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A question of length

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When Charles Darwin accepted the invitation to accompany Captain Fitzroy on HMS Beagle as the ship's naturalist, little did he know that he would bring back with him material that was to haunt him – one way or another - until the end of his days. Amongst the many mineral, plant and animal specimens which were unloaded from the ship on its return in October 1836, there were a number of preserved finches which Darwin had found on the Galapagos Islands. It was the study of these finches, which later became known as 'Darwin's finches', that helped to forge the notion of the transmutation of species. In other words, any given species had the capacity to adapt, evolve and undergo transformations – and it turned out to be in the name of survival. With regards to finches, their beaks were different depending on the kind of diet they had. Charles Darwin had no idea how such changes could occur within a species. Today, we are getting closer and closer to understanding how it happens on the molecular level. And it seems that a protein known as calmodulin has a major role.

'Brown Beakface', by Kaitlin Beckett

Courtesy of the artist

As he set foot on *terra firma* after five years of sailing and as many of nausea, Darwin had no idea that fourteen of the many specimens of birds he brought back to England were in fact all finches. What is more, they seemed to be finches which bore many similarities to a type of finch found along the coast of South America. Darwin had identified them as different birds altogether but when he handed them over to the renowned ornithologist of the time – John Gould – it turned out that these fourteen birds were in fact representatives of twelve different species of finch. Until then, Darwin had believed that there were as many centres of creation as there were of species despite the fact that – within each centre – phenotypical change could occur. With Gould's findings and Darwin's knowledge of the geographical and ecological niches where he had found the birds, he shifted his theory: what if every species of finch on the Galapagos Islands had originated from the one same species on the South American coastline? It marked the very beginnings of his theory on the origin of species.

In those days, the description of specimens – whichever kingdom they belonged to – depended on a keen eye, a pencil and paper. Today, thanks to novel molecular methods, observation has been magnified by the millions – and scientists are able to see or imagine processes which are going on well beneath the level of feathers and petals. Finding links between a specific gene and the effect it has on an organism is now routine. In this way, scientists discovered that the protein calmodulin – from CALcium MODULated proteIN – has a direct role in the shape of a finch's beak. What is more, they discovered that calmodulin seemed to have an effect only on the length of the birds' beak and not its width, or depth – which are dependent on another gene. From an evolutionary point of view, this is not really surprising since it gives natural selection a form of plasticity. In other words, evolution is fine-tuned.

How can calmodulin affect the length of a finch's beak? It seems difficult to believe that one molecule could have such a massive effect on an organism's appearance. In fact, it doesn't. At least not directly. It happens to be at the very beginning of important molecular processes. Indeed, calmodulin has the power to trigger off a wide variety of biological pathways and, in turn, many activities such as muscle contraction, short-term and long-term memory, intracellular movement, inflammation, nerve growth and the immune response to name a few. It uses calcium ions, which are present in all kinds of tissues both inside the cell and outside it. Calmodulin is just one of the many molecules which use calcium ions to induce a reaction. Nevertheless, without it and calcium, a lot of what goes on inside us would go haywire.

At rest, calmodulin looks a little like a dumbbell. It is composed of two arms attached by a helix hinge. Each arm can hold up to two calcium ions. Once bound, the structural conformation of calmodulin is modified and ready to bind to specific target proteins which it does by wrapping its arms around it in a sort of molecular hug. What is more, depending on the amount of calcium ions bound – up to four – and the kind of post-translational modification calmodulin has undergone, the protein can bind to a great variety of targets ranging from kinases, phosphatases and phosphodiesterases to ion channels, cyclases and cytoskeleton receptors. In turn, each of these target proteins will trigger off cellular processes – from the regulation of metabolism and the cytoskeleton, to ion transport, protein folding and cell proliferation. With regards to the length of finch's beaks, researchers discovered that the long-beaked finches always express a higher level of calmodulin than the shorter and wider-beaked species. And when they upregulated the calmodulin gene in chicken, this had a direct effect on the length of their beaks!

Although a number of anti-calmodulin products had already been described in the 1980s, by the 1990s interest had faded. However, owing to the more recent discoveries of the involvement of calmodulin in so many different physiological processes, there has been a drastic increase in its interest, especially within the world of therapy and drug design. Some synthetic inhibitors are already used clinically as anti-cancer and anti-psychotic agents for example. But scientists have already described over one hundred natural inhibitors, the most potent of which are animal venoms. Such naturally-occurring compounds could be used to develop herbicides or to design drugs for neurodegenerative diseases for example. The future certainly seems bright for calmodulin. HMS Beagle took Darwin around the world; little did the founder of the theory of the origin of species know where his finches would take him.

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