proteinspotlight
> ONE MONTH, ONE PROTEIN <

Issue 273, October 2024
www.proteinspotlight.org

shift

Vivienne Baillie Gerritsen

When humans migrated from Africa to other parts of the globe, they carried with them a certain set of genes. Over the many thousands of years that have passed since, a good deal of these genes have been subjected to minor or perhaps major changes as our ancestors adapted – by the grace of natural selection – to their new environments. One such gene is ACTN3 that produces a protein known as α-actinin-3, itself an integral part of muscle. About 20 years ago, researchers discovered, quite by chance, that many humans – an estimated 1.5 billion today! – have no α-actinin-3 at all in their muscle. Yet they are perfectly healthy individuals. The researchers also observed that humans who had no α-actinin-3 had greater endurance, while those who did sport the protein were usually good sprinters. The absence or presence of α-actinin-3 in muscle depends on a specific mutation whose effect can actually change the nature of muscle fibre. This may have been a consequence of adapting to colder climates, but the side effects are fortunate for athletes: either they have the ability to run far effortlessly or the skill to run a short distance fast.

The Runners (*ca.* 1930)

by Cyril Power (1872-1951)

Exactly twenty years ago, a team of researchers discovered that the absence of an important muscle fibre protein in individuals, α-actinin-3, has no pathogenic effect. Probably because an isoform of α-actinin-3, α-actinin-2, was acting as a substitute. More surprising, perhaps, was the find that an estimated 18% of the human population have no α-actinin-3 at all – which would imply some kind of evolutionary benefit. It turns out that the lack of α-actinin-3 provides resilience to the cold thanks to muscle-generated heat – which could explain why humans migrating to colder climates gradually shed their α-actinin-3 simply to keep warm. And the mutation has come with unexpected side effects: elite athletes who carry α-actinin-3 are usually good sprinters, while those who have no α-actinin-3 have greater endurance.

Muscles are very organised tissues that are composed of muscle cells, or muscle fibres, of which there are two kinds: fast fibres and slow fibres. These two fibres differ, mainly, in their number of mitochondria and myoglobin. Each muscle fibre is a tightly packed bundle of fibrils, or myofibrils. Myofibrils are, themselves, an intricate assembly of two major proteins: myosin and actin that support muscle contraction – although interactions with myriads of other proteins are necessary for muscle integrity and metabolism too. Among these: α-actinins.

α-actinins are a very ancient family of proteins, possibly predating the divergence of eukaryotes and prokaryotes, which is thought to have occurred about 3 million years ago. This just goes to show how crucial α-actinins must be for living organisms. For years, scientists thought that α-actinins had a purely structural role in muscle. This is because they were first observed bridging actin filaments in myofibrils in a zone known as the Z band. Much like in Lego, myofibrils are an assembly of contractile units called sarcomeres. The zone where one sarcomere meets another, and that can be visualized as a disc, is the Z band. It is here that

α-actinins stretch from one actin filament to another to anchor them while stabilising the overall muscle apparatus. Over the years, however, it has become apparent that α-actinins have more than just a structural role: they are also involved in signalling and metabolic pathways during muscle contraction.

There are various α-actinins but α-actinin-3 seems to be the most specialised and is found only in fast fibres in skeletal muscle. Like all α-actinins, α-actinin-3 has a distinctive domain structure. It begins with an N-terminal actin-binding domain (ABD), followed by a central rod made up of a varied amount of repeats (Sel1-like repeats or SLRs), and a C-terminal domain that contains two EF hand regions (an EF hand is said to resemble a stretched out forefinger and thumb, with a clenched middle finger). α-actinin-3 monomers bind via their central rod repeats to form active antiparallel dimers. The formation of head to tail dimers has two important consequences. First, both ends are capable of binding to an actin filament. Secondly, within the same dimer, the N-terminal end of one α-actinin-3 monomer can interact with the C-terminal end of the other. This is important since α-actinin-3 is believed to be at the heart of several important pathways in skeletal muscle, and not only to form a stable sarcomeric lattice.

So what happens when α-actinin-3 is deficient? First of all, α-actinin-2 can step in and do its job. However, a total lack of α-actinin-3 does modify the overall behaviour of the muscle fibre. α-actinin-3 is only found in fast fibres. Fast fibres rely on an anaerobic pathway to produce the energy muscles need (ATP) to contract. In the absence of α-actinin-3, the fibres turn to the more efficient aerobic (oxidative) pathway to produce energy – a pathway usually preferred by slow fibres. So there is a shift from fast fibre properties to slow fibre properties without a structural change of the fibre itself! How can this happen? It may have to do with glycogen metabolism. Fast fibres rely on a readily available source of glycogen to supply energy. When α-actinin-3 is deficient, it could be that the key enzyme glycogen phosphorylase, which is involved in glycogen breakdown, is altered to favour an oxidative pathway. Moreover, glycogen phosphorylase has been reported to interact with α-actinins.

So switching from fast fibre type to slow fibre type will have helped our ancestors resist cold as they migrated northwards – and perhaps even famine. Unknown to them, of course, was the change this shift brought about in muscle function with respect to physical performance. α-actinin-3 deficiency in individuals reduces their ability to use muscle glycogen as a source of energy for muscle contraction. This would, in turn, reduce their ability to generate the energy they need for power sports. This said, an athlete's performance not only depends on their genetic makeup but also on environmental parameters such as diet and training. It did not take long for ACTN3 to join the growing list of genetic markers associated with athletic performance. But this does not, in any way, deprive us of what ACTN3 represents in the field of molecular evolution. Here we have a protein which, in a way, seems to have become redundant though what it has really done is step aside so that our ancestors could survive in a hostile environment.

Cross-references to UniProt

Alpha-actinin-3, *Homo sapiens* (Human): Q08043
Alpha-actinin-3, *Mus musculus* (Mouse): O88990

References

1. Lee F.X.Z., Houweling P.J., North K.N., Quinlan K.G.R.
   How does α-actinin-3 deficiency alter muscle function? Mechanistic insights into ACTN3, the 'gene for speed'
   Biochimica et Biophysica Acta 1863:686-693(2016)
   PMID: 26802899

2. MacArthur D.G., North K.N.
   A gene for speed? The evolution and function of α-actinin-3
   BioEssays 26:786-795(2004)
   PMID: 15221860

Protein Spotlight *(ISSN 1424-4721), http://www.proteinspotlight.org, is published by the Swiss-Prot group at the Swiss Institute of Bioinformatics (SIB).*

Authorization to photocopy or reproduce this article for internal or personal use is granted by the SIB provided its content is not modified. Please enquire at spotlight@isb-sib.ch for redistribution or commercial usage.