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> ONE MONTH, ONE PROTEIN <

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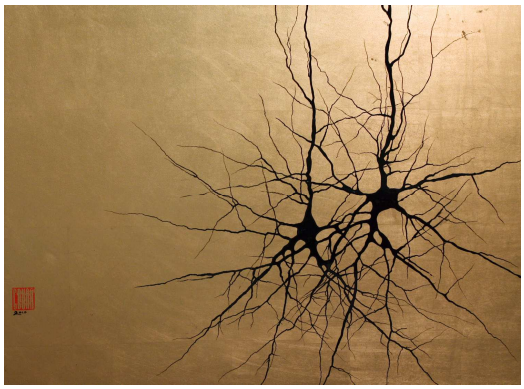
something else

Vivienne Baillie Gerritsen

Knives were crafted to cut. Yet how many of us use them to slit an envelope. Or prise open a lid. Nature too has its ways of perverting a design so that its initial role is altered to become another. This is exactly what happened to a protein known as osteocrin. Osteocrin was first discovered in bone. Though it remains unclear how it works in detail, it seems to influence longitudinal bone growth. Almost a decade later, scientists found out that osteocrin is also expressed in the primate brain where data suggest a role in neuron growth. This may not come as a surprise – here is a protein that promotes growth both in bones and in the brain. What is intriguing, however, is that it seems to drive neuron growth in the anthropoid primate only, whereas its role in bone growth, for instance, is shared by many other species too. Osteocrin has acquired this new explicitly-primate skill following a series of mutations which changed the way it is expressed. Would this imply, then, that it is partially responsible for intelligence?



Two Pyramidals, Greg Dunn 2010
enamel on composition gold leaf

Courtesy of the artist

It took ages for the human brain to become what it is today. It all began when cells discovered the benefits of communicating with one another. As far back as 850 million years ago, single-celled organisms were already talking to each other by way of electrical pulses and chemical signals. It wasn't long before actual cells specifically designed for communication appeared, in other words: the very first neurons. In time, neurons themselves joined forces, thus creating the rough contours of a central nervous system and lending organisms the ability to interact with ever-increasing sophistication. Brain structure *per se* seems to have appeared in worms about 500 million years ago where it drove basic functions such as breathing, heart beat regulation and motor movements. As time rolled on, these functions were preserved while evolution added more intricate structures and skills. In a nutshell: between 360 million years ago, when our ancestors emerged from water and today, brains have changed dramatically both in size and complexity, especially with regards to anthropoid apes, and in particular humans.

The brain of the great apes has indeed changed very little when compared to that of their immediate ancestors. The human brain, however, started to expand 2.5 million years ago. Why? Serendipity probably played a part. In those days, humans had also begun to innovate and adopt smarter lifestyles, which probably created a positive feedback effect. So much so that, in the past 2 million years, human brain size has increased by a factor of 3. However, in the past 200,000 years our brain has ceased to grow. It has, in fact, shrunk a little in size. This may have something to do with giving birth to babies with big heads. But none of this really matters; Nature found out that increasing the complexity of neuron wiring and cellular diversity was just as good a way of giving room to intelligence as increasing the size of the brain itself – besides all the feedback loops involving our diet, culture, technology, social relationships and, of course, our genes.

Synaptic plasticity – or the ability for a brain to remain influenced by the environment – is a crucial feature of the human brain, from the moment we are born to pre-adulthood. During this rather long period, sensory experience drives the maturation and function of the nervous system by inducing changes in gene expression networks which, in turn, influence synapse development. As a result, our

brain continues to develop in the first years of our life. To date, little is known about genes involved in brain development and whether these genes are actually species-specific. The case of osteocrin, however, may imply that species-specific genes are indeed responsible for the complexity of the primate brain for instance.

What does osteocrin do? It is a secreted peptide that was initially discovered in bone-forming cells or osteoblasts, hence its name. Expression of the protein seems to be influenced by periods of fasting and feeding, following which it binds to the natriuretic clearance receptor – NPR-C – present on the surface of osteoblasts. Upon binding to NPR-C, osteocrin influences the downstream network which stimulates the proliferation and differentiation of growth plate chondrocytes leading to longitudinal bone growth. Afflictions such as dwarfism or bone overgrowth can occur when something goes wrong in such a pathway.

This is what osteocrin does for bones, and possibly in all mammals. In the brain, osteocrin probably also binds to NPR-C, leading this time to dendritic growth. The thing is: it only does this in the anthropoid primate brain, i.e. monkeys, apes and humans. As far as expression goes, osteocrin is found in the early stages of human cortical development before all synapses are established. Expression peaks are observed in mid and late foetal development, and remain high throughout adolescence during which time osteocrin is mainly restricted to the neocortex. What happened for the protein to be specifically active in the primate brain? Over the years and following a small number of nucleotide mutations, osteocrin gradually acquired a unique DNA regulatory element, or enhancer, to which binds an activity-regulated transcription factor known as MEF2. Upon sensory excitation, MEF2 binds to this newly-acquired enhancer and stimulates the expression of osteocrin in the primate brain.

It is still not clear how exactly things happen downstream. In the human neocortex, brain osteocrin seems to influence downstream networks which are involved in restricting dendritic growth. In so doing it has a role in dendritic arborisation and hence the overall complexity of a brain's neuronal layout. The enhancer motifs are specifically conserved in anthropoid primates but are not present in prosimian primates for instance, suggesting that these motifs are particular to anthropoid evolution only. This is a very neat demonstration of how the sum of certain mutations specific to a species acquires the ability to influence gene networks and cell behaviour – in this case human neural circuit development.

So Nature and time can twist a gene's fate. This may constitute one of the answers to the unresolved question: How can mammals as far apart as mice and humans be not only the owners of the same set of genes but also of brains that are so different both in complexity and size? As always, nothing can be reduced to a mere set of genes. The environment also has its say, as do an organism's lifestyle and socio-cognitive skills. Understanding better how the brain develops will help to identify mental disorders such as autism, which currently affects about 1 in 68 children. Grasping the subtle differences between the human brain and animal models will also help scientists to model diseases and develop drugs, besides outlining with an ever-finer pen the contours of human intelligence.

Cross-references to UniProt

Osteocrin, *Homo sapiens* (Human): P61366
Osteocrin, *Mus musculus* (Mouse): P61364

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