Addressing joint issues through mitochondria

By Olivia Hall

As an equine surgeon, Michelle Delco '98, D.V.M. '03, Ph.D. '16, frequently treats horses with arthritis and fractures that go into the joint. As a researcher, she hopes to figure out how to help her patients much sooner. "There are many reasons why horses break down on the track," said Delco, an assistant research professor in the Department of Clinical Sciences, "but in many cases, the first domino to fall is probably a low-grade cartilage injury."

Joints that have suffered even mild damage often develop arthritis, but it can take months, years, sometimes decades for the first, painful symptoms to show up. At that point, the joint damage is irreversible. Currently no replacement exists for healthy cartilage, which cushions the ends of bones and ensures frictionless joint movement. When cartilage is lost, the underlying bone is exposed to repeated microtrauma and may become brittle and ripe for fracture.

"So my motivation is to try to find out why we get ongoing tissue damage after a joint injury," Delco explained. "What can we do to prevent and treat it before it's too late?" The answers, she believes, lie in the mitochondria.

Often referred to as "the powerhouses of the cell," mitochondria evolved from bacteria that lived symbiotically in other organisms, converting nutrients and oxygen into energy for normal tissue functioning and repair. "I totally geek out when I talk about mitochondria, because they're just amazing little organelles," Delco said. "They even have their own genome, which is separate and different from the DNA in our chromosomes."

This unique attribute, however, can cause problems when mitochondria dysfunction and release mitochondrial damage-associated molecular patterns (mDAMPs). The body's immune system interprets mitochondrial DNA as a foreign invader and fights back, creating inflammation and ongoing tissue damage.

While this process is known to take place in other tissues, Delco's research on mDAMPs in cartilage is new. The concept stems from her previous work. "We know that mitochondria in cartilage cells dysfunction when you already have arthritis, but we were the first to look at mitochondria immediately after a joint injury," she said. These earlier studies showed that impact injury to live cartilage causes chondrocytes (cartilage cells) to undergo mitochondrial dysfunction. The next piece of the puzzle is to determine how this cell dysfunction turns into a joint-wide problem with self-perpetuating tissue damage — that's where mDAMPs come in.

Delco is running four experiments to assess the role of mDAMPS in early joint injury and arthritis: First, she is stressing chondrocytes on a dish with chemicals that cause mitochondria to fail in different ways. "I'll see what makes them spit out mitochondrial DNA, which will tell me some of the mechanisms going on inside the cell," she explained. Zooming out, another study will determine if mitochondrial dysfunction caused by mechanical injury to chunks of cartilage results in mDAMP release. Delco hopes these studies will reveal the most sensitive indicators of mitochondrial dysfunction and early cartilage injury.

To gauge the relationship between cartilage injury and mDAMPs in live animals, Delco is drawing on joint fluid samples collected a few years ago for her doctoral work on experimental high-speed injuries to articular cartilage in horses. Finally, she plans to look at mDAMPs in samples collected from horses being treated for naturally occurring joint injuries.

Ultimately, Delco hopes her research will help turn mDAMPs in joint fluid into a useful biomarker — a non-invasive diagnostic and prognostic tool after joint injury. "If mDAMPs are signaling ongoing inflammation and tissue damage, acting as the fuel of arthritis, can we figure out how to cut this off at the pass?" Delco said. "If we can understand some of these early links in the chain, it gives us new ways to intervene — not only in horses but also in humans."

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