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Learning lessons about muscle wasting from insect larvae

Tobacco hornworm pupae (top; photo credit: Mike Kanost and Michelle Coca Mora) and dissected intersegmental muscles (bottom; photo credit: Erika Geisbrecht).

Muscle loss is an inevitable aspect of ageing, but disease and injury can also cause muscles to waste, leading to weakness and instability. 'Unfortunately, low muscle mass limits normal daily activities – even simple tasks, such as eating or stair climbing – thus reducing quality of life', says Erika Geisbrecht from Kansas State University, USA, who would like to understand why muscles waste with age in the hope of designing treatments to help people remain active for longer. However, investigating the molecular components of muscle deterioration is not ideal in a species that routinely lives for more than 70 years. Fortunately, Geisbrecht knew of an animal that experiences muscle wasting as a natural part of its 1–2 month life cycle, the tobacco hawk moth (*Manduca sexta*): '[muscle] atrophy occurs normally in a subset of muscles, called the intersegmental muscles, during the pupal stage', says Geisbrecht, adding that the large pupae are ideal for identifying key components of the molecular machinery from individual animals.

She and David Brooks set about investigating how the muscle proteins changed over the course of the tobacco hawk moth's metamorphosis. 'The hardest part … was carefully controlling temperature and time points to make sure our developmental stages were precise', says Geisbrecht, who had to collect muscles from the pupae first thing in the morning 15 days after the eggs were laid – just before the muscles began to waste – and then 3 days later, toward the end of the wasting process. Then, Brooks painstakingly removed the pupae's muscles and analysed the proteins that comprised them, identifying 244 that differed between the normal and wasted muscles. Not surprisingly, the insects had mobilised proteins that digest and dispose of proteins as the muscle broke down over 3 days, in addition to increasing the levels of the proteins that contribute to energy generation, to fuel protein digestion. They also discovered that the metamorphosing moth pupae were producing less of the proteins that comprise the contracting muscle filaments: actin and myosin. However, Geisbrecht was most surprised when she realised that the quantity of myosin in the muscle increased as the actin dwindled, suggesting that the wasting process is tightly coordinated.

So, how does this help us to understand muscle loss in elderly and sick people, which look nothing like moth pupae? Fortunately, at a genetic level, humans and insects share ∼75% of the same genes, so, having identified some of the key proteins involved in muscle wasting in the tobacco hawk moth, Geisbrecht could switch to focus on muscle wasting in another insect, *Drosophila*, which comes complete with a sophisticated box of molecular tools that could be used to uncover the roles of specific genes in the process. But first she had to identify a gene in the versatile insect that she could switch off to prevent muscle wasting on demand. Kumar Vishal and Simranjot Bawa (both from Kansas State University) tested six *Drosophila* strains that had been adapted to allow specific genes to be switched off and struck gold when they found that deactivating an actin filament regulator, Ciboulot – which promotes the growth of actin filaments on one face of the actin molecule – prevented the muscle from wasting during metamorphosis.

The team had found a gene in the insect that they can now use to control muscle wasting to begin identifying key components in the process. In addition, Giesbrecht is eager to find out whether Ciboulot is also a key player in muscle loss in elderly and ill people, in the hope of developing new treatments for people suffering from muscle loss.

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