Ancestral Skeleton Amplifies Swimming

Evolution has left us with many mementos from our fishy past, most of which vanish early in development, and the notochord is one of them. All vertebrates develop a notochord, a form of rigid hydrostatic skeleton, early in gestation. The notochord soon becomes enclosed by short sections of bone that develop into individual vertebrae that eventually form the vertebral column. But hagfish didn't evolve a mineralised skeleton. John Long explains that hagfish are a 'mosaic of ancestral and derived features', with the features that remain from the past providing a link to our ancestors. He adds that their undulating swimming style could also be related to the way our aquatic ancestors swam. Long wondered whether the hagfish could tell us anything about how a notochord functioned in swimming from the past through to the present. Together with his colleagues, Long has discovered that the hagfish's notochord has an amazing mechanical property; the notochord is mechanically tuned for maximum swimming efficiency with minimum effort (p. 3821).

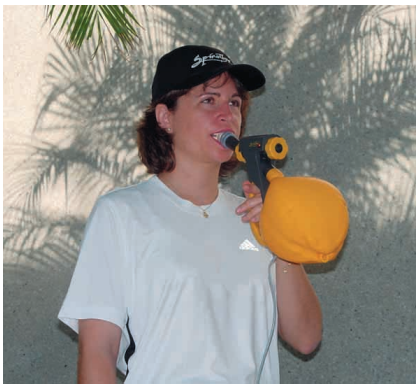
Long knew that if he wanted to analyse how the fish's hydrostatic skeleton contributed to its undulating swimming stroke, he would have to understand the fish's undulating swimming motion first. Fortunately, Long didn't have to go trawling around the ocean floor to catch specimens, as the fish are caught in fisheries off the North American coast. Working with Magdalena Koob-Emunds and Thomas Koob, they began videoing the fish in the lab, as they wiggled through a tank. Despite the fish's unpleasant habit of 'sliming' on anyone that touched them, they were remarkably cooperative swimmers, and the team were able to get accurate measurements for the fish's natural flexibility at cruising speeds. But measuring the fish's stiffness was more tricky.

The team clamped the slippery fish in a specially designed bending machine, and reproduced the fish's swimming movements while measuring the body's stiffness. Then they looked at how the stiffness varied as they stripped the fish down to its notochord. Long was amazed when he realised that the narrow notochord contributed 80% of the body's stiffness, even though it only contributed 20% of the body's diameter.

Knowing that biological material's mechanical properties are highly variable, Long and his colleagues began testing how the notochord's flexibility changed as the fish swam over a variety of speeds. He explains that biological materials have complex viscoelastic properties, and the notochord stiffness varied enormously over the fish's natural range of swimming speeds. Long wondered if this variable stiffness could some how be tuned to help the fish swim efficiently.

One way to improve a fish's swimming efficiency, is for the fish to undulate close to the resonant frequency of its body, taking advantage of the way that the resonance naturally amplifies each movement, at no extra cost. When he looked at the amount that each undulation of the body was amplified as the fish swam, Long realised that the notochord's mechanical properties were tuned to give each sweep a sevenfold amplification, no matter what speed it is swimming at.

Long believes that other species could be using this trick to power themselves along. He explains that although notochord material is every bit as rigid as the pads in vertebral columns, fish that have stuck to notochords have the mechanical bonus of an internal amplification system that takes the effort out of swimming.



Hyperventilate for Fitness

Running to catch the bus might be the only exercise some of us get during the day, but your leg muscles aren't the only muscles getting an unexpected workout. Christina Spengler explains that our respiratory systems also have to rise to the challenge. But when an endurance athlete runs for the bus at the same speed, they hardly get out of breath, because they breathe less. Spengler also knew that the athlete's peripheral chemosensory system, the system which constantly monitors the body's levels of key metabolites as well as carbon dioxide and oxygen, is less sensitive than untrained people's. Spengler wondered if it was the act of exercising the whole body that reset the chemoreceptors, or could heavy breathing alone reduce the chemoreceptors' sensitivity? Working with her team, she tested how endurance athletes' respiratory systems responded to six weeks of heavy breathing training, and was astonished to find that the breathing exercises alone had somehow reduced the athlete's chemoreceptor's sensitivity (p. 3937)!

But training by hyperventilating isn't straightforward, because heavy breathing makes you dizzy. Spengler explains that when we are sitting still, we exhale as much carbon dioxide as our low metabolism generates, keeping the carbon dioxide levels in the body at about 5%. But as soon as you begin breathing heavily, without exercising, the body's carbon dioxide level falls, causing a sudden dizzy spell. Over the last ten years, Spengler and her colleague Urs Boutellier have overcome this problem by developing a portable rebreathing system that can be used by athletes to top-up the amount of carbon dioxide that an individual inhales, keeping their carbon dioxide levels high enough to prevent a dizzy spell.

Spengler and her team recruited ten fit young men to begin the unorthodox training regime. First they measured the length of time each athlete could cycle at a speed close to their top speed. Then the athletes began half hour respiratory training periods, using the partial rebreathing device. After six weeks of ventilatory training, Spengler's team tested the cyclist's performance, and found that the athletes could cycle longer at high speed, and their breathing had not changed.

Next, Spengler compared the athlete's chemoreceptors' sensitivity, before and after the six weeks of respiratory training. She was amazed to find that by simply breathing hard, the athlete's had reduced the receptors' sensitivity, although she adds that how the receptors get reset is a mystery.

