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> ONE MONTH, ONE PROTEIN <

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the matchmaker

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The smallest of things can have drastic consequences. A rash gesture. A reckless statement. A moment's hesitation. Likewise, the smallest of chemical changes can be the cause of serious afflictions such as cancer, Alzheimer's disease, cystic fibrosis or haemophilia. Noonan syndrome is one such affliction and affects a newborn in one to two thousand. Typically, a Noonan child has a wide space between its eyes, is web-necked and small in stature. Unfortunately, the condition is also associated with congenital heart disease, learning problems, impaired blood clotting as well as many other features whose range and severity vary hugely in patients. Everyday, a child is born with Noonan syndrome, and one of the culprits is the tiniest of modifications which occurs on a protein known as SHOC2.

"Human misery" by Paul Gauguin (1848-1903)

Source: www.paul-gauguin.net

Noonan syndrome was named after Jacqueline Noonan, a paediatric cardiologist. Though the very first description of Noonan syndrome is credited to a certain Koblinsky, a medical student who attended the Russian Estonian University of Dorpat in the 1880s, Jacqueline Noonan was the first to notice that a rare type of heart defect in children was more often than not associated with short stature, a webbed neck, a wide space between the eyes and ears set lower than the norm. Her first paper on the condition was published in the early 1960s and it was the human geneticist John Marius Opitz, then a medical student where Dr Noonan had her practise, who suggested the term "Noonan's syndrome". Finally, the condition was officially named after the lady paediatrician in 1971.

If so many symptoms are the result of one protein, the said protein must be at the heart of an essential pathway which involves growth and development. Indeed, SHOC2 is part of the MAPK pathway which has a vital role in cell proliferation, growth, differentiation and migration. Many proteins are involved in the MAPK pathway which relays signals from the cell's surface all the way to its DNA in the nucleus, switching genes off and on depending on the need and the moment. To meddle with such a pathway is sure to create chaos, and many forms of cancer are the result of such systems that have gone haywire.

SHOC2 is an in-between protein. It is neither on the cell's surface, nor in its nucleus, but in the cell's cytoplasm where it acts as a scaffold protein for two other proteins involved in the MAPK pathway: RAS and RAF. This does not come as a surprise since SHOC2 is made up of many leucine-rich repeats which are known to enhance protein-protein interactions. And which protein interaction does SHOC2 enhance? SHOC2's role is to grab RAS armed with GTP and save it for RAF. The SHOC2/RAS duet then binds to RAF, and in so doing releases a

phosphate, which in turn causes RAS and RAF to dissociate. The released signal phosphate continues further downstream, as it is transferred from protein to protein, until it reaches the nucleus and the cell's DNA where it will activate – or indeed inactivate – the transcription factor of a given gene.

RAS and RAF are perfectly capable of binding to one another without the assistance of SHOC2 – but SHOC2, like a matchmaker, brings them together much faster so there is no delay in the pathway. So what happens to SHOC2 in the event of Noonan syndrome? One missense mutation in the SHOC2 sequence introduces a site for lipid modification known as myristoylation, which is irreversible. As a result, SHOC2 is rushed off to the wrong destination and, instead of being targeted to the cytoplasm to unite RAS and RAF, it is diverted to the cell's plasma membrane where it remains. Consequently, the MAPK pathway loses its normal "dating service" regulated by SHOC2. The result leads to a perturbed MAPK pathway, and hence confusion in normal embryonic development which will result in the physical and physiological drawbacks specific to Noonan syndrome.

Naturally, SHOC2 is not the only protein which is implicated in Noonan-like syndromes. Other proteins involved in the MAPK pathway, and that are hindered one way or another, are prone to trigger off similar syndromes. The singularity of SHOC2 is that it is seemingly the first example of an acquired N-terminal lipid modification, in this case N-myristoylation, of a protein which actually causes a human disease – which is hardly a comfort for parents who discover that their child is suffering from congenital heart defects. However, a greater understanding of the role of SHOC2 will certainly help elucidate the ins and outs of the MAPK pathway which is central in the development of many cancers. In time, this will hopefully lead to the design of drugs that could reverse the effects of a protein which is sending off the wrong signal – a huge revenge on the tiniest of malefactors.

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