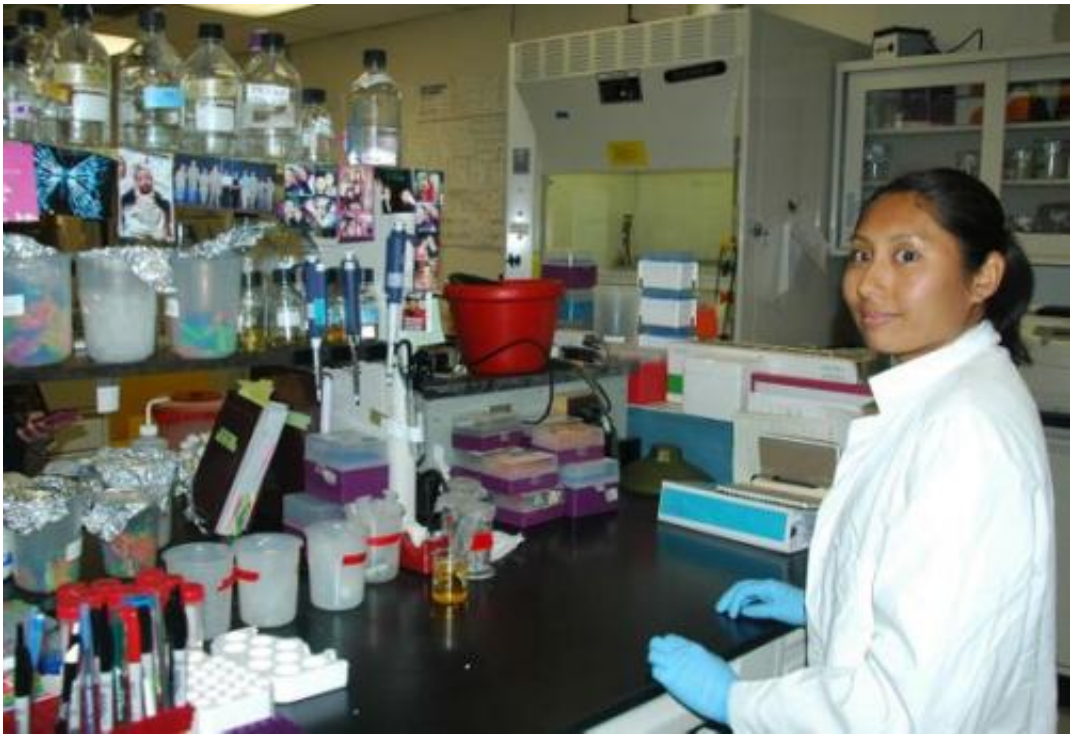

Sandy Oas identified one of the control proteins that regulates alternative splicing and instructs flight muscles to produce their form of the protein.

Scientists at the University of New Mexico have moved a step closer to improving medical science through research involving muscle manipulation of fruit flies. They discovered in the flight muscles of Drosophila a new regulator of a process called alternative splicing. Their findings give additional hope that could help treat diseases such as

myotonic dystrophy, a multisystem disorder affecting skeletal and smooth muscle as well as the eye, heart, endocrine system and central nervous system.

The research, titled "Arrest is a regulator of fiber-specific alternative splicing in the indirect flight muscles of Drosophila," was published recently in the *Journal of Cell Biology*.

"Though previous studies have suggested the involvement of alternative mRNA splicing in the formation of different muscle fiber types—a process critical to normal human physiology—Dr. Cripps and his colleagues have provided mechanistic insights into exactly how this happens," said Tanya Hoodbhoy, of the National Institutes of Health's National Institute of General Medical Sciences. "Such details about the biology underlying correct muscle fiber type specification will help researchers better understand the development of diseases where alternative splicing is affected, such as myotonic dystrophy 1."

This study, led by Master's candidate Sandy Oas, builds upon previous research established by herself in collaboration with her co-authors on the paper, UNM Department of Biology's Professor Richard Cripps and Research Assistant Professor Anton Bryantsev. They focus their studies on two very distinct muscle types – flight muscle and jump muscle – as a model to understand how different muscle types are formed.

In her new paper, Oas used the same fly system to understand how alternative splicing is regulated. In all animals and plants, the function of a gene is to produce a protein inside of a cell. Cells also have a mechanism called alternative splicing, which enables a single gene to produce multiple slightly different proteins. In this study, Oas identified one of the control proteins that regulates alternative splicing and thereby instructs the flight muscles to produce their form of the protein.

"Looking at flight muscle and jump muscles, we know that several genes are spliced one way to produce one form of a protein in the flight muscles; and another way to produce another form of the same protein in the jump muscles," Cripps said. "Controlling which form is produced is this process called alternative splicing."

In her research, Oas discovered a new protein called "Arrest" that regulates splicing, and deciphered through several experiments that Arrest has a flight muscle specific function.

"This protein was previously known to function in the ovaries. It was not known to be in flight muscles whatsoever so it was really novel and the reason why we were really excited to discover something like this regulator," Oas said.

Initially, the researchers performed a behavioral test where they took flies that were missing this protein in their flight muscles and asked, 'are they flightless?'

Oas and colleagues found that the flies were flightless, and when they performed further testing through molecular work, they discovered that the splicing had changed from the flight muscle pattern to that of the jump muscle pattern.

"It was kind of like this reverse thought process – if Arrest was removed, then you'd predict splicing in the flight muscles to be more like a jump muscle if Arrest is a regulator for flight muscle, and that's what we saw," Oas said.

After that, the researchers wondered what happens when you express Arrest in a place where it's not normally expressed. They expressed it in a jump muscle and discovered that the jump muscles now splice in a pattern more like the flight muscles, indicating that Arrest is a very

powerful regulator of flight muscle alternative splicing.

As part of her research, UNM student Sandy Oas used a confocal microscope, which enables researchers to look at structures inside cells in unprecedented detail.

The researchers also discovered that in young muscle cells Arrest is deposited to a unique location inside the nucleus of flight muscle cells.

"We discovered Arrest was only found in the flight muscle from very early in development, and continued this expression to the adult fly," Oas said. "We then looked more closely and discovered that Arrest was located in a very concentrated site within the nucleus."

"While we know of several structures within the nucleus, the concentrated deposit of Arrest was a previously-unidentified structure,"

said Cripps, which the researchers named the B-body for Bruno Body. Scientists around the world are currently working hard to understand the internal structure and organization of the nucleus, and the findings of Oas and colleagues also provide new insight into how the "brain" of the cell works.

The authors point out that their research would not have been possible without the recent purchase in Biology of a confocal microscope, which enables researchers to look at structures inside cells in unprecedented detail.

"We are very appreciative of the support of the Department of Biology, the College of Arts & Sciences, and the Office of the Vice Provost for Research and Economic Development, who helped us purchase this instrument," said Cripps.

Provided by University of New Mexico