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> ONE MONTH, ONE PROTEIN <

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the making of crooked

Vivienne Baillie Gerritsen

Moving any one of our limbs is not something most of us have to think twice about. Rising from a chair to make a cup of coffee or picking your nose is usually a piece of cake. Yet the natural mobility of our legs – for instance – can be dependent on the existence or not of molecular loops. Nature can tease us with very little. Any one of our movements is made possible thanks not only to the existence of motor neurons but their growth and differentiation. Growth and differentiation are, in turn, dependent on many cellular activities, in particular the trafficking of entities from one end of a nerve cell to another. If the trafficking is checked for any given reason, the neuron does not react the way it should and whatever limb it activates will suffer the consequences. Spastin is an enzyme which has a central role in the building of highways for neuron traffic and we now know that it is also guilty of causing a neurodegenerative disease in the lower limbs, known as hereditary spastic paraplegia.

"Leg Wheel & Jew Harp" by Rima Staines

Courtesy of the artist

Hereditary spastic paraplegia (HSP) is a disease which causes progressive spasticity and weakness of the legs of those who suffer from it. Also known as the Strumpell-Lorrain disease, it was first described by the German neurologist Adolph Strümpell (1853-1925) in 1883, and characterized in greater detail by the French physician, Maurice Lorrain in 1888. The 20th century has shed molecular light onto HSP and researchers now know that the main culprit was the mutated form of an enzyme, known as spastin. Spastin is found in many tissues, amongst which nerve tissues where it populates motor neurons both in the nucleus and the cytoplasm. It is still unclear what spastin does in the nucleus – if anything at all – but much has been revealed about its role in the cytoplasm.

Spastin interacts with microtubulin. Microtubulin dimers assemble – or disassemble – to build microtubules which are used to reinforce the cell's cytoskeleton, for example, or to build molecular roads on which all sorts of micro- and macromolecules travel. If you could see the inside of a cell, you would observe the continuous lengthening and shortening of hundreds of microtubules as they serve their purpose. Once a road has been used, there is no point in keeping it built, so it is destroyed and the units used to build another road. Conversely, every road needs a place to start. These are the centrosomes which represent the beginning of any microtubule and onto which microtubulin dimers are added. Unsurprisingly, spastin is dense around the centrosomes.

As mentioned, spastin has a major role in the building of microtubule highways. In fact, spastin fine-tunes the dynamics and integrity of microtubulin assembly thanks to two roles which may seem paradoxical: spastin not only knows how to sever microtubules but it also knows how to create small bundles of microtubules. Naturally, there must be a host of

co-factors which are also part of the fine-tuning and the timing of bundling or severing. Yet, spastin has a central role since a mutated form of the enzyme disrupts the balance between microtubule bundles and severing altogether.

What is it that makes spastin choose the right time to bundle or sever? Spastin functions either as an ATPase or not, and these two modes are undoubtedly governed by other co-factors. When spastin is not functioning as an ATPase, it binds to microtubules and promotes their bundling. Conversely, the presence of ATP promotes the formation of a spastin homohexamer which looks a little like a cogwheel with a hollow centre. Each monomer carries two loops, positioned one above the other and which line the inner ring of the wheel. These particular loops are critical for mictrotubulin recognition and severing.

How does spastin sever microtubulin? Specific domains on spastin recognise the tail of assembled microtubulin and sucks it into the hole in the middle of the hexamer. Following successive cycles of ATP hydrolysis, two possible processes occur: severing is achieved either by pulling on the microtubulin tail and untying a knot the way you would undo a shoelace, or by flipping the position of the microtubulin dimer within the polymer thereby making it impossible for further microtubulin stacking and hence microtubulin growth.

Without the loops, microtubule severing would not be possible. In HSP, a mutation in spastin affects one of the two loops. As a result, the dynamics of microtubules are impaired, cellular trafficking is affected, neuron growth is stunted and those with the mutated form of spastin suffer an awkward gait with weakness in the legs. And there is growing evidence that some families may also suffer from dementia. Much is known about spastin – its structure, its cellular distribution, its function – yet still more needs to be known to design therapies which can help those living with the shadow of HSP hanging over them so that the simple act of walking to the coffee machine is less of an ordeal.

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