Spengler explains that she had wondered if resetting the athlete's chemoreceptors would reset their breathing, but as the athlete's breathing had not changed after six weeks of heavy breathing, she knew that the change in the chemoreceptor's sensitivity could not have changed the athlete's breathing. So trained athletes, who breathe less than other more unfit mortals, seem to breathe less for some reason other then a reset chemosensory system.

And has respiratory training contributed to any famous sporting victories? Apparently some successful athletes have used the rebreathing device as part of their training program, but the chances of it getting the rest of us fit enough to take to the Olympic starting blocks isn't high.

Could Kinases Resist Resistance?

For many people in the west, a nematode infestation is an unpleasant, but rare event. Unfortunately, the same cannot be said for the inhabitants of many less developed countries, where nematodes are rife and cause many crippling diseases. Fortunately, modern medicine is equipped with a battery of drugs to rid patients of unwanted parasites. But the threat remains that the nematodes will eventually outsmart the pharmacologists and become resistant to the three major classes of drug currently in use. Which is why Richard Martin is keen to understand how one of these nematode targeting drugs, levamisole, attacks the nematode, *Ascaris suum*. He hopes this will help us to design new therapies to keep medicine ahead of the nematode in the race to beat resistance (p. 3979).

Martin explains that many of the drugs, called anthelmic drugs, which are currently so effective in treating roundworm infections, were originally developed for use in western veterinary practice. He explains that many of these drugs have been used to treat agricultural animals for many years. Most pharmacological and physiological studies on round worms have been carried out on parasites that infest agricultural animals. *Ascaris suum* is a pig parasite, and Martin explains that it is ideal to study because it is large and easily available from local abattoirs.

The drug levamisole cures animals and humans by paralysing the nematode so that it is flushed out of the host's body. The drug acts by specifically targeting an ion channel in the parasite's muscle, opening the ion channel, so that the muscle depolarises and contracts, paralysing the worm.

Fifteen years ago, Martin discovered that the drug targets an ion channel that is known as the nicotinic receptor. This type of channel opens when it binds the neurotransmitter acetylcholine. Many of nicotinic channels are also regulated by protein kinases, which phosphorylate the channel.

Martin knew the *Ascaris suum* ion channel might also be regulated by kinases, and he wondered if the level of kinase activity might also affect levamisole's potency. If he could find a link between a kinase and levamisole's affect on the ion channel, he might be able to find a way of reversing the nematode's resistance to the drug, should it ever develop.

But first he had to find out if kinases could regulate the protein's function. Martin's team used a technique where they could monitor the cell membrane's resistance and potential in response to the drug and kinase inhibitors.

First they treated muscle cells from the parasite with levamisole, and measured how the cells depolarized. Then they treated cells with levamisole and a kinase inhibiting drug, to see if switching the kinase off changed the drug's effect on the ion channel. By testing four inhibitor drugs that targeted different kinases, Martin and his team saw that when tyrosine kinase and calcium calmodulin kinase were inhibited, the depolarisation response decreased. When Martin repeated the experiments with acetylcholine instead of levamisole, the kinase inhibitors also reduced the depolarisation.

Martin explains that this means that both kinases somehow help the ion channels to open. He hopes eventually to find a way to use kinases to enhance the effects of levamisole to combat drug resistance. But fortunately, that day hasn't arrived yet.

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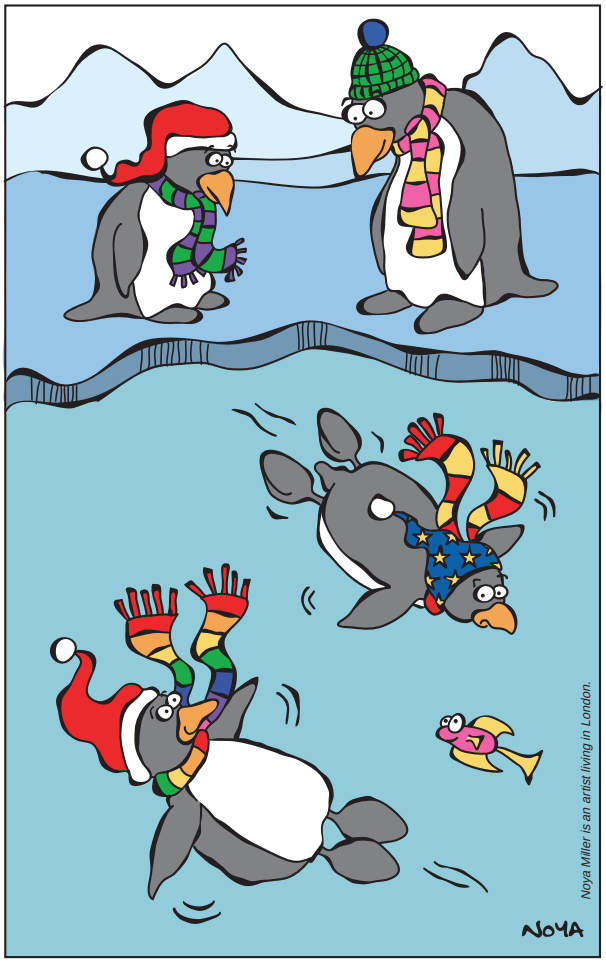

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Penguins Take the Plunge

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