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> ONE MONTH, ONE PROTEIN <

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a short story

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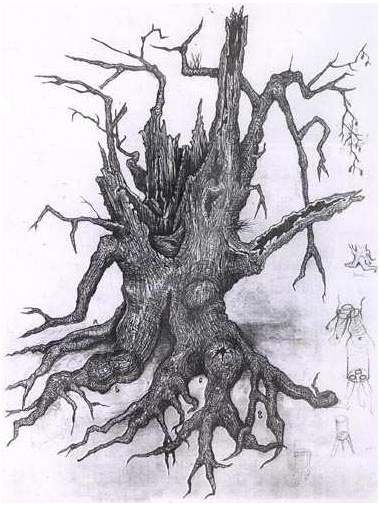
When I was a child I remember seeing little girls and boys of my own age whose arms had not grown to their full length. There were not many but enough for me to find it almost normal. What I did not know is that there were other little boys and girls whose legs had not grown either. But we never saw them. As we never knew of all the little babies who died shortly after birth and whose limbs – and other parts of their bodies – were grossly malformed or simply absent. Such deformities were the doings of a drug known as thalidomide, and the children were known as thalidomide children. My mother refused to take thalidomide to treat her morning sickness when she was pregnant with her first child. Many other mothers, however, did not. And it was not long before the link between thalidomide and gross deformities found in newborns was made. How thalidomide created such handicaps remained a mystery for many years. Today, there are a number of hypotheses, one of which involves the protein cereblon which has turned out to be one of thalidomide's direct targets.



"Oak Tree" by Rima Staines

Courtesy of the artist

Thalidomide was introduced onto the market in 1957, by a German pharmaceutical company, as a sedative and a successful drug against insomnia, colds and headaches. Though this particular company secured a patent in 1954, it is believed that thalidomide was first synthesized by the Germans during World War II as an antidote to nerve gases such as sarin. Despite a report in the British Medical Journal in 1958 of the possible harmful effects of thalidomide, and a near ban of the drug by the United States of America until further investigation on its effects had been made, thalidomide was widely prescribed.

Unfortunately, when it was given to pregnant women, the result could be disastrous for their progeny. Consequently, thalidomide was withdrawn from the European market in 1961, marking the beginning of a new era where a drug could only receive approval if tests on its safety during pregnancy had been previously done. The British government made an official apology to its population in January 2010 – 50 years after the first thalidomide children had been born. The apology came as a relief for many, in particular mothers who had felt guilty for having taken the drug in the first place.

Thalidomide is a derivative of glutamic acid. How can such a tiny chemical entity create such havoc? It has taken years to find the beginnings of an answer. Once thalidomide has been ingested, it is distributed throughout the body. It seems to be able to act on its own by inserting itself into DNA in specific regions. By doing so, it interferes with gene promoter regions thus stalling the production of proteins which are involved in developmental programs – such as the genesis of blood vessels. Consequently, the growth of limbs in an embryo can be hindered. But how does thalidomide interfere with the cereblon protein? And what happens when it does?

The cereblon protein is found throughout the organism, although it seems to be hugely expressed in the brain. Hence the beginning of its name. It also sports what is known as a Lon domain in its primary sequence – a domain which is highly conserved in ATP-dependent Lon proteases, although there is no evidence to date that cereblon has any such role. However, in the brain, cereblon seems to bind to the alpha unit of large-conductance calcium-activated potassium channels and is responsible for their proper assembly as well as their surface expression in neurons. Such a role is of great importance in proper brain development, especially in learning and memory. Indeed, an inherited mutated form of cereblon is known to cause mild mental retardation due to memory and learning deficits.

Besides its role in a certain form of intelligence, elsewhere in the organism cereblon seems to be part of what is known as the E3 ubiquitin ligase complex. Probably by way of developmental and/or transcriptional regulators, this particular complex is important for limb outgrowth. Which is where thalidomide comes in… A dysfunctional E3 ubiquitin ligase leads to the disruption, or the abnormal regulation, of downstream pathways which are important for the proper development of limbs. Indeed, thalidomide is capable of binding directly to cereblon, thus interfering with its usual function. As a result, developmental pathways are interrupted, or hindered, leading to stunted limb growth.

Such findings are of great interest. Here is a protein which is involved both in cognitive processes but also in developmental programs as important as limb growth, or blood vessel maturity. Not only will it help to understand the mechanisms underlying processes as essential as memory and learning – and possibly give a better insight into conditions such as Alzheimer's and autism for instance – but a greater understanding of the 3D structure of cereblon and its intimate behaviour should help to design thalidomide derivatives which have no teratogenic drawbacks. Indeed, though used with great caution since the 1960s, thalidomide has shown to have great therapeutic value in the treatment of multiple myeloma and certain forms of leprosy. Clearly, thalidomide has had a very dark history but seems to be in for a brighter future.

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Protein cereblon, *Homo sapiens* (Human) : Q96SW2

